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A putative causal variant in SLC38A8 segregating with foveal hypoplasia in an autosomal recessive family with primary exotropia

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Authors Zia Chaudhuri, Jibin John, Anirban Mukhopadhyay, Satinder Aneja, BK Thelma

Publication date 2018/7/13

Journal Investigative Ophthalmology & Visual Science

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Publisher The Association for Research in Vision and Ophthalmology

Description Purpose: To identify putative causal variants for foveal hypoplasia (FH), low vision (LV), nystagmus and exotropia (XT) in two siblings, fifth and seventh of a cohort of seven siblings with deceased parents.

Methods: This large two-generation informative family (Figure 1), with presumptive autosomal recessive (AR) inheritance pattern was recruited from the ophthalmic outpatients department (OPD) of Lady Hardinge Medical College, New Delhi. Whole exome sequencing (WES) was performed on four out of seven siblings [two affected and two unaffected] using Agilent V5+ UTR on an Illumina platform and the data analysed.

Results: WES based variant analysis demonstrated a homozygous stop gain mutation,(c. 264 C> G: pY88*, exon 2, MAF SAS= 0.00006) in SLC38A8 (16q23. 3) segregating with the phenotype of sub-normal best-corrected visual acuity (BCVA) with FH and nystagmus. The unaffected siblings were heterozygous for the mutation (Figure 2). While normal as far as BCVA and absence of nystagmus was concerned, one unaffected sibling (No. 15) had FH on optical coherence tomography [OCT] though to a lesser extent than the affected siblings.

Conclusions: Mutations in SLC38A8 have been previously reported in the European Caucasian and south Asian populations to be causal for the FH, optic-nerve-decussation defects and anterior segment dysgenesis (FHONDA) syndrome, with functional validation in medaka fish (Oryzias latipes) model. This mutation in SLC38A8 was novel for the phenotype of FH, nystagmus and subnormal BCVA, found in the study family. This novel index mutation was however not obtained in extended ...

Not to be included in 2018 - 2023 NAAC cycle

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Dopamine-β-monooxygenase inhibitors obtained by structure based methods exhibited anti-hypertensive effect in L-NAME induced hypertensive rats

Authors Sanjay Kumar Dey, Pankaj Prabhakar, Manisha Saini, Toyanji Joseph, BK Thelma, Subir K Maulik, Suman Kundu

Publication date 2018/4

Journal The FASEB Journal

Volume 32

Pages 797.5-797.5

Publisher The Federation of American Societies for Experimental Biology

Description Introduction

Hypertension is the leading cause of mortality worldwide (Kwan G.F. et. al., Circulation, 2016). While classical anti-hypertensives like ACE inhibitors, ARBs, calcium channel blockers, beta blockers and diuretics are widely used, they have their own limitations and no new type of drugs emerged in the last few years that use body's own blood pressure lowering mechanism. Dopamine β-monooxygenase (DBM), expressed in noradrenergic nerve terminals as well as in adrenal medullary chromaffin cells, which convert dopamine into norepinephrine, is a novel target whose inhibition has been shown to help the treatment of hypertension with several advantages over the classical antihypertensives. However, DBM inhibitors are few in number, often result in side-effects and are frequently non-responsive to specific population, probably since the known inhibitors so far have been designed on ligand based ...

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journal homepage: www.elsevier.com/locate/yabio

Single-wall carbon nanotube based electrochemical immunoassay for leukemia detection

Payal Gulati[a], Prabhjot Kaur[b], M.V. Rajam[b], Tapasya Srivastava[b], Prabhash Mishra[a], S.S. Islam[a,*]

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ARTICLE INFO

Keywords:
P-glycoprotein (P-gp)
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ABSTRACT

A label-free electrochemical immunosensor is fabricated using high quality single-walled carbon nanotube for early detection of leukemia cells. It is based on P-glycoprotein (P-gp) expression level detection; by effective surface immune-complex formation with the monoclonal anti-P-glycoprotein antibodies bound to an epoxy modified nanotube surface. The expression level of P-gp on the leukemia cell surface detected by cyclic voltammetry is in good agreement with immunofluorescence microscopy studies. The proposed biosensor could be used for the detection of P-gp expressing cells within a linear range of 1.5×10^3 cells/mL – 1.5×10^7 cells/mL where lowest detection limit is found to be 19 cells/mL. A calibration plot of peak current v/s the logarithm of concentration of leukemia K562 cells is found linear with a regression coefficient of 0.935. This strategy promises high sensitivity, low-cost, fast, and repeatable recognition of cancer cells. The immunosensor was stable for three weeks and showed good precision with the relative standard deviation (RSD) of 3.57% and 2.12% assayed at the cell concentrations of 1.5×10^3 and 1.5×10^5 cells mL^{-1} respectively. The proposed single-wall carbon nanotube based immunosensor showed better analytical performance in comparison to similar leukemia electrochemical sensors reported.

Introduction

Cancer is the second major cause of global mortality and also a leading cause for 8.8 million deaths in 2015 [1]. Leukemia, a malignancy of the early blood cells, mostly starts in the bone marrow and infiltrates in the blood. It is the most common cancer in children and teens, where it is acute or fast-growing in nature. In adults, leukemia is mostly chronic and slow growing. According to the American cancer society, leukemia is ranked 7th in the estimated death rate in 2018 (24,370 people) and 10th in the estimated new cases in 2018 (60,300 cases) [2]. Early detection leads to a better disease outcome and therefore, has spurred the need for both biomarkers as well as improved technology [3–5]. Early, efficient, and specific detection of cancer are the key features that can determine the therapeutic regimen for a patient. Fabrication of biosensors for detection of low cancer cell count is now being done using nanomaterials that increase the surface area for maximum detection [6]. In this work, we have used P-glycoprotein (P-gp), a protein over expressed in drug resistant cells, responsible for pumping drugs out of the cells resulting in failure of chemotherapy treatment [7–11]. Expressed on the cell surface, P-gp emerges as a good candidate for detection of difficult to treat cancers. In this paper, we show that P-gp expressing leukemia cells bind to their respective antibodies on the transducer surface, resulting in immune-complex formation; thereby, generating changes in the bioelectro-chemical signal in an electrochemical cell.

Different nanomaterials have been used for biosensors fabrication. Diverse nanomaterials successfully utilized as biosensors include gold nanoparticles, polymers, quantum dots, carbon nanoparticles and nanowires. Gold nanoparticles (AuNPs) have huge advantage in the field of bio-nanotechnology owing to their biocompatibility, diminished cytotoxicity, large surface area, good optical and electrical properties, although their high cost is a disadvantage [12]. The ability of AuNP to mediate electron transfer between the electroactive biological analyte and electrode reduces redox enzyme biosensing because a non-negligible amount of these molecules is lost in solution while diffusing to the electrode surface [13]. Quantum dots, a nanomaterial used widely in photo-electrochemical and optical sensing, also face challenges due to crystal lattice structural defects that trap electrons and holes leading to non-radiative relaxation [14]. Additionally, quantum dots require biocompatible coating on their surface to facilitate immobilization of biomolecules on it [15]. Magnetic nanoparticle a new entrant as a biosensor material forms a highly sensitive transducer not susceptible

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Leukemia biomarker detection by using photoconductive response of CNT electrode: Analysis of sensing mechanism based on charge transfer induced Fermi level fluctuation

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P-glycoprotein

ABSTRACT

We report here leukemia biomarker detection by monitoring the charge transfer dependent Fermi level fluctuation due to adsorption of chemical or biological species at semiconductor surface, leading to detection of CML at an early stage. This technique demonstrates a new way to understand the operation of biosensor, where an in-depth analysis is presented here to understand the sensing mechanism. The sensor performance is optimized by tuning silane binding time, antibody concentration and its binding time on the CNTs surface. In every step during adsorption of chemical and biological molecules, complementary studies such as Raman, FTIR and FESEM analysis were done to cross check the claim. This sensor shows a lower limit-of-detection (LOD) of 27 cells/ml within a concentration range of CML cells (1.1×10^7–2×10^3cells/mL). The obtained data are equally competitive to the reported sensors relying on other conventional techniques where a series of rigorous steps were followed to obtain the expected data. Thus, the use of photoconductivity measurement to monitor the Fermi level fluctuation in CNTs for detection of target species proves to be a unique sensitive platform, less prone to contamination and human error unlike the conventional techniques and can be used for point-of-care cancer diagnostics.

1. Introduction

Quantification of chronic myeloid leukemia (CML) is extremely important for early diagnosis/prognosis for the survival of blood cancer patient. CML, a type of blood cancer, has recently been reported to victimize ~15% of adult globally [1]. It can be categorized into three phases including chronic phase, accelerated phase and blastic phase [2–4]. Blastic phase (also called acute phase or blast crisis) is the most serious and therefore, numerous techniques have been developed for its detection [5]. At present, the main tools for leukemia detection are biopsy, imaging techniques like computer tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) [2–5]. Another approach known as cytogenetic testing, involves diagnosis of Philadelphia chromosome positive cells. However, it is limited by low sensitivity, longer turnaround time, requirement of bone marrow sample and high cost [6]. FISH (Fluorescence in situ Hybridization) is another approach which overcomes these issues but suffers from the loss of cells during processing [6,7]. Likewise, flow cytometry method also has certain limitations such as it is very complex system requires trained personnel, needs single cell and loss of tissue structure during measurements [8]. To overcome these problems and their invasiveness, researchers have explored some electrochemical-based immunosensors [9–25]. While retaining the exciting performance of these immunosensors such as high specificity, lower detection limit, good sensitivity, fast response, and low cost [9–26]; nanostructured materials offer further improvements for detection of cancerous biomolecules.

Nanomaterials with different shapes such as nanotubes, nanowires, quantum dots, nanorods, and nanosheets are explored to construct immunosensor devices. Their exciting properties like large surface area to enhance surface reactivity, wide range of absorption spectrum, and confinement of both electrons and holes leading to non-radiative relaxation, have attracted the researchers to engineer semiconductor based electronic devices.

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0925-4005/

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Genetics of ulcerative colitis: putting into perspective the incremental gains from Indian studies

[HTML] from springer.com
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Authors Garima Juyal, Ajit Sood, Vandana Midha, BK Thelma

Publication date 2018/12

Source Journal of genetics

Volume 97

Pages 1493-1507

Publisher Springer India

Description Ulcerative colitis (UC), one of the two clinical subtypes of inflammatory bowel disease is perceived as a potential 'sleeping giant' in the Indian subcontinent. Clinical manifestation is overall believed to be the same across ethnic groups but overwhelming genetics from large European and fewer non-European studies have revealed shared as well as unique disease susceptibly signatures between them, pointing to population specific differences at genomic and environmental levels. A systematic recount of the four major eras in UC genetics spanning earliest linkage analysis, cherry picked candidate gene association studies, unbiased genomewide association studies, their logical extension in trans-ethnic setting (Immunochip study), lastly whole exome sequencing efforts for rare variant burden; and lessons learnt thereof in context of genetically distinct Indian population was attempted in this review. Genetic ...

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Status of newborn screening and inborn errors of metabolism in India

[HTML] from springer.com
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Authors Seema Kapoor, BK Thelma

Publication date 2018/12

Source The Indian Journal of Pediatrics

Volume 85

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Publisher Springer India

Description Inborn errors of metabolism (IEM) are a heterogeneous group of genetic disorders that cause significant neonatal and infant mortality. Expanded newborn screening which detects these disorders at birth is the standard preventive strategy in most countries. Prospective studies to evaluate the impact of these in the Indian population are lacking. The imminent need to address this lacuna warrants a review of available pan India data, as well as efforts for a carefully conducted prospective assessment of the burden of IEM. Published data on IEM in the Indian population comprising universal prospective screening and screening in selected subgroups (patients admitted to pediatric/neonatal ICUs, patients with developmental delay/mental retardation) was collected through a systematic search. The primary focus was to get an estimate of the disease burden in the Indian population. A true prevalence of IEM in ...

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Functional characterisation of ADP ribosylation factor-like protein 15 in rheumatoid arthritis synovial fibroblasts

[PDF] from researchgate.net

Authors	Sujit Kashyap, Uma Kumar, Anuj Kumar Pandey, Maumita Kanjilal, Patralika Chattopadhyay, Chandrashekhar Yadav, BK Thelma
Publication date	2018/2/14
Journal	Clinical and Experimental Rheumatology
Volume	36
Issue	4
Pages	581-588
Description	Objective ARL15 is a novel susceptibility gene identified in a recent GWAS in a north Indian rheumatoid arthritis (RA) cohort. However, the role of ARL15 or ARF family genes in RA aetiology remains unknown. Therefore, we aimed to i) establish the expression of ARL15 in rheumatoid arthritis synovial fibroblasts (RASF) and ii) its functional characterisation by assessing its effects on major inflammatory cytokines and interacting partners using a knockdown approach.
Total citations	Cited by 3

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Advances in the discovery of genetic risk factors for complex forms of neurodegenerative disorders: contemporary approaches, success, challenges and prospects

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Authors: Sumeet Kumar, Navneesh Yadav, Sanjay Pandey, BK Thelma

Publication date: 2018/7

Source: Journal of genetics

Volume: 97

Issue: 3

Pages: 625-648

Publisher: Springer India

Description: Neurodegenerative diseases constitute a large proportion of disorders in elderly, majority being sporadic in occurrence with ~ 5–10% familial. A strong genetic component underlies the Mendelian forms but nongenetic factors together with genetic vulnerability contributes to the complex sporadic forms. Several gene discoveries in the familial forms have provided novel insights into the pathogenesis of neurodegeneration with implications for treatment. Conversely, findings from genetic dissection of the sporadic forms, despite large genomewide association studies and more recently whole exome and whole genome sequencing, have been limited. This review provides a concise account of the genetics that we know, the pathways that they implicate, the challenges that are faced and the prospects that are envisaged for the sporadic, complex forms of neurodegenerative diseases, taking four most common ...

J Biosci
DOI: 10.1007/s12038-018-9753-6

Deletion of *Dictyostelium discoideum* Sir2A impairs cell proliferation and inhibits autophagy

RAKHEE LOHIA[1,2,†], PUNITA JAIN[1,3,†], MUKUL JAIN[1], HIMANSHU MISHRA[1], PRADEEP KUMAR BURMA[2], ANJU SHRIVASTAVA[3] and SHWETA SARAN[1]*

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Sirtuins are a family of deacetylases (Class III histone deacetylases) with evolutionarily conserved functions in cellular metabolism and chromatin regulation. Out of the seven human Sirtuins, the function of Sirt2 is the least understood. The purpose of the present study was to investigate the role of Sir2A, a homolog of human Sirt2 in *Dictyostelium discoideum (Dd)*, a lower eukaryote. We created both overexpressing and deletion strains of *Ddsir2A* to analyse its functions. We observed *sir2A* mRNA expression throughout development and the transcript was present in the prespore/spore region of multicellular structures developed. They show a preference towards prestalk/stalk pathway when co-developed with wild-type cells during chimera formation. Deletion strain showed a multi-tipped phenotype, decrease in cell proliferation and inhibition of autophagy. In conclusion, our results show low cAMP levels, reduced cell-adhesion, weak cell migration and impaired autophagy to be responsible for the phenotype shown by the null cells. This study provides new insights into the functions of *Ddsir2A*.

Keywords. Autophagy; development; *Dictyostelium*; patterning; *sir2A*

1. Introduction

Sirtuins are NAD^+ dependent deacetylases (North and Verdin 2004) that play a crucial role in response to oxidative, metabolic or genotoxic stress (Chalkiadaki and Guarente 2012) and participate in various functions like adaptations to stress, development, differentiation and maintenance of metabolic homeostasis (Martínez-Redondo and Vaquero 2013). Sirtuins are conserved in evolution and mainly exert their functions by affecting the chromatin (Bannister and Kouzarides 2011) largely via gene silencing, chromatin modulation, DNA repair, cell cycle regulation etc. (Bosch-Presegué and Vaquero 2011) involving deacetylation of histone and non-histone proteins.

There are seven sirtuins (Sirt1–7) in humans, which are dependent on NAD^+ binding but target different substrates (Li and Kazgan 2011). They show distinct but not exclusive subcellular localizations (Sack and Finkel 2012). Out of these seven sirtuins, Sirt2 is the least understood. Several studies support a role for Sirt2 as a tumour suppressor protein that is down regulated in human gliomas (Hiratsuka *et al.* 2003). They maintain genomic integrity by releasing the damaged cells from mitotic arrest and forcing them into apoptosis. Also, it has been linked to microtubule dynamics, cell migration, inhibition of differentiation and oxidative stress response (Serrano *et al.* 2013). Sirt2 is up regulated during mitosis and overexpression induces the lengthening of mitosis (Dryden *et al.* 2003) and shortening of G1 phase (Bae *et al.* 2004). In addition, it inhibits oocyte maturation and embryonic cell division in starfish (Borra *et al.* 2002). Primary mouse embryonic fibroblasts derived from Sirt2 knockout mice show a very limited decrease in the length of mitosis but a longer G1 and shorter S phases – a finding that confirms that Sirt2 has a significant role in cell cycle and a direct impact on G1/S (Vaquero *et al.* 2006). Sirt2 is primarily a cytosolic protein but can shuttle into the nucleus suggesting its ability to deacetylate both cytosolic and nuclear proteins (North and Verdin 2007).

Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12038-018-9753-6) contains supplementary material, which is available to authorized users.

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ISSN 2231-3354

Synthesis, Characterization of Novel PLGA Encapsulated Indole Nanoparticles and Study of its cytotoxic potential against A549 lung cancer cell line

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Nanoparticles; biomaterials; polymers; sustained release; cytotoxicity.

ABSTRACT

Objectives: Indole and its derivatives are gaining importance because of their anti-cancer activity. Here, we have reported the synthesis and characterization of novel polymeric poly D, L-lactide-co-glycolide (PLGA) indole nanoparticles, and investigated their cytotoxic potential against A549 lung cancer cells. **Materials and methods:** Nanoparticles were synthesized by solvent emulsion-diffusion-evaporation method. Size determination was done by Transmission Electron Microscopy (TEM), encapsulation efficiency using UV-Vis spectra, release kinetics using dialysis, measurement of drug-polymer interaction by Fourier Transform Infra Red Spectroscopy (FTIR) and surface charge by zeta potential. Cell viability of lung cancer cells (A549) was determined by (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and morphological analysis. **Results:** Nanoparticles were spherical in shape with an average diameter of 65 nm, encapsulation efficiency was found to be about 78% and zeta potential was −15.2mV. Drug-loaded nanoparticles showed sustained release kinetics fitting well in exponential Higuchi and Zero order Model. FTIR studies showed a broadening of the peak of PLGA indole nanoparticles at 2100-3400 cm^{-1} indicating the formation of drug-loaded nanoparticles. These nanoparticles showed about 95% cytotoxicity against A549 lung cancer cell lines. Results were supported by visible morphological changes in cells. **Conclusion:** PLGA encapsulated Indole nanoparticles were stable, having sustained release and good cytotoxic potential.

INTRODUCTION

Cancer has emerged as a debilitating complex disease over the last many decades. Although advances in research in some cancers have led to the successful prognosis of the disease, in most cases especially in advanced stages, it continues to remain incurable. Development of new generation of drugs with minimal side effects continues to be the mainstay of all research work undertaken to combat this deadly disease. The advent of nanotechnology has brought new hope in cancer treatment by targeted delivery, increased half-life, better stability and sustained release of the drug and hence helped in mitigating the problem of side effects (Hariharan *et al.*, 2006). There are reports of different classes of nanoparticles that might serve as potential anti-cancer agents themselves. The class of nanoparticles ranges from transition metal oxides (Pandey *et al.*, 2016; Tarnuzzer *et al.*, 2005; Sankar *et al.*, 2014), chitosan derivatives (El-Sayed *et al.*, 2017) to ceramics (which includes hydroxyapatite nanoparticles) (Kundu *et al.*, 2013). However, an alternate and popular approach in the field of nanomedicine is by either encapsulating the anti-cancer agent or adsorbing it in delivery vesicles i.e. nanoparticles (Mirza and Siddiqui). The agents that are used for encapsulating the drugs

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A novel de novo heterozygous deletion at 13q14. 2-q21. 1 in two siblings with mild intellectual disability

[HTML] from sciencedirect.com

Authors: Kirti Mittal, Laxmi Kirola, Sridevi Hegde, Mitesh Shetty, Madhulika Kabra, BK Thelma

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Journal: Gene Reports

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Publisher: Elsevier

Description: Intellectual disability (ID) is characterized by limited intellectual functioning and adaptive behavior, with a global prevalence of ~1–2%. Around 50% of ID cases have a genetic basis, with chromosomal and single gene mutations accounting for ~17–19% and rare *de novo* copy number variations (CNVs) for ~15% of the total cases. Thus, ~30–50% of the cases still remain unexplained. We investigated a north-eastern Indian family with two male children affected with mild syndromic ID. Both the affected siblings were first screened for mutations in genes implicated with syndromic ID on clinical suspicion (*NHS* and *OCRL*) in this family and found to be negative. Further, CNV analysis was carried out in the family using HumanCytoSNP-12 oligonucleotide array. Analysis revealed a 9.8 Mb *de novo* heterozygous deletion at 13q14.2-q21.1 that was shared among the affected siblings but not with their unaffected brother ...

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Expanding the canvas of PARKIN mutations and clinical phenotypes in familial and early onset Parkinson's disease patients

Authors S Pandey, L Tomar, S Kumar, B Thelma

Publication date 2018/10/1

Conference MOVEMENT DISORDERS

Volume 33

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Scholar articles Expanding the canvas of PARKIN mutations and clinical phenotypes in familial and early onset Parkinson's disease patients
S Pandey, L Tomar, S Kumar, B Thelma - MOVEMENT DISORDERS, 2018

Identification and characterization of the promoter of a gene expressing mainly in the tapetum tissue of cotton (Gossypium hirsutum *L.*)

Kumar Paritosh, Amarjeet Kumar Singh, Amita Kush Mehrotra, Deepak Pental & Pradeep Kumar Burma

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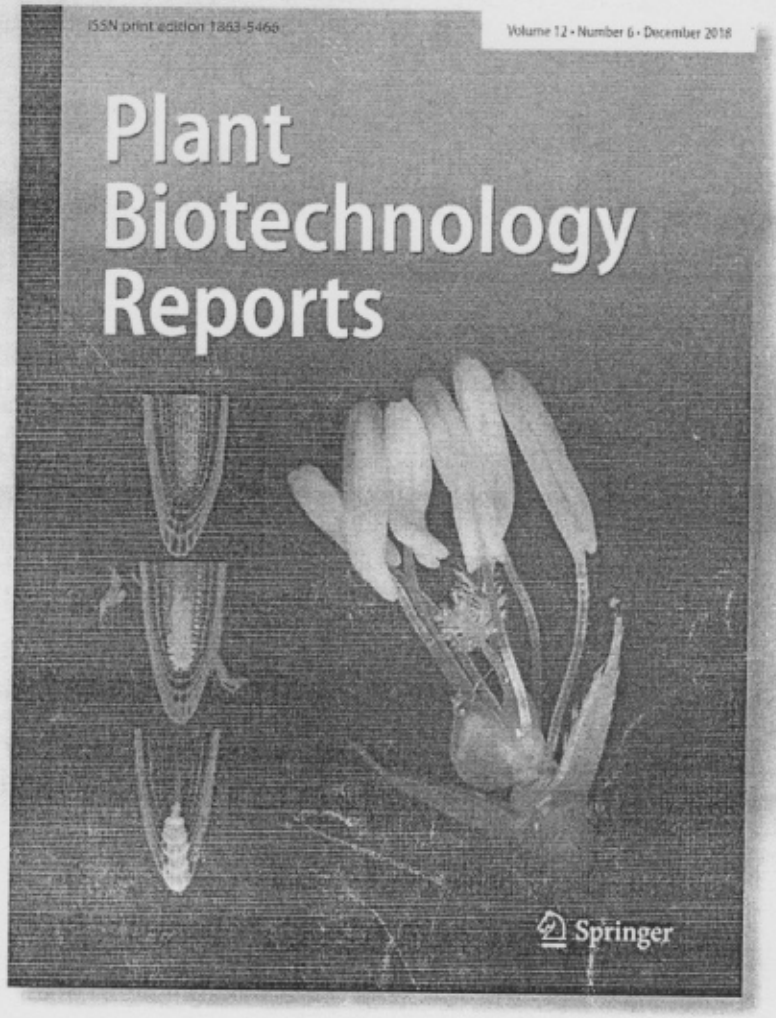

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Determination of dopamine-β-hydroxylase activity in human serum using UHPLC-PDA detection

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Authors Toyanji Joseph Punchaichira, Smita Neelkanth Deshpande, BK Thelma

Publication date 2018/12

Journal Neurochemical Research

Volume 43

Issue 12

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Publisher Springer US

Description Dopamine-β-hydroxylase (DBH, EC 1.14.17.1) is an enzyme with implications in various neuropsychiatric and cardiovascular diseases and is a known drug target. There is a dearth of cost effective and fast method for estimation of activity of this enzyme. A sensitive UHPLC based method for the estimation of DBH activity in human sera samples based on separation of substrate tyramine from the product octopamine in 3 min is described here. In this newly developed protocol, a Solid Phase Extraction (SPE) sample purification step prior to LC separation, selectively removes interferences from the reaction cocktail with almost no additional burden on analyte recovery. The response was found to be linear with an $r^2 = 0.999$. The coefficient of variation for assay precision was < 10% and recovery > 90%. As a proof of concept, DBH activity in sera from healthy human volunteers (n = 60) and schizophrenia ...

Molecular Plant Pathology

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Genome-wide association mapping in *Arabidopsis* identifies novel genes underlying quantitative disease resistance to *Alternaria brassicae*

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SUMMARY

Quantitative disease resistance (QDR) is the predominant form of resistance against necrotrophic pathogens. The genes and mechanisms underlying QDR are not well known. In the current study, the *Arabidopsis–Alternaria brassicae* pathosystem was used to uncover the genetic architecture underlying resistance to *A. brassicae* in a set of geographically diverse *Arabidopsis* accessions. *Arabidopsis* accessions revealed a rich variation in the host responses to the pathogen, varying from complete resistance to high susceptibility. Genome-wide association (GWA) mapping revealed multiple regions to be associated with disease resistance. A subset of genes prioritized on the basis of gene annotations and evidence of transcriptional regulation in other biotic stresses was analysed using a reverse genetics approach employing T-DNA insertion mutants. The mutants of three genes, namely At1g06990 (GDSL-motif lipase), At3g25180 (CYP82G1) and At5g37500 (GORK), displayed an enhanced susceptibility relative to the wild-type. These genes are involved in the development of morphological phenotypes (stomatal aperture) and secondary metabolite synthesis, thus defining some of the diverse facets of quantitative resistance against *A. brassicae*.

Keywords: *Arabidopsis*, *CYP82G1*, *GORK*, GWA mapping, necrotrophs, quantitative resistance.

INTRODUCTION

Fungal pathogens are one of the highly evolved groups of microorganisms affecting various plant species and strongly differ in important life history traits, such as dispersal mechanisms, type of reproduction and modes of parasitism. Pathogenic fungi obtain resources from their hosts principally in two different ways: as biotrophs or necrotrophs. Necrotrophic pathogens extract nutrients from dead cells of the host killed during invasion. In crops, economic damage caused by fungal diseases is estimated to be above US$200 billion annually (Birren *et al.*, 2002). A recent survey has indicated that losses caused by necrotrophic pathogens far exceed those resulting from biotrophic pathogens (Murray and Brennan, 2009). Broad host-range necrotrophs (BHNs), such as *Sclerotinia sclerotiorum* and *Botrytis cinerea*, can infect more than 300 different plant species. BHNs typically deploy a diverse arsenal of effectors, including cell-wall degrading enzymes (CWDEs), phytotoxic compounds and reactive oxygen species (ROS), to induce necrosis. The diversity of virulence strategies thus warrants a multifaceted defence by the host to successfully ward off the attack (Roux *et al.*, 2014). In contrast, narrow host-range necrotrophs (NHNs), such as *Cochliobolus victoriae*, *Pyrenophora tritici-repentis* and *Stagonosporum nodorum*, tend to rely on host-specific toxins (HSTs) that are directed at specific targets present only in some species or subtypes of a particular species (Condon *et al.*, 2013; Lorang *et al.*, 2012). The recognition of these HSTs by the host machinery thus leads to susceptibility. Plant disease resistance can be either qualitative, which is conferred by single resistance (*R*) genes, or quantitative, which is mostly mediated by multiple genes. Host resistance against BHNs is known to be usually quantitative (St Clair, 2010). Some of the quantitative resistance loci (QRLs) for the paradigmatic BHNs, such as *B. cinerea*, *S. sclerotiorum* and *Plectosphaerella cucumerina*, have been identified, but the underlying mechanisms of most of these QRLs are unknown (Denby *et al.*, 2004; Llorente *et al.*, 2005; Micic *et al.*, 2004; Rowe and Kliebenstein, 2008). Few genes which recognize the HSTs of NHNs have been identified (Faris *et al.*, 2010; Friesen *et al.*, 2007; Liu *et al.*, 2012; Lorang *et al.*, 2007). Unlike NHNs, necrotrophs such as *Alternaria brassicae* and *Alternaria brassicicola* infect only the members of the Brassicaceae family, including the wild and cultivated species (Sharma *et al.*, 2002). These necrotrophs thus represent an intermediate class between BHNs and NHNs. The genetic architecture of resistance to these necrotrophs is relatively unexplored when compared with that of BHNs and NHNs. There are currently no known resistance loci identified in any of the natural hosts (*Brassica* crops) for resistance to *A. brassicae*.

Arabidopsis has been used as a model host to study the host–pathogen interactions of many plant pathogens. *Arabidopsis* has a

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2018 27: 443-452

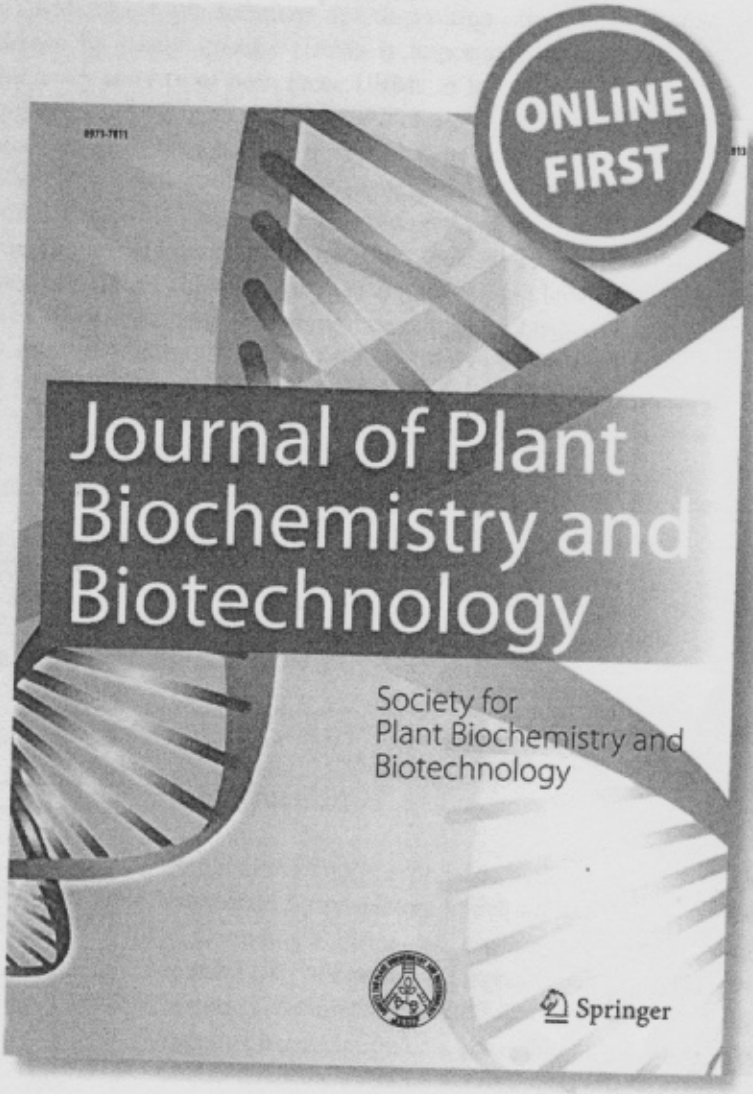
Analysis of activity driven by upstream regulatory modules (URM) of tapetum specific genes TA29 and A9 at ectopic locations in tobacco transgenics

Preeti Apurve Sharma, Neetu Verma & Pradeep Kumar Burma

Journal of Plant Biochemistry and Biotechnology

ISSN 0971-7811

J. Plant Biochem. Biotechnol.
DOI 10.1007/s13562-018-0453-y



Springer

Scientific Research Publishing

American Journal of Molecular Biology, 2018, 8, 13-25
http://www.scirp.org/journal/ajmb
ISSN Online: 2161-6663
ISSN Print: 2161-6620

An *in silico* Analysis of Upstream Regulatory Modules (URMs) of Tapetum Specific Genes to Identify Regulatory *cis*-Elements and Transcription Factors

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https://doi.org/10.4236/ajmb.2018.81002

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Published: December 18, 2017

Abstract

The present work presents an *in silico* analysis of Upstream Regulatory Modules (URMs) of genes expressed in tapetum specific manner in dicotyledon and monocotyledon plants. In the current analysis, we identified several motifs conserved in these URMs of which ten were observed to be part of known *cis*-elements using tools and databases like MEME, PLACE, MAST and TFSEARCH. We also identified that binding sites for two transcription factors, DOF and WRKY71 were found to be present in majority of the URMs.

Keywords

Tapetum Specific Promoter, *cis*-Elements, Transcription Factors

1. Introduction

Tapetum is the innermost layer of the anther wall of plants. It performs the function of a nourishing tissue that remains in continuity with the pollen mother cell through plasmadesmatal connections till the formation of meiocytes occurs in young anther. Tapetum varies from unilayer to multilayer in different plant species and can be uninucleate or multinucleate. Although tapetum cells form a single or at-most a few cell layers in the anther tissue, several studies have been carried out to understand how these cell layers develop and the functions played by them in pollen cell development [1] [2] [3] [4]. These studies have led to the identification of several genes expressed in tapetum specific manner. Such genes have mainly been identified by analyzing comparative cDNA libraries, subtractive hybridization, microarray analysis, *in-situ* hybridization and in recent years

Published OnlineFirst March 13, 2018; DOI: 10.1158/0008-5472.CAN-17-2316

Tumor Biology and Immunology

Cancer Research

Inhibin Is a Novel Paracrine Factor for Tumor Angiogenesis and Metastasis

Priyanka Singh[1], Laura M. Jenkins[1], Ben Horst[1], Victoria Alers[1], Shrikant Pradhan[1], Prabhjot Kaur[2], Tapasya Srivastava[2], Nadine Hempel[3], Balázs Győrffy[4], Eugenia V. Broude[5], Nam Y. Lee[6], and Karthikeyan Mythreye[1,5]

Abstract

Inhibin is a heterodimeric TGFβ family ligand that is expressed in many cancers and is a selective biomarker for ovarian cancers; however, its tumor-specific functions remain unknown. Here, we demonstrate that the α subunit of inhibin (INHA), which is critical for the functionality of dimeric inhibin A/B, correlates with microvessel density in human ovarian tissues and is predictive of poor clinical outcomes in multiple cancers. We demonstrate that inhibin-regulated angiogenesis is necessary for metastasis. Although inhibin had no direct impact on tumor cell signaling, both tumor cell-derived and recombinant inhibin elicit a strong paracrine response from endothelial cells by triggering SMAD1/5 activation and angiogenesis *in vitro* and *in vivo*. Inhibin-induced angiogenesis was abrogated via anti-inhibin α antibodies. The endothelial-specific TGFβ receptor complex comprising ALK1 and endoglin was a crucial mediator of inhibin signaling, offering a molecular mechanism for inhibin-mediated angiogenesis. These results are the first to define a role for inhibin in tumor metastasis and vascularization and offer an antibody-based approach for targeting inhibin therapeutically.

Significance: Inhibin is a predictor of poor patient survival in multiple cancers and is a potential target for antiangiogenic therapies. *Cancer Res; 78(11); 2978–89. ©2018 AACR.*

Introduction

Inhibition of angiogenesis, the growth of new blood vessels from preexisting vasculature, is a clinically validated anticancer strategy for numerous tumor types. However, although the VEGF/VEGF receptor (VEGFR) signaling axis is widely recognized as the principal target of this therapeutic approach, current FDA-approved anti-VEGF drugs have demonstrated sub-optimal responses in the clinic. In many cases, including in ovarian cancers (OVCA), patient relapse, acquired resistance and cytotoxicity is commonly observed following anti-VEGF therapy. The identification of new vascular targets with potentially fewer adverse effects is therefore critical for improving therapeutic outcomes.

TGFβ family members, particularly TGFβ1 and BMP9, are essential regulators of angiogenesis (1). Targeting these for anti-angiogenic therapy remains a formidable challenge due to their nonendothelial pleiotropic functions. Here, we focus on the unique TGFβ family member inhibin, an endocrine hormone that sharply declines at the onset of menopause in healthy normal women and remains low (2) unlike other TGFβ family members and prototypical angiogenic factors like VEGF. Importantly, when inhibin becomes elevated in postmenopausal women, this elevation becomes a diagnostic and prognostic marker for OVCA where along with CA125 detects 95% of ovarian tumors with 95% specificity (3, 4).

Inhibin is a heterodimeric member of the TGFβ family composed of an alpha (α; coded by *INHA*) and β subunit (*INHBA* or *INHBB*). Combinations of these subunits give rise to either inhibin A ($\alpha\beta_A$) or inhibin B ($\alpha\beta_B$; 5). Although inhibin null mice ($INHA^{-/-}$) are viable, they present with alterations to the ovarian vasculature and result in spontaneous gonadal tumors (6). In humans, however, inhibin levels are elevated in multiple cancer types, including ovarian, prostate, adrenal, stomach, and pancreatic cancers with indications for a role for inhibin in prostate cancer metastasis (7–11). Despite these findings, the functional consequences of elevated tumor-derived inhibin have yet to be determined.

Several inhibin-binding proteins/receptors were previously reported (12). However, unlike other TGFβ members, whose signal transduction mechanisms have been well studied, the mechanisms of inhibin signaling remain largely unclear. The best-characterized inhibin-binding protein is the epithelial cell surface TGFβ coreceptor TβRIII/betaglycan (13). Inhibin binding to betaglycan fails to activate any discernable downstream pathways in epithelial cells. Others and we previously demonstrated, several tumor suppressor functions for betaglycan, which is lost in the majority of human cancers (14), but little is known about the impact of elevated inhibin on nonepithelial cells that do not express significant betaglycan.

[1]Department of Chemistry and Biochemistry, University of South Carolina, Columbia, South Carolina. [2]Department of Genetics, University of Delhi, South Campus, India. [3]Department of Pharmacology, Penn State University College of Medicine, Hershey, Pennsylvania. [4]MTA TTK Lendület Cancer Biomarker Research Group, Institute of Enzymology, and Semmelweis University 2nd Department of Pediatrics, Budapest, Hungary. [5]Department of Drug Discovery and Biomedical Sciences, School of Pharmacy, Ohio State University, Columbus, Ohio. [6]Division of Pharmacology, College of Pharmacy, Ohio State University, Columbus, Ohio.

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

P. Singh and L.M. Jenkins contributed equally to this article.

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doi: 10.1158/0008-5472.CAN-17-2316

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A preliminary study of association of genetic variants with early response to olanzapine in schizophrenia

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Authors Anmol Singh, Ram Pratap Beniwal, Prachi Kukshal, Triptish Bhatia, BK Thelma, Smita N Deshpande

Publication date 2018/1

Journal Indian Journal of Psychiatry

Volume 60

Issue 1

Pages 10

Publisher Wolters Kluwer--Medknow Publications

Description Background:

Treatment response can be predicted in schizophrenia by DNA information in the drug metabolism pathways. This study aimed to examine clinical characteristics and genetic determinant (s) of early response to olanzapine treatment in schizophrenia using specified drug metabolizing genes.

Materials and Methods:

Consenting participants (n= 33) suffering from schizophrenia were diagnosed on Diagnostic Interview for Genetic Studies. Oral olanzapine was administered in an incremental dose up to 10 mg (2 weeks) and 20 mg (6 weeks). All participants were tested on Positive and Negative Syndrome Scale, Clinical Global Impressions, and Global Assessment of Functioning at 0, 2, and 6 weeks. Side effects were also evaluated. After 2 weeks, 11 (33.33%) fulfilled criteria for early response, whereas 17 (51.52%) responded at 6 weeks. We investigated the contribution of clinical factors and five ...

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A simple phenotypic classification for celiac disease

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Authors Ajit Sood, Vandana Midha, Govind Makharia, BK Thelma, Shivalingappa S Halli, Varun Mehta, Ramit Mahajan, Vikram Narang, Kriti Sood, Kirandeep Kaur

Publication date 2018/4/30

Journal Intestinal research

Volume 16

Issue 2

Pages 288-292

Publisher Korean Association for the Study of Intestinal Diseases

Not to be included in 2018 - 2023 NAAC cycle

Description Methods

Various variables identified for phenotypic classification included age at diagnosis, age at onset of symptoms, clinical presentation, family history and complications. These were applied to the existing registry of 1,664 patients at Dayanand Medical College and Hospital, Ludhiana, India. In addition, age was evaluated as below 15 and below 18 years. Cross tabulations were used for the verification of the classification using the existing data. Expert opinion was sought from both international and national experts of varying fields.

Results

After empirical verification, age at diagnosis was considered appropriate in between A1 (< 18) and A2 (≥ 18). The disease presentation has been classified into 3 types–P1 (classical), P2 (non-classical) and P3 (asymptomatic). Complications were considered as absent (C0) or present (C1). A single phenotypic classification based on these 3 characteristics, namely age at the diagnosis, clinical presentation, and intestinal complications (APC classification) was derived.

Conclusions

APC classification (age at diagnosis, presentation, complications) is a simple disease explanatory classification for patients with celiac disease aimed at providing a composite diagnosis.

Total citations Cited by 8

2018 2019 2020 2021 2022 2023

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IDDF2019-ABS-0253 Explained variance and predictability of inflammatory bowel diseases by genetic risk score in five asian populations (results from the international IBD ...

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Authors Shifteh Abedian, Sunny H Wong, Suzanne Van Sommeren, Atsushi Takahashi, Jae Hee Cheon, Homayoon Vahedi, Keiko Yamazaki, Won Ho Kim, BK Thelma, Nasser E Daryani, Michiaki Kubo, Suk-Kyun Yang, Rupa Banerjee, Reza Malekzadeh, Rinse K Weersma, Siew C Ng, Behrooz Z Alizadeh

Publication date 2019/6/1

Source Gut

Volume 68

Issue Suppl 1

Pages A110-A110

Publisher BMJ Publishing Group

Description Background

In the absence of properly designed studies, the clinical implication of genetic findings in Inflammatory Bowel Disease (IBD) is a matter of persistent debate especially in Asian population where the prevalence of IBD including Crohn's Disease (CD) and Ulcerative Colitis (UC) is rising. We aimed to investigate the predictability of IBD, CD, and UC by the means of Genetic Risk Score (GRS), in yet unaffected high-risk individuals from East Asia (EA) and Central Asia (CA).

Methods

This present study included 9,698 subjects, consisting of 2,003 CD, 2,730 UC and 4,965 countries, age and gender-matched controls, genotyped on the Immunochip array of three EA (Japan, South-Korea and China) and two CA countries (India and Iran). We generated a multi-locus GRS for each population by combining information from up to 201 known genome-wide significant IBD associated variants to summarize a total load ...

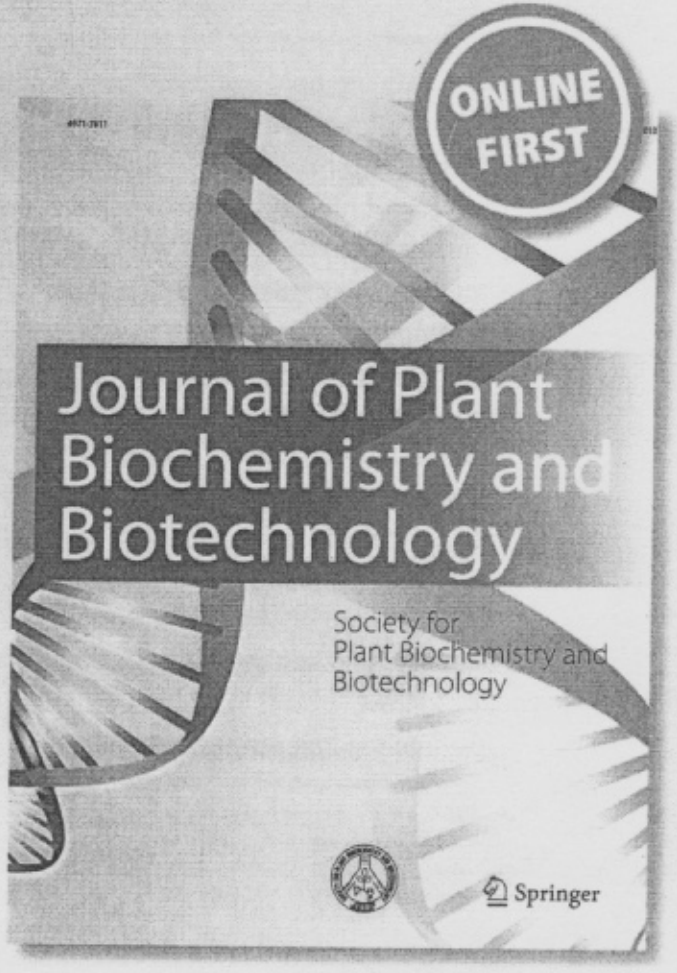
Evaluating the effect of codon optimization on expression of bar *gene in transgenic tobacco plants*

Parul Agarwal, Taru Gautam, Amarjeet Kumar Singh & Pradeep Kumar Burma

ournal of Plant Biochemistry and iotechnology

SN 0971-7811

Plant Biochem. Biotechnol.
OI 10.1007/s13562-019-00506-2



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Association study identified biologically relevant receptor genes with synergistic functions in celiac disease

[HTML] from nature.com

Authors: Pratibha Banerjee, Sandilya Bhagavatula, Ajit Sood, Vandana Midha, BK Thelma, Sabyasachi Senapati

Publication date: 2019/9/25

Journal: Scientific Reports

Volume: 9

Issue: 1

Pages: 13811

Publisher: Nature Publishing Group UK

Description: Receptors are essential mediators of cellular physiology, which facilitate molecular and cellular cross-talk with the environment. Nearly 20% of the all known celiac disease (CD) genes are receptors by function. We hypothesized that novel biologically relevant susceptibility receptor genes act in synergy in CD pathogenesis. We attempted to identify novel receptor genes in CD by re-analyzing published Illumina Immunochip dense genotype data for a north Indian and a European (Dutch) cohort. North Indian dataset was screened for 269 known receptor genes. Association statistics for SNPs were considered with minor allele frequency >15% and association $P \le 0.005$ to attend desired study power. Identified markers were tested for cross-ethnic replication in a European CD dataset. Markers were analyzed *in-silico* to explain their functional significance in CD. Six novel SNPs from *MOG* (rs29231, p = 1.21e-11 ...

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Novel Association of G-quadruplex SNPs in Schizophrenia Candidate Genes with Cognition and Tardive Dyskinesia in a Schizophrenia Cohort

Authors	Upasana Bhattacharyya, Smita N Deshpande, Bittianda Kuttapa Thelma
Publication date	2019/10/1
Conference	GENETIC EPIDEMIOLOGY
Volume	43
Issue	7
Pages	867-867
Publisher	WILEY
Scholar articles	Novel Association of G-quadruplex SNPs in Schizophrenia Candidate Genes with Cognition and Tardive Dyskinesia in a Schizophrenia Cohort U Bhattacharyya, SN Deshpande, BK Thelma - GENETIC EPIDEMIOLOGY, 2019

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Novel Association of G-quadruplex SNPs in Schizophrenia Candidate Genes with Cognition and Tardive Dyskinesia in a Schizophrenia Cohort

Authors Upasana Bhattacharyya, Smita N Deshpande, Bittianda Kuttapa Thelma

Publication date 2019/10/1

Conference GENETIC EPIDEMIOLOGY

Volume 43

Issue 7

Pages 867-867

Publisher WILEY

Scholar articles Novel Association of G-quadruplex SNPs in Schizophrenia Candidate Genes with Cognition and Tardive Dyskinesia in a Schizophrenia Cohort
U Bhattacharyya, SN Deshpande, BK Thelma - GENETIC EPIDEMIOLOGY, 2019

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Construction and benchmarking of a multi-ethnic reference panel for the imputation of HLA class I and II alleles

Authors Frauke Degenhardt, Mareike Wendorff, Michael Wittig, Eva Ellinghaus, Lisa W Datta, John Schembri, Siew C Ng, Elisa Rosati, Matthias Hübenthal, David Ellinghaus, Eun Suk Jung, Wolfgang Lieb, Shifteh Abedian, Reza Malekzadeh, Jae Hee Cheon, Pierre Ellul, Ajit Sood, Vandana Midha, BK Thelma, Sunny H Wong, Stefan Schreiber, Keiko Yamazaki, Michiaki Kubo, Gabrielle Boucher, John D Rioux, Tobias L Lenz, Steven R Brant, Andre Franke

Publication date 2019/6/15

Journal Human molecular genetics

Volume 28

Issue 12

Pages 2078-2092

Publisher Oxford University Press

Description Genotype imputation of the human leukocyte antigen (HLA) region is a cost-effective means to infer classical HLA alleles from inexpensive and dense SNP array data. In the research setting, imputation helps avoid costs for wet lab-based HLA typing and thus renders association analyses of the HLA in large cohorts feasible. Yet, most HLA imputation reference panels target Caucasian ethnicities and multi-ethnic panels are scarce. We compiled a high-quality multi-ethnic reference panel based on genotypes measured with Illumina's Immunochip genotyping array and HLA types established using a high-resolution next generation sequencing approach. Our reference panel includes more than 1,300 samples from Germany, Malta, China, India, Iran, Japan and Korea and samples of African American ancestry for all classical HLA class I and II alleles including *HLA-DRB3/4/5*. Applying extensive cross-validation ...

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Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

Vertically aligned multi-walled carbon nanotubes based flexible immunosensor for extreme low level detection of multidrug resistant leukemia cells

Payal Gulati[a], Prabhjot Kaur[b], M.V. Rajam[b], Tapasya Srivastava[b], Prabhash Mishra[a], S.S. Islam[a,*]

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ARTICLE INFO

Keywords:
Electrochemical immunosensing
Immunofluorescence analysis
Anti-P-glycoprotein
Doxorubicin
Fermi-level fluctuations

ABSTRACT

We report an advanced flexible immunosensor for extreme low level detection of multidrug resistant myeloid leukemia cells. The detection mechanism is analyzed in terms of novel nanoscale interactions of target molecules with vertically aligned multi-walled carbon nanotubes (VA-MWNT). The immunosensor is fabricated by transferring VA-MWNTs on a polyethylene terephthalate substrate by hot press technique without losing CNTs' pristine character. Sensing is performed using doxorubicin treated leukemia K562 cells in varying concentrations from 1.5×10^2 cells mL^{-1} to 1.5×10^7 cells mL^{-1} and sensor showed detection limit of 10 cells mL^{-1}. The calibration plot of peak current versus logarithmic concentration of DOX/leukemia K562 cells exhibited good linearity with a regression coefficient of ~0.98. Sensing mechanism is explained in terms of charge transfer induced Fermi level shift of sub μeV order, causing band bending at the interface of CNT-molecular species; and it is reflected in lowering detection limit of the fabricated sensor. Theoretical analysis is done to correlate Fermi energy shift with sensitivity of the device on cancer cell immobilization. Additionally, the developed immunosensor shows good stability, reproducibility and fast detection vis-à-vis the devices reported so far. The notable advantages of proposed flexible sensor are its durability, chemical and moisture resistance, making it a potentially competitive device for point-of-care diagnostics.

1. Introduction

Leukemia is a malignant progressive disease that mainly starts in bone marrow. It affects both myeloid and lymphoid cells, leading to anemia because of the formation of immature abnormal blood cells. It shows both type of nature- chronic and acute; if chronic type is not treated in time, it leads to acute leukemia. Leukemia is mainly treated with chemotherapy in which chemotherapeutic drugs are given orally or intravenously. In most of the cases, the treatment with chemo drugs such as Doxorubicin (DOX), etc. goes into remission. This remission problem occurs due to acquired resistance amid the course of therapy from one or many structurally different drugs; thus rendering the cells to be multi drug resistant (MDR). MDR is a major cause of treatment failure, because of various processes involvement such as ABC transporters (a membranous transporter), metallothionein (MT), glutathione-S-transferases (GST), thymidylate synthase (TS), DNA Topoisimerase II, etc. [1]. The function of DOX is against topoisomerase-II causes DNA damage, leading to cell apoptosis [2,3]. The efficacy of the drug (DOX) is reduced due to P-glycoprotein (P-gp), where P-gp is one of the ABC (ATP binding cassette) transporters with a molecular weight of 170 kilo-dalton (Kd). And it is responsible for the efflux of drug molecules out of the cell, thereby preventing drugs to reach to its target site [4,5]. P-gp is encoded by MDR-1, a multi-drug resistance gene. The clinical significance of P-gp over-expression is observed at the time of diagnosis. Targeting this biomarker using specific monoclonal antibodies, would lead to remove the difficulties of early detection. The enhanced P-gp expression could greatly increase the sensitivity of sensor by detecting lowest cell count. Thus, highly sensitive electrochemical sensor can be fabricated by using the potential of immunoassay at the nanoscale.

The early detection of cancer is mandatory for the patient's survival and proper prognosis of the disease; therefore, sensitive and specific methods are required. Recently, nano-biotechnology has gained huge attention in the field of cancer diagnosis. Nanomaterials allow enhanced quantity of biomolecules immobilization, because of their large surface area to volume ratio; thereby enhancing the performance of

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Available online 28 August 2019
0925-4005/

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Ethics in measurement practices

[PDF] from 14.99.160.67

Authors	Munishwar Nath Gupta, Bittianda Kuttapa Thelma
Publication date	2019
Journal	Research and Governance
Pages	45
Description	Tom Clancy has written many best sellers. In more than one, these contain a line:"If you don't write it down, it never happened."(Clancy, 1995). A properly and neatly written laboratory record is important. David Baltimore became a Nobel Laureate at the age of 37. In late 1980's, he was involved in a controversy regarding one of his publications. The US secret service's forensic sciences division examined the lab records and found "evidence of sloppiness in the laboratory note books" of his collaborator. The above anecdote should convince us the relevance of maintenance of proper lab records in the context of ethical practices in science.
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MN Gupta, BK Thelma - Research and Governance, 2019
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Rare variants in tissue inhibitor of metalloproteinase 2 as a risk factor for schizophrenia: evidence from familial and cohort analysis

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Authors Jibin John, Aditya Sharma, Prachi Kukshal, Triptish Bhatia, Vishwajit L Nimgaonkar, Smita N Deshpande, BK Thelma

Publication date 2019/1/1

Journal Schizophrenia Bulletin

Volume 45

Issue 1

Pages 256-263

Publisher Oxford University Press

Description Candidate gene and genome-wide association study based common risk variant identification is being complemented by whole exome sequencing (WES)/whole genome sequencing based rare variant discovery in elucidation of genetic landscape of schizophrenia (SZ), a common neuropsychiatric disorder. WES findings of de novo mutations in case-parent trios have further implied genetic etiology, but do not explain the high genetic risk in general populations. Conversely, WES in multiplex families may be an insightful strategy for the identification of highly penetrant rare variants in SZ and possibly enhance our understanding of disease biology. In this study, we analyzed a 5-generation Indian family with multiple members affected with SZ by WES. We identified a rare heterozygous missense variant (NM_003255: c.506C>T; p.Pro169Leu; MAF = 0.0001) in Tissue Inhibitor of Metalloproteinase 2 (*TIMP2* ...

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Rare variants in Protein tyrosine phosphatase, receptor type A (PTPRA) in schizophrenia: Evidence from a family based study

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Authors Jibin John, Prachi Kukshal, Aditya Sharma, Triptish Bhatia, VL Nimgaonkar, SN Deshpande, BK Thelma

Publication date 2019/4/1

Journal Schizophrenia research

Volume 206

Pages 75-81

Publisher Elsevier

Description The contribution of both common and rare risk variants to the genetic architecture of schizophrenia (SZ) has been documented in genome-wide association studies, whole exome and whole genome sequencing approaches. As SZ is highly heritable and segregates in families, highly penetrant rare variants are more likely to be identified through analyses of multiply affected families. Further, much of the gene mapping studies in SZ have utilized individuals of Caucasian ancestry. Analysis of other ethnic groups may be informative. In this study, we aimed at identification of rare, penetrant risk variants utilizing whole exome sequencing (WES) in a three-generation Indian family with multiple members affected. Filtered data from WES, combined with *in silico* analyses revealed a novel heterozygous missense variant (NM_080841:c.1730C>G:p.T577R; exon18) in Protein tyrosine phosphatase, receptor type A (*PTPRA* ...

Oligogenic rare variant contributions in schizophrenia and their convergence with genes harbouring *de novo* mutations in schizophrenia, autism and intellectual ...

Authors Jibin John, Prachi Kukshal, Triptish Bhatia, Ricardo Harripaul, VL Nimgaonkar, SN Deshpande, BK Thelma

Publication date 2019/11/12

Journal bioRxiv

Pages 829101

Publisher Cold Spring Harbor Laboratory

Description Clinical and genetic heterogeneity has been documented extensively in schizophrenia, a common behavioural disorder with heritability estimates of about 80%. Common and rare *de novo* variant based studies have provided notable evidence for the likely involvement of a range of pathways including glutamatergic, synaptic signalling and neurodevelopment. To complement these studies, we sequenced exomes of 11 multimember affected schizophrenia families from India. Variant prioritisation performed based on their rarity (MAF <0.01), shared presence among the affected individuals in the respective families and predicted deleterious nature, yielded a total of 785 inherited rare protein sequence altering variants in 743 genes among the 11 families. These showed an enrichment of genes involved in the extracellular matrix and cytoskeleton components, synaptic and neuron related ontologies and neurodevelopmental pathways, consistent with major etiological hypotheses. We also noted an overrepresentation of genes from previously reported gene sets with *de novo* protein sequence altering variants in schizophrenia, autism, intellectual disability; FMRP target and loss of function intolerant genes. Furthermore, a minimum of five genes known to manifest behavioural/neurological and nervous system abnormalities in rodent models had deleterious variants in them shared among all affected individuals in each of the families. Majority of such variants segregated within and not across families providing strong suggestive evidence for the genetically heterogeneous nature of disease. More importantly, study findings unequivocally support the ...

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Rare variant based evidence for oligogenic contribution of neurodevelopmental pathway genes to schizophrenia

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Authors Jibin John, Prachi Kukshal, Triptish Bhatia, VL Nimgaonkar, SN Deshpande, BK Thelma

Publication date 2019/8

Journal Schizophrenia research

Volume 210

Pages 296

Publisher NIH Public Access

Description Family and twin studies suggest a multi-factorial polygenic thresh-old model (MFPT) in schizophrenia (SZ)(Gottesman, 1991). This is supported by genome-wide association studies (GWASs)(Ripke et al., 2014) and also polygenic burden of rare variants reported in individuals with SZ (Purcell et al., 2014). However, this model focusing on rare variants has been rarely checked in families and whole exome sequencing (WES) of multiply affected families and findings thereof, may facilitate testing the model. Two multigenerational families of north Indian ancestry with multiple affected and unaffected members (Fig. 1a, b) were recruited as previously described (John et al., 2018). WES was performed on three affected members each from the two families, using Agilent SureSelectXT Human All Exon V5+ UTR kit for library preparation and sequenced (101 bp paired end mode) on Illumina HiSeq 2000 sequencer, using a ...

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ROS accumulation and associated cell death mediates susceptibility to *Alternaria brassicae* in *Arabidopsis* accessions

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ARTICLE INFO

Keywords:
ROS
Cell death
Alternaria brassicae
RBOH
Jasmonic acid

ABSTRACT

Alternaria brassicae is a necrotrophic fungal pathogen capable of infecting most of the agriculturally important *Brassica* species. The mechanisms underlying invasion of *A. brassicae* and host responses are unknown. In the present study, we exploited the natural variation in *Arabidopsis* to understand the molecular and cellular mechanisms underlying resistance to *A. brassicae*. Using a subset of resistant (Ei-2, Ull2-3, Lz-0, and Cvi-0) and susceptible (Gre-0, Est-1, and Zdr1) accessions, we show that the susceptibility to *A. brassicae* is associated with higher ROS accumulation and cell death. Susceptibility to *A. brassicae* was reduced in the *rboh* (*D, E* and *F*) mutants that are incapable of producing ROS, suggesting that *RBOH D, E and F* may act as negative regulators of defence against this pathogen. Additionally, our data also supports the hypothesis that the Jasmonic acid (JA), Ethylene (ET) and Abscisic acid (ABA) signalling pathways positively contribute to resistance against necrotrophic pathogens. In summary, these results reveal the central role of ROS and cell death in the pathogenesis of *A. brassicae* and expand our understanding of plant-necrotroph interactions.

1. Introduction

Necrotrophic pathogens actively kill host tissues as they invade the host and obtain their nutrients from the dead tissues/cells. Pathogenesis of necrotrophs usually involves extensive necrosis and tissue maceration. This is in stark contrast to the biotrophic pathogens, which derive their nutrients from living host tissues. The infection processes, nature of secretory proteins and associated host defence responses vary significantly between biotrophs and necrotrophs. One of the key differences is how cell death in the host affects the pathogenesis of biotrophs and necrotrophs.

Cell death or Hypersensitive Reaction (HR)-induced cell death in the host effectively stops biotrophic infection and is considered a typical resistance response of the host plant species. Cell death confines biotrophs by limiting or cutting off the nutrient supply and restricting the pathogen growth. However, cell death can be successfully used by necrotrophs to proliferate within the host. Activation of cell death pathways has been shown to promote susceptibility to broad range necrotrophs such as *Botrytis cinerea* and *Sclerotinia sclerotiorum* [1–3].

A typical hypersensitive reaction is initiated by the generation of Reactive Oxygen Species (ROS) followed by localised cell death. Besides defense, ROS is produced by plants as by-products of many key processes such as respiration, primary metabolism, photosynthesis, and responses to abiotic stresses. Rapid production of ROS or oxidative burst is one of the earliest responses of plants to pathogen attacks. Various studies have shown the involvement of ROS in cell death [4]. H_2O_2, a versatile reactive oxygen species, has multiple functions in plant-pathogen interactions. In addition to a direct antimicrobial effect, it also triggers cell wall cross-linking, induces resistance gene expression and hypersensitive response [5]. The rapid accumulation of ROS, cell death and callose deposition correlate with disease resistance in many biotrophic and hemibiotrophic pathosystems [6,7]. The necrotrophic pathogens, in contrast, thrive on the cell death caused by excessive ROS production during the recognition phase. Earlier studies have shown the importance of pathogen-responsive host H_2O_2 in promoting cell death in the host thereby causing expansion of disease lesions to facilitate necrotrophic fungal infection [8]. Williams et al. [9], showed that oxalic acid produced by *S. sclerotiorum* induces host ROS in compatible interactions. The role of ROS in facilitating infection is therefore seemingly contradictory and depends on the pathogen's lifestyle. However, the mechanisms involving the spatiotemporal control of ROS metabolism during plant-pathogen interactions are largely unknown.

Resistance to necrotrophic pathogens is based on defence responses

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Expanding the canvas of PRKN mutations in familial and early-onset Parkinson disease

Authors Sanjay Pandey, Laxmikant Ramkumarsingh Tomar, Sumeet Kumar, Shreya Dinesh, BK Thelma

Publication date 2019/9/1

Journal Parkinsonism & Related Disorders

Volume 66

Pages 216-219

Publisher Elsevier

Description Background

Mutations in *PRKN* (PARK2) are commonly encountered in early-onset Parkinson disease (PD).

Objectives

To screen for *PRKN* mutations in a clinically well-characterized cohort of early-onset PD patients with a family history (FEOPD; ≤50 years at onset) or sporadic (SEOPD; ≤50 years at onset) and late-onset familial patients (FLOPD; >50 years at onset).

Methods

A total of 97 patients including 52 SEOPD and 45 familial PD (FEOPD: 23; FLOPD: 22) were screened for variants in *PRKN* by PCR- Sanger sequencing. *PRKN* dosage and variants in known PD genes were screened by qPCR and whole-exome sequencing in a subset of samples.

Results

A total of 25 (25.77%) patients (SEOPD: 12, FEOPD: 6, and FLOPD: 7) were positive for *PRKN* variants. Of these, two patients manifested homozygous variants; while one patient was carrying three *PRKN* variants and two patients were carrying two ...

Rajarammohan et al. BMC Genomics (2019) 20:1036
https://doi.org/10.1186/s12864-019-6414-6

BMC Genomics

RESEARCH ARTICLE Open Access

Comparative genomics of *Alternaria* species provides insights into the pathogenic lifestyle of *Alternaria brassicae* – a pathogen of the *Brassicaceae* family

Sivasubramanian Rajarammohan[1,2], Kumar Paritosh[3], Deepak Pental[3] and Jagreet Kaur[1*]

Abstract

Background: *Alternaria brassicae*, a necrotrophic pathogen, causes *Alternaria* Leaf Spot, one of the economically important diseases of *Brassica* crops. Many other *Alternaria spp.* such as *A. brassicicola* and *A. alternata* are known to cause secondary infections in the *A. brassicae*-infected Brassicas. The genome architecture, pathogenicity factors, and determinants of host-specificity of *A. brassicae* are unknown. In this study, we annotated and characterised the recently announced genome assembly of *A. brassicae* and compared it with other *Alternaria spp.* to gain insights into its pathogenic lifestyle.

Results: We also sequenced the genomes of two *A. alternata* isolates that were co-infecting *B. juncea* using Nanopore MinION sequencing for additional comparative analyses within the *Alternaria* genus. Genome alignments within the *Alternaria spp.* revealed high levels of synteny between most chromosomes with some intrachromosomal rearrangements. We show for the first time that the genome of *A. brassicae*, a large-spored *Alternaria* species, contains a dispensable chromosome. We identified 460 *A. brassicae*-specific genes, which included many secreted proteins and effectors. Furthermore, we have identified the gene clusters responsible for the production of Destruxin-B, a known pathogenicity factor of *A. brassicae*.

Conclusion: The study provides a perspective into the unique and shared repertoire of genes within the *Alternaria* genus and identifies genes that could be contributing to the pathogenic lifestyle of *A. brassicae*.

Keywords: *Alternaria spp.*, Comparative genomics, Destruxin B, Dispensable chromosome, Necrotroph

Background

The genus *Alternaria* belonging to the class of *Dothideomycetes* contains many important plant pathogens. Diseases in the *Brassicaceae* family caused by *Alternaria spp.* result in significant yield losses [1]. *Alternaria spp.* have a wide host range within the *Brassicaceae*, infecting both the vegetable as well as the oilseed crops. Some of the most damaging species include *Alternaria brassicae*, *A. brassicicola*, *A. alternata*, *A. raphani*, *A. japonicus*, and *A. tenuissima*. *A. brassicae* preferentially infects the oleiferous *Brassicas* while the others are more devastating on the vegetable *Brassicas*. *A. brassicae* is particularly more damaging in the hilly regions of the Indian subcontinent, where conducive climatic conditions allow it to profusely reproduce and cause infections on almost all parts of the plant. Extensive screening for resistance to *A. brassicae* in the cultivated *Brassica* germplasms has not revealed any source of resistance [2].

The factors that contribute to the pathogenicity of *A. brassicae* are relatively unknown. Pathogenicity of many *Alternaria spp.* has been mainly attributed to the secretion of host-specific toxins (HSTs). HSTs induce pathogenesis on a rather narrow species range and are mostly indispensable for pathogenicity. At least 12 *A. alternata* pathotypes have been reported to produce HSTs and thereby cause disease on different species [3]. Many of

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Rare And Ultra-Rare Variants In Familial Schizophrenia-An Update From India

Authors BK Thelma, Jibin John, Prachi Kukshal, Triptish Bhatia, VL Nimgaonkar, SN Deshpande

Publication date 2019/1/1

Journal European Neuropsychopharmacology

Volume 29

Pages S744-S745

Publisher Elsevier

Description Family, twin and adoption studies have indicated the role of genetic and environmental factors in the etiology of schizophrenia (SZ) with perceptible heterogeneity and heritability has been estimated at ~80%. Genome-Wide Association Studies (GWAS) utilizing common variants from across the genome have identified large number of mostly non-coding common variants with small affects. Recent efforts using whole exome sequencing (WES) approach have identified a large number of rare de novo variants and a few family based studies have also helped identify some variants that segregated with disease phenotype. Sharing of such rare but highly penetrant variants/mutations, in different families is believed to be not by chance alone but may reflect the role of a few major pathways in the etiology of the disease. Such data generated from the genetically distinct north Indian population is hypothesized to be very ...

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SA120FAMILY BASED RARE VARIANT STUDY SUPPORTS THE CUMULATIVE CONTRIBUTION OF NEURODEVELOPMENTAL PATHWAY GENES IN SCHIZOPHRENIA ETIOLOGY

Authors BK Thelma, Jibin John, Prachi Kukshal, Triptish Bhatia, Vishwajit Nimgaonkar, Smita Deshpande

Publication date 2019/1/1

Journal European Neuropsychopharmacology

Volume 29

Pages S1254-S1255

Publisher Elsevier

Description Background: Clinical and genetic heterogeneity is well documented in schizophrenia (SZ), a common debilitating neurodevelopmental disorder with a life time prevalence of~ 1%. The contribution of both common and rare risk variants to the genetic architecture of SZ has been witnessed by genome-wide association studies, whole exome and whole genome sequencing approaches. Both common and de novo variants have provided notable evidence to likely involvement of a range of pathways including glutamatergic, synaptic signalling, neurodevelopmental etc. but they have been very limited in their contribution to total disease heritability and relative risk estimation. As SZ is highly heritable and segregates in families, highly penetrant rare variants are more likely to be identified through analyses of multiply affected families. Further, much of the gene mapping studies in SZ have utilized individuals of Caucasian ...

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An optimal capillary screen cut-off of thyroid stimulating hormone for diagnosing congenital hypothyroidism: data from a pilot newborn screening program in Delhi

Authors Prashant Verma, Seema Kapoor, Mani Kalaivani, Pallavi Vats, Sangeeta Yadav, Vandana Jain, SERB-NBS Initiative Group, BK Thelma

Publication date 2019/4

Journal Indian Pediatrics

Volume 56

Pages 281-286

Publisher Springer India

Description Objective

To determine an appropriate cut-off of capillary Thyroid stimulating hormone (TSH) for congenital hypothyroidism.

Study design

Cross-sectional.

Participants

174,000 neonates born in different hospitals of Delhi, India, from November 2014 to October 2016.

Main outcome measures

Correlation between initial and repeat capillary TSH level and subsequent venous free thyroxine (fT4) level.

Results

102 newborns with initial/repeat capillary TSH level of ≥20 mIU/L (n=174) were confirmed to have congenital hypothyroidism at mean (SD) age of 5 (4) days. A good correlation between capillary TSH level and confirmatory venous fT4 level and postnatal age of sampling was obtained (r -0.6, -0.4). The area under the ROC curve (AUC) was 0.81 (95 ...

Association between neonatal thyroid stimulating hormone status and maternal urinary iodine status

Authors Haseena Sait, Seema Kapoor, Ankur Jindal, Ritika Garg, Ravi Shankar Belwal, Sangita Yadav, Sangeeta Gupta, BK Thelma

Publication date 2019/6

Journal Indian pediatrics

Volume 56

Pages 472-475

Publisher Springer India

Description Background

Maternal urinary iodine concentration (MUIC) and percentage of neonates with Thyroid stimulating hormone (TSH) >5 mIU/L are amongst the parameters suggested for assessing adequate iodine status.

Objective

To assess the correlation between MUIC and neonatal TSH levels.

Study design

Cross-sectional.

Settings

Tertiary care center in Delhi, India, between November 2015 to November 2016.

Participants

Postnatal mother-neonate dyads.

Methods

TSH levels assessed among neonatal samples were stratified as below and above 5 mIU/L. MUIC was measured in 544 mothers, 400 mother-neonate dyads with neonatal TSH levels >5 mIU/L (cases) and 144 mother-neonate newborn mother dyads with ...

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Pharmacophore modeling and virtual screening in search of novel Bruton's tyrosine kinase inhibitors

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Authors Aditya Sharma, BK Thelma

Publication date 2019/7

Journal Journal of Molecular Modeling

Volume 25

Pages 1-15

Publisher Springer Berlin Heidelberg

Description Bruton's tyrosine kinase (BTK) is a known drug target for B cell malignancies and autoimmune diseases like rheumatoid arthritis. Consequently, efforts to develop BTK inhibitors have gained momentum in the last decade, resulting in a number of potential inhibitory molecules. However, to date, there are only two FDA approved drugs for B cell malignancies (Ibrutinib and Acalabrutinib), thus continued efforts are warranted. A large number of molecular scaffolds with potential BTK inhibitory activity are already available from these studies, and therefore we employed a ligand-based approach towards computer-aided drug design to develop a pharmacophore model for BTK inhibitors. Using over 400 molecules with known half maximal inhibitory concentrations (IC_{50}) for BTK, a four-point pharmacophore hypothesis was derived, with two aromatic rings (R), one hydrogen bond acceptor (A) and one hydrogen ...

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Cumulative effect of aging and SARS-CoV2 infection on poor prognosis in the elderly: Insights from transcriptomic analysis of lung and blood

Authors Upasana Bhattacharyya, BK Thelma

Publication date 2020/6/16

Journal bioRxiv

Pages 2020.06. 15.151761

Publisher Cold Spring Harbor Laboratory

Description The ongoing pandemic COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected over seven million people worldwide to date. It most commonly affects the respiratory system but can also damage kidney, blood vessels, heart, neurological systems etc. Currently there are no FDA approved prophylactics or therapeutics for COVID-19. Probability of contracting this highly contagious infection is similar across age groups but disease severity and reported global case-fatality rate among aged patients with or without comorbidities are notably higher. We hypothesized that expression of genes that changes during aging, may get further augmented on SARS-CoV-2 infection, leading to severe outcome in elderly patients. To test this, we performed a comparative analysis of transcriptome data from Broncho Alveolar Lavage Fluid (BALF)/lung/blood of healthy aging group with i) COVID-19 patients and; and ii) data of host genes interacting with SARS-COV-2 proteins. We observed i) a significant overlap of gene expression profiles of patients' BALF and blood respectively with lung and blood of the healthy aging group; ii) this overlap was more pronounced in blood compared to lung; and iii) a similar overlap between host genes interacting with SARS-CoV-2 and transcriptome profile of aging blood but not lung. Pathway enrichment analysis of the resulting overlapping gene sets suggests that SARS-Cov-2 infection alters expression of genes that are involved in pro-inflammatory response, apoptosis, T cell polarization, viral replication suppression etc. that are already dysregulated in the elderly population, this ...

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Age-related gene expression alterations by SARS-CoV-2 infection contribute to poor prognosis in elderly

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Authors: Upasana Bhattacharyya, BK Thelma

Publication date: 2020/12

Journal: Journal of Genetics

Volume: 99

Issue: 1

Pages: 80

Publisher: Springer India

Description: The ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected millions of people worldwide and with notable heterogeneity in its clinical presentation. Probability of contracting this highly contagious infection is similar across age groups but disease severity and fatality among aged patients with or without comorbidities are reportedly higher. Previous studies suggest that age associated transcriptional changes in lung and immune system results in a proinflammatory state and increased susceptibility to infectious lung diseases. Similarly, SARS-CoV-2 infection could augment ageing-related gene expression alterations resulting in severe outcomes in elderly patients. To identify genes that can potentially increase covid-19 disease severity in ageing people, we compared age associated gene expression changes with disease-associated expression changes in ...

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Multiple rare inherited variants in a four generation schizophrenia family offer leads for complex mode of disease inheritance

Authors Jibin John, Upasana Bhattacharyya, Navneesh Yadav, Prachi Kukshal, Triptish Bhatia, VL Nimgaonkar, Smita N Deshpande, BK Thelma

Publication date 2020/2/1

Journal Schizophrenia research

Volume 216

Pages 288-294

Publisher Elsevier

Description Schizophrenia is a clinically and genetically heterogeneous neuropsychiatric disorder, with a polygenic basis but identification of the specific determinants is a continuing challenge. In this study, we analyzed a multigenerational family, with all healthy individuals in the first two generations, and four progeny affected with schizophrenia in the subsequent two generations, using whole exome sequencing. We identified five rare protein sequence altering heterozygous variants, in five different genes namely *SMARCA5*, *PDE1B*, *TNIK*, *SMARCA2* and *FLRT* shared among all affected members and predicted to be damaging.

Variants in *SMARCA5* and *PDE1B* were inherited from the unaffected father whereas variants in *TNIK*, *SMARCA2* and *FLRT1* were inherited from the unaffected mother in all the three affected individuals in the third generation; and notably all these five variants were transmitted by an affected mother ...

Prof. Thelma B.K

Novel and reported variants in Parkinson's disease genes confer high disease burden among Indians

Authors Sumeet Kumar, Navneesh Yadav, Sanjay Pandey, Uday B Muthane, Shyla T Govindappa, Masoom M Abbas, Madhuri Behari, BK Thelma

Publication date 2020/9/1

Journal Parkinsonism & Related Disorders

Volume 78

Pages 46-52

Publisher Elsevier

Description Background

Genetic heterogeneity in Parkinson's disease (PD) has been unambiguously reported across different populations. Assuming a higher genetic load, we tested variant burden in PD genes to an early onset PD cohort from India.

Methods

Whole exome sequencing was performed in 250 PD patients recruited following MDS-UPDRS criteria. The number of rare variants in the 20 known PD genes per exome were used to calculate average rare variant burden with the 616 non-PD exomes available in-house as a comparison group. SKAT-O test was used for gene level analysis.

Results

80 patients harboured rare variants in 20 PD genes, of which six had known pathogenic variants accounting for 2.4% of the cohort. Of 80 patients, 12 had homozygous and nine had likely compound heterozygous variants in recessive PD genes and 59 had heterozygous variants in only dominant PD genes. Of the 16 novel ...

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Evidence for contribution of compound heterozygous variants in Wiskott-Aldrich syndrome like (*WASL*) gene for early onset Parkinson's disease

Authors Sumeet Kumar, Masoom M Abbas, Shyla T Govindappa, Uday B Muthane, Sanjay Pandey, BK Thelma

Publication date 2020/8/26

Journal medRxiv

Pages 2020.08. 24.20181024

Publisher Cold Spring Harbor Laboratory Press

Description Background

Knowledge of genetic determinants in Parkinson's disease is still limited. Familial forms of the disease continue to provide a rich resource to capture the genetic spectrum in disease pathogenesis, and this approach has been exploited in this study.

Methods

Informative members from a three-generation family of Indian ethnicity manifesting a likely autosomal recessive mode of inheritance of PD were used for whole exome sequencing. Variant data analysis and *in vitro* functional characterisation of putative disease causal variant(s) identified thereof were carried out in HEK-293 and SH-SY5Y cells using gene constructs of interest.

Results

In a rather uncommon observation, two compound heterozygous variants, a rare missense (c.1139C>T:p.P380L) and a novel splice variant (c.1456+5TAGAG>G) in Wiskott-Aldrich syndrome like gene (*WASL*, 7q31), both predicted to be deleterious were shared among the proband and her two affected siblings. *WASL*, a gene hitherto unreported for PD is known to regulate actin polymerisation via Arp2/3 complex. Based on exon trapping assay using pSPL3 vector in HEK-293 cells, the splice variant showed skipping of exon10. Functional characterisation of the missense variant in SH-SY5Y cells demonstrated: i) significant alterations in neurite length and number; ii) decreased ROS tolerance in mutation carrying cells on TBPH induction, and iii) increase in alpha-synuclein protein. Screening for WASL variants in two independent PD cohorts identified four individuals with heterozygous but none with biallelic variants.

Conclusion

WASL, with demonstrated functional relevance in neurons may be yet another ...

J. Plant Biochem. Biotechnol.
https://doi.org/10.1007/s13562-020-00615-3

ORIGINAL ARTICLE

Coping with stress: role of Arabidopsis phytoglobins in defence against *Sclerotinia sclerotiorum*

Nitika Mukhi[1,3] · Suman Kundu[2] · Jagreet Kaur[1]

Received: 2 April 2020 / Accepted: 22 September 2020

Abstract
Phytoglobins (Pgbs) are multifaceted stress-responsive proteins implicated in regulating various physiological and stress-responsive pathways in plants. Previous work has demonstrated NO dioxygenase and peroxidase-like activity of *Arabidopsis* phytoglobin 3 (AHb3) and its potential role in defense against *Sclerotinia sclerotiorum*. The work reported here highlights the significance of the other two classes of Arabidopsis phytoglobins (AHb1 and AHb2) in response to *S. sclerotiorum*. Constitutive expression of AHb1 (OEAHb1) and AHb2 (OEAHb2) conferred marginal tolerance towards *S. sclerotiorum* whereas respective knockdown (RNAi) lines displayed enhanced susceptibility, with AHb1 RNAi (RNAi-1) lines being more susceptible in comparison to AHb2 RNAi (RNAi-2) lines. Interestingly, transgenic lines with a simultaneous reduction in the transcripts of AHb1 and AHb2 (RNAi-F) displayed greater disease spread in comparison to individual knockdown lines indicative of their additive effect. The enhanced susceptibility upon pathogen challenge correlated with the elevated NO and H_2O_2 levels in these lines. Furthermore, detailed structural analysis hints towards an alternate mechanism of NO dioxyegnation by AHbs. Taken together, the current investigation illustrates the NO dioxygenase and peroxidase-like activity of AHbs and highlights their role in defense against stem rot pathogen *S. sclerotiorum*.

Keywords *Arabidopsis* phytoglobins · *Sclerotinia sclerotiorum* · Nitric oxide dioxygenase · peroxidase

Abbreviations

Pgbs	Phytoglobins
AHb	Arabidopsis phytoglobin
NO	Nitric oxide
ROS	Reactive oxygen species
OE	Overexpression
H_2O_2	Hydrogen peroxide.

Introduction

Three classes of phytoglobin genes (Pgbs) can be distinguished in plant genomes. Each class displays unique kinetic and structural fingerprints (Trevaskis et al. 1997; Watts et al. 2001). Depending upon the plant species, Pgbs are expressed across diverse plant organs throughout all developmental stages and display huge diversity in their expression profiles (Hunt et al. 2001; Garrocho-Villegas et al. 2007; Hebelstrup et al.2007; Bacana et al. 2020). The presence of phytoglobin genes in metabolically active and stressed tissue implicates their role in plant development as well as in mediating various biotic and abiotic stress responses possibly by binding to a wide variety of gaseous ligand including O_2, NO, H_2O_2, etc. (Hebelstrup et al. 2007; Smagghe et al. 2007; Dordas 2009). Attributed to their high oxygen affinities (esp. class I Pgbs), phytoglobins have been implicated to function as O_2 scavengers or in O_2 signaling and maintain cellular redox balance by modulating the levels of Nitric oxide (NO) produced under various biotic/abiotic stress conditions (Seregelyes and Dudits 2003).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13562-020-00615-3) contains supplementary material, which is available to authorized users.

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Original Paper

Allicin Overcomes Hypoxia Mediated Cisplatin Resistance in Lung Cancer Cells through ROS Mediated Cell Death Pathway and by Suppressing Hypoxia Inducible Factors

Namita Pandey[a] Gunjan Tyagi[b] Prabhjot Kaur[a] Shrikant Pradhan[a] M. V. Rajam[a] Tapasya Srivastava[a]

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Key Words
NSCLC • Hypoxia • Allicin • Reactive Oxygen Species (ROS) • Cisplatin

Abstract
Background/Aims: The hypoxic microenvironment in NSCLC has been widely accepted as a contributor to both therapeutic resistance and tumor progression. In this study, we have explored Allicin, a key organosulfur compound present in garlic for its previously unreported effectiveness in the heterogeneous hypoxic tumor microenvironment of NSCLC. ***Methods:*** The effect of Allicin on the viability of NSCLC cells was determined by MTT assay. To determine the migration rate of treated cells compared to the control, scratch and transwell migration assays were performed. Flowcytometry was done to explore cell cycle distribution, apoptosis and ROS production in cells. Fluorescence microscopy was used to examine autophagy and DNA damage in cells. Dot blot was done to check genome wide methylation. RNA expression was detected by RT-PCR and protein expression by western blotting. ***Results:*** Allicin significantly decreases cell viability, proliferation and migration of NSCLC cells in both normoxia and hypoxia. It elicits both apoptosis and autophagy pathway in A549 cells by ROS accumulation and facilitating S/G2-M phase arrest in both normoxia as well as hypoxia. We suggest that ROS/MAPK and ROS/JNK signaling pathway together govern the cytotoxic effect of allicin in NSCLC cells. Notably, allicin suppresses the expression of HIF-1α and HIF-2α in hypoxic cells, pointing towards a mechanism of its effectiveness in hypoxia. A long term passive demethylation was observed, with decreased mC and no change in TET expression, thereby ruling out active demethylation by allicin. Furthermore, allicin synergistically enhances growth inhibitory

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Association of regulatory variants of dopamine β-hydroxylase with cognition and tardive dyskinesia in schizophrenia subjects

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Authors Toyanji J Punchaichira, Anirban Mukhopadhyay, Prachi Kukshal, Triptish Bhatia, Smita N Deshpande, BK Thelma

Publication date 2020/3

Journal Journal of Psychopharmacology

Volume 34

Issue 3

Pages 358-369

Publisher SAGE Publications

Description Background: Dopamine-β-hydroxylase (DBH, EC 1.14. 17.1), which converts dopamine to norepinephrine, is a candidate gene in neuropsychiatric diseases.

Aim: To assess the effect of regulatory variants in DBH on schizophrenia and its endophenotypes–cognition and tardive dyskinesia. Methods: We tested association of functional variants 19bp Ins/Del, rs1989787 and rs1611115 in DBH with i) schizophrenia (1236 cases, 1136 controls), ii) tardive dyskinesia (83 positive, 162 negative) and iii) performance functions of cognition (357 cases, 306 controls) estimated by the Penn Computerized Neurocognitive Battery.

Results: A modest haplotypic (Ins-C; 19bp Ins/Del–rs1989787 C> T; p= 0.04) association was observed with schizophrenia. We observed~ 39% reduction in activity of 19bp Del allele on luciferase assay. Analysis of covariance revealed interactions of tardive dyskinesia status and: i) 19bp Ins/Del ...

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The effect of rs1076560 (DRD2) and rs4680 (COMT) on tardive dyskinesia and cognition in schizophrenia subjects

Authors Toyanji Joseph Punchaichira, Prachi Kukshal, Triptish Bhatia, Smita Neelkanth Deshpande, BK Thelma

Publication date 2020/10

Journal Psychiatric genetics

Volume 30

Issue 5

Pages 125

Publisher NIH Public Access

Description Objective

The aim of the study is to test the association of a functional variant each in DRD2 and COMT genes with schizophrenia and its endophenotypes.

Prof. Thelma B.K

Factors associated with transient neonatal hyperthyrotropinemia

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Authors	Ritika Garg, Haseena Sait, Ankur Jindal, Monica Juneja, Sangeeta Gupta, BK Thelma, Seema Kapoor
Publication date	2020/6
Journal	The Indian Journal of Pediatrics
Volume	87
Issue	6
Pages	482-483
Publisher	Springer India
Description	(TNH) is defined as temporary postnatal elevation of thyroid stimulating hormone (TSH) levels (10 mIU/L–20 mIU/L) with normal fT4 levels but TSH returning to normal (< 10 mIU/L) when measured at 14 d of life [1]. It is important to recognise TNH as these newborns have a higher risk of developing permanent hypothyroidism with repercussion on developmental status [2, 3]. Thus, we aimed at evaluating the neonatal and maternal factors associated with TNH and their developmental and thyroid status on follow up at 3 mo of age. This case control study was conducted as a part of newborn screening at a tertiary care centre in North India from January 2016–2017. Institutional Ethical Committee approval was obtained. Seventy neonates each, in case and control group, were enrolled. Neonates requiring intensive care were excluded. Neonates of case group were subjected to the estimation of immediate venous fT3 ...
Total citations	Cited by 2

2020 2021 2022

Scholar articles Factors associated with transient neonatal hyperthyrotropinemia
R Garg, H Sait, A Jindal, M Juneja, S Gupta, BK Thelma... - The Indian Journal of Pediatrics, 2020
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Prof. Thelma B.K

Building Quantum Calculation-Based Protein Polarization Effect Into Protein-Inhibitor Binding Dynamics for Lead Molecule Prioritization

Authors Gurvisha Sandhu, BK Thelma

Publication date 2020

Journal Proceedings of International Conference on Drug Discovery (ICDD)

Description Reliable quantitative description of protein structure and dynamics of protein-inhibitor binding is quintessential for the evaluation of novel inhibitor designs and electrostatic interactions play a critical role in achieving this. The local electrostatic environment inside a folded protein is not homogeneous but largely determined by amino-acid residue location, specific conformation and dielectric environment. However, conventional molecular mechanical force fields (like AMBER) employ fixed atomic charges, which makes them incapable of accurately modeling biomolecular interactions. Therefore, current research focus is to enable incorporation of polarization effects into force field based molecular simulations.

View article

Newborn screening and diagnosis of infants with congenital adrenal hyperplasia

Authors Pallavi Vats, Aashima Dabas, Vandana Jain, Anju Seth, Sangeeta Yadav, Madhulika Kabra, Neerja Gupta, Preeti Singh, Rajni Sharma, Ravindra Kumar, Sunil K Polipalli, Prerna Batra, BK Thelma, Seema Kapoor

Publication date 2020/1

Source Indian pediatrics

Volume 57

Pages 49-55

Publisher Springer India

Description Congenital adrenal hyperplasia (CAH) is an autosomal recessive endocrine disorder which can manifest after birth with ambiguous genitalia and salt-wasting crisis. However, genital ambiguity is not seen in male babies and may be mild in female babies, leading to a missed diagnosis of classical CAH at birth. In this review, we provide a standard operating protocol for routine newborn screening for CAH in Indian settings. A standardization of first tier screening tests with a single consistent set of cut-off values stratified by gestational age is also suggested. The protocol also recommends a two-tier protocol of initial immunoassay/time resolved fluoroimmunoassay followed by liquid chromatography tandem mass spectrometry for confirmation of screen positive babies, wherever feasible. Routine molecular and genetic testing is not essential for establishing the diagnosis in all screen positive babies, but has significant ...

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View article

Prediction of Inflammatory Bowel Diseases using Genetic Risk Score in Asian populations

Authors Shifteh Abedian, Sunny H Wong, Suzanne Van Sommeren, Atsushi Takahashi, Jae Hee Cheon, Ajit Sood, Homayoon Vahedi, Keiko Yamazaki, Won Ho Kim, BK Thelma, Nasser E Daryani, Michiaki Kubo, Suk-Kyun Yang, Rupa Banerjee, Reza Malekzadeh, Rinse K Weersma, Siew C Ng, Behrooz Z Alizadeh

Publication date 2021/2/24

Description Methods

We studied 9,698 subjects–4,733 IBD patients (2,003 CD; 2,730 UC) and 4,965 matched controls–who had been genotyped using Immunochip. The subjects were from three East Asian (Japan, South Korea and China) and two Central Asian populations (India and Iran). We generated GRS for each population by combining information from up to 201 genome-wide significant IBD-associated variants to summarize the total load of genetic risk for each phenotype. We then estimated the explained variance and predictability of IBD using the GRS.

Results

IBD GRS could explain up to 4.40% and 4.14% of IBD variance at a significant level in East Asian and Central Asian populations, respectively, but, given a prevalence of 0.01% and 0.04% for IBD, these yield limited predictive probability. GRS for CD and UC separately proved less significant than GRS for IBD.

Conclusion

GRS alone can explain only a limited percentage of disease occurrence (< 5% of disease susceptibility) and cannot be used to predict IBD in Asian populations at this time. Our results highlight the significant missing heritability, which may be due to genetic epistasis, gene-environment interactions, or rare variants.

Prof. Thelma B.K

Multiple allelic associations from genes involved in energy metabolism were identified in celiac disease

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Full View

Authors Sandilya Bhagavatula, Pratibha Banerjee, Ajit Sood, Vandana Midha, BK Thelma, Sabyasachi Senapati

Publication date 2021/9

Journal Journal of Biosciences

Volume 46

Issue 3

Pages 61

Publisher Springer India

Description Energy metabolism is a critical factor that influences disease pathogenesis. Recent high-throughput genomic studies have enabled us to look into disease biology with greater details. Celiac disease (CD) is an inflammatory autoimmune disease where ~60 non-HLA genes were identified which in conjunction with HLA genes explain ~55% of the disease heritability. In this study we aimed to identify susceptibility energy metabolism genes and investigate their role in CD. We re-analysed published Immunochip genotyping data, which were originally analysed for CD association studies in north Indian and Dutch population. 269 energy metabolism genes were tested. Meta-analysis was done for the identified SNPs. To validate the functional implications of identified markers and/or genes, *in silico* functional annotation was performed. Six SNPs were identified in north Indians, of which three markers from two loci were ...

Revisiting schizophrenia from an evolutionary perspective: an association study of recent evolutionary markers and schizophrenia

Authors Upasana Bhattacharyya, Smita N Deshpande, Triptish Bhatia, BK Thelma

Publication date 2021/5/1

Journal Schizophrenia bulletin

Volume 47

Issue 3

Pages 827-836

Publisher Oxford University Press

Description The persistence of schizophrenia in human populations at a high prevalence and with a large heritability estimate despite reduced fertility and increased mortality rate is a Darwinian paradox. This may be likely if the genomic components that predispose to schizophrenia are also advantageous for the acquisition of important human traits, such as language and cognition. Accordingly, an emerging group of genomic markers of recent evolution in humans, namely human accelerated regions (HARs), since our divergence from chimpanzees, are gaining importance for neurodevelopmental disorders, such as schizophrenia. We hypothesize that variants within HARs may affect the expression of genes under their control, thus contributing to disease etiology. A total of 49 HAR single nucleotide polymorphisms (SNPs) were prioritized from the complete repertoire of HARs (n = 2737) based on their functional relevance ...

3 Biotech (2021) 11:451
https://doi.org/10.1007/s13205-021-02987-2

ORIGINAL ARTICLE

Scouting for common genes in the heterogenous hypoxic tumor microenvironment and their validation in glioblastoma

Ashish Bhushan[1] · Ranbala Kumari[2] · Tapasya Srivastava[1]

Received: 19 June 2021 / Accepted: 4 September 2021 / Published online: 26 September 2021

Abstract
Investigating the therapeutic and prognostic potential of genes in the heterogeneous hypoxic niche of glioblastoma. We have analyzed RNA expression of U87MG cells cultured in hypoxia compared to normoxia. Common differentially expressed genes (DEGs) from GSE45301 and GSE18494 and their functional enrichment was performed using MetaScape and PANTHER. Hub genes and their ontology were identified using MCode cytoHubba and ClueGO and validated with GlioVis, Oncomine, HPA and PrognoScan. Using the GEO2R analysis of GSE45301 and GSE18494 datasets, we have found a total of 246 common DEGs (180 upregulated and 66 downregulated) and identified 2 significant modules involved in ribosome biogenesis and TNF signaling. Meta-analysis of key genes of each module in cytoHubba identified 17 hub genes (*ATF3, BYSL, DUSP1, EGFR, JUN, ETS1, LYAR, NIP7, NOLC1, NOP2, NOP56, PNO1, RRS1, TNFAIP3, TNFRSF1B, UTP15, VEGFA*). Of the 17 hub genes, *ATF3, BYSL, EGFR, JUN, NIP7, NOLC1, PNO1, RRS1, TNFAIP3* and *VEGFA* were identified as hypoxia signatures associated with poor prognosis in Glioma. Ribosome biogenesis emerged as a vital contender of possible therapeutic potential with *BYSL, NIP7, NOLC1, PNO1* and *RRS1* showing prognostic value.

Keywords Hypoxia · Glioma · PPI network · GEO2R · Hub genes · Ribosome biogenesis

Introduction

Glioblastoma (GBM) is the most common primary brain tumor in adults and presents with high morbidity and mortality (Jones et al. 2012). It comprises approximately 30% of brain and central nervous system (CNS) tumors (Song et al. 2016). It also accounts for 80% of brain glioma with a median survival rate of a dismal 10–15 months (Norden et al. 2010). The standard treatment is surgical intervention, chemotherapy and radiotherapy (Khosla 2016).

GBM have hypoxic interiors with characteristic necrotic foci and the heterogeneous hypoxia surrounding the niche consist of migrating GBM cells that exhibit a highly invasive phenotype (Rong et al. 2006; Wang et al. 2011). Hypoxic conditions of glioma cells arise from morphological and functionally inappropriate neovascularization, anemia and irregular blood flow that demands high oxygen consumption for rapidly proliferating cancerous cells (Jensen 2009). Hypoxia has been shown to drive activation of endothelial to mesenchymal transition, induction of angiogenesis, inhibition of cell death, modulation of cellular metabolism, and tumor immune escape (Murat et al. 2009; Hu et al. 2012; Kucharzewska et al. 2015; Yaghi et al. 2016; Monteiro et al. 2017). Lack of oxygen alters the expression of genes involved in cell proliferation and angiogenesis facilitating tumor growth and metastasis (Li et al. 2009). The glioma niche consists of a microenvironment that hampers standard chemotherapy and allows glioma stem cells to initiate tumorigenesis leading to recurrence (Lathia et al. 2015). In vitro experimental research with hypoxia enriches genes that facilitate adaptation to altered metabolism and helps in identifying molecules associated with the interiors of the glioma niche.

High throughput technology such as microarray has been used to detect the global gene expression pattern and molecular classification of different types of cancer (Ramasamy et al. 2008). It offers a wide range of medical oncology applications, particularly in the exploration of potential prognostic biomarkers and therapeutic targets (Russo et al.

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SHORT COMMUNICATION

Pradeep Kumar Burma
GPG Journal of Science Education
Vol. 2 Issue 2 2021 : pp 8 - 11

An alternative approach to how biology practicals are currently conducted in the Indian education system

Pradeep Kumar Burma
Department of Genetics
University of Delhi South Campus
Benito Juarez Road, New Delhi 110021, India

Abstract
In the current Indian education system, science practical demonstrations or experiments have been reduced to tasks performed by the students in predetermined structured fashion for evaluation at the end of a semester. In most cases the expected result is known before the task is completed. Through this method the students may develop an understanding of and learn new techniques but are not challenged to evaluate experimental observations and discover the underlying concepts. In the current communication, using two examples, I propose an alternate approach, wherein students are not informed about learning outcomes or the aim of the activity before performing the experiment. The observations made are then discussed through a set of questions, to highlight its usability in biological experiments or in understanding a concept.

Keywords: School practical work, Capture-recapture method; Population size; Mendel's Laws and Probability

(Received 6 February, 2021; Accepted 21 July, 2021; Published 25 July, 2021)

'Practicals' are integral part of the Indian science education at every level beginning at school level. However, in a majority of cases the practical component has been reduced to a set of tasks to be performed by students, reported in practical sheets (colloquially called as 'practical copy') in a predetermined structured manner to be evaluated at the end of a semester. The predetermined structure consists of reporting the (i) aim of the experiment, (ii) material needed (iii) procedure in a point wise manner (iv) observations as tables, figures or graphs (v) discussion and (vi) precautions. In several cases, the outcome of the task is already known and the student simply goes through the motion of completing the task presented to him/her. While this strategy expose students to different methods of analysis (as proposed in the aim), the essence of building concepts through experimentation or an in-depth analysis of observations made, is not enhanced. While the proposed approach is based on the observation of the Indian education system, the same can be adapted for other countries.

In this article, two simple examples are proposed as alternate methods of conducting a biology practical. The cited examples in this paper are aimed mainly at students in Grades 11 and 12 (of about 17 – 18 years of age) but the approach is applicable to higher levels of education. In this method, students are not informed about learning outcomes or the aim of the activity but are first required

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Prof. Thelma B.K

Transethnic analysis of the human leukocyte antigen region for ulcerative colitis reveals not only shared but also ethnicity-specific disease associations

Authors Frauke Degenhardt, Gabriele Mayr, Mareike Wendorff, Gabrielle Boucher, Eva Ellinghaus, David Ellinghaus, Hesham ElAbd, Elisa Rosati, Matthias Hübenthal, Simonas Juzenas, Shifteh Abedian, Homayon Vahedi, BK Thelma, Suk-Kyun Yang, Byong Duk Ye, Jae Hee Cheon, Lisa Wu Datta, Naser Ebrahim Daryani, Pierre Ellul, Motohiro Esaki, Yuta Fuyuno, Dermot PB McGovern, Talin Haritunians, Myhunghee Hong, Garima Juyal, Eun Suk Jung, Michiaki Kubo, Subra Kugathasan, Tobias L Lenz, Stephen Leslie, Reza Malekzadeh, Vandana Midha, Allan Motyer, Siew C Ng, David T Okou, Soumya Raychaudhuri, John Schembri, Stefan Schreiber, Kyuyoung Song, Ajit Sood, Atsushi Takahashi, Esther A Torres, Junji Umeno, Behrooz Z Alizadeh, Rinse K Weersma, Sunny H Wong, Keiko Yamazaki, Tom H Karlsen, John D Rioux, Steven R Brant, MAAIS Recruitment Center, Andre Franke, International IBD Genetics Consortium

Publication date 2021/3/1

Journal Human molecular genetics

Volume 30

Issue 5

Pages 356-369

Publisher Oxford University Press

Description Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gut. Genetic association studies have identified the highly variable human leukocyte antigen (HLA) region as the strongest susceptibility locus for IBD and specifically DRB1*01:03 as a determining factor for ulcerative colitis (UC). However, for most of the association signal such as delineation could not be made because of tight structures of linkage disequilibrium within the HLA. The aim of this study was therefore to further characterize the HLA signal using a transethnic approach. We performed a comprehensive fine mapping of single HLA alleles in UC in a cohort of 9272 individuals with African American, East Asian, Puerto Rican, Indian and Iranian descent and 40 691 previously analyzed Caucasians, additionally analyzing whole HLA haplotypes. We computationally characterized the binding of associated HLA alleles to human self ...

Prof. Thelma B.K

Trans-ethnic analysis of the human leukocyte antigen region for ulcerative colitis reveals shared but also ethnicity-specific disease associations

Authors MAAIS Recruitment Center, Frauke Degenhardt, Gabriele Mayr, Mareike Wendorff, Gabrielle Boucher, Eva Ellinghaus, David Ellinghaus, Hesham ElAbd, Elisa Rosati, Matthias Hübenthal, Simonas Juzenas, Shifteh Abedian, Homayon Vahedi, BK Thelma, Suk-Kyun Yang, Byong Duk Ye, Jae Hee Cheon, Lisa Wu Datta, Naser Ebrahim Daryani, Pierre Ellul, Motohiro Esaki, Yuta Fuyuno, Dermot PB McGovern, Talin Haritunians, Myhunghee Hong, Garima Juyal, Eun Suk Jung, Michiaki Kubo, Subra Kugathasan, Tobias L Lenz, Stephen Leslie, Reza Malekzadeh, Vandana Midha, Allan Motyer, Siew C Ng, David T Okou, Soumya Raychaudhuri, John Schembri, Stefan Schreiber, Kyuyoung Song, Ajit Sood, Atsushi Takahashi, Esther A Torres, Junji Umeno, Behrooz Z Alizadeh, Rinse K Weersma, Sunny H Wong, Keiko Yamazaki, Tom H Karlsen, John D Rioux, Steven R Brant

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Prof. Thelma B.K

Data-driven Approaches to Explore Precision Medicine

Authors Sara Garcia

Publication date 2021/4

Publisher DTU Health Technology

Description The PhD project was carried out at the department of Health Technology at the Technical University of Denmark between January 2018 and April 2021 to fulfil the requirements for acquiring a PhD degree. The project was funded by Fondation Idella. This thesis consists of a general introduction followed by four research articles: one published, two submitted, and one in preparation. Additionally, one application note in preparation is included in chapter 8, as well as a description of the work done during my remote external stay at St. Jude Children's Research hospital in chapter 9. The projects were carried out under the main supervision of associate professor Ramneek Gupta and co-supervision of professor BK Thelma, senior researcher Marlene Danner Dalgaard, and associate professor Elena Papaleo.

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IRC3 Regulates Mitochondrial Translation in Response to Metabolic Cues in *Saccharomyces cerevisiae*

Jaswinder Kaur,[a] Kaustuv Datta[a]

[a]Department of Genetics, University of Delhi, New Delhi, India

ABSTRACT Mitochondrial oxidative phosphorylation (OXPHOS) enzymes have a dual genetic origin. Mechanisms regulating the expression of nucleus-encoded OXPHOS subunits in response to metabolic cues (glucose versus glycerol) are well understood, while the regulation of mitochondrially encoded OXPHOS subunits is poorly defined. Here, we show that *IRC3*, a DEAD/H box helicase gene, previously implicated in mitochondrial DNA maintenance, is central to integrating metabolic cues with mitochondrial translation. Irc3 associates with mitochondrial small ribosomal subunits in cells consistent with its role in regulating translation elongation based on the Arg8^{m} reporter system. *IRC3*-deleted cells retained mitochondrial DNA despite a growth defect on glycerol plates. Glucose-grown $\Delta irc3\rho^{+}$ and *irc3* temperature-sensitive cells at 37°C have reduced translation rates from the majority of mRNAs. In contrast, when galactose was the carbon source, a reduction in mitochondrial translation was observed predominantly from Cox1 mRNA in $\Delta irc3\rho^{+}$ cells but no defect was observed in *irc3* temperature-sensitive cells, at 37°C. In support of a model whereby *IRC3* responds to metabolic cues to regulate mitochondrial translation, $\Delta irc3$ suppressor strains isolated for restoration of growth on glycerol medium restore mitochondrial protein synthesis differentially in the presence of glucose versus glycerol.

KEYWORDS mitochondria, OXPHOS, RNA helicase, metabolic cues, translation

Mitochondria, which are best known as the powerhouse of the cell, require coordinated gene expression of two spatially distinct genetic materials. Mitochondria are essential for an organism's viability and normal physiology, and any disruption in its functioning leads to a myriad of cellular defects, including cancer (1–3). *Saccharomyces cerevisiae* has been an invaluable system for deciphering mitochondrial function, due to its ability to survive without respiration as well as mitochondrial DNA (mtDNA), permitting the characterization of mutants that impair mitochondrial functioning. In *Saccharomyces cerevisiae*, mtDNA encodes eight proteins, seven of which are transmembrane proteins that are essential components of oxidative phosphorylation (OXPHOS) machinery and one, soluble protein Var1, that is an essential component of mitochondrial small ribosomal subunits. In addition to these eight protein coding genes, mtDNA also encodes rRNAs (15S and 21S) and a complete set of tRNAs required for gene expression. The remainder of the proteins that make up the OXPHOS subunits, factors required for mitochondrial transcription and translation, including mitochondrial ribosomal proteins, are encoded by the nuclear genome, which is translated in the cytosol and imported into the mitochondria (4).

Translation of mitochondrial mRNA, in addition to general translation factors such as Tuf1 (EF-Tu) and Mef1 and Mef2 (EF-G), require membrane-bound mRNA-specific translation activators (5–11). In the absence of either Shine-Dalgarno sequences or a 5′ cap on mitochondrial transcripts, these mRNA-specific translation activators recognize the 5′ untranslated region (UTR) of mRNA to localize them to the mitochondrial inner membrane, where they aid in the loading of membrane-bound ribosomes to initiate mitochondrial translation (12–18). In fact, each mitochondrial mRNA has its specific set of translation activators (19, 20). Interestingly, altered levels or activities of these translation activators are thought to allow

Citation Kaur J, Datta K. 2021. *IRC3* regulates mitochondrial translation in response to metabolic cues in *Saccharomyces cerevisiae*. Mol Cell Biol 41:e00233-21. https://doi.org/10.1128/MCB.00233-21

Address correspondence to Kaustuv Datta, kdatta@south.du.ac.in

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Prof. Thelma B.K

Compound heterozygous variants in Wiskott-Aldrich syndrome like (WASL) gene segregating in a family with early onset Parkinson's disease

[HTML] from sciencedirect.com

Authors: Sumeet Kumar, Masoom M Abbas, Shyla T Govindappa, Uday B Muthane, Madhuri Behari, Sanjay Pandey, Ramesh C Juyal, BK Thelma

Publication date: 2021/3/1

Journal: Parkinsonism & Related Disorders

Volume: 84

Pages: 61-67

Publisher: Elsevier

Description: Background

Knowledge of genetic determinants in Parkinson's disease is still limited. Familial forms of the disease continue to provide a rich resource to capture the genetic spectrum in disease pathogenesis, and this approach is exploited in this study.

Methods

Informative members from a three-generation family of Indian ethnicity manifesting a likely autosomal recessive mode of inheritance of Parkinson's disease were used for whole exome sequencing. Variant data analysis and *in vitro* functional characterisation of variant(s) segregating with the phenotype were carried out in HEK-293 and SH-SY5Y cells using gene constructs of interest.

Results

Two compound heterozygous variants, a rare missense (c.1139C > T:p.P380L) and a novel splice variant (c.1456 + 2 delTAGA, intron10) in Wiskott-Aldrich syndrome like gene (*WASL*, 7q31), both predicted to be deleterious were shared among the proband and two ...

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Scholar articles: Compound heterozygous variants in Wiskott-Aldrich syndrome like (WASL) gene segregating in a family with early onset Parkinson's disease
S Kumar, MM Abbas, ST Govindappa, UB Muthane... - Parkinsonism & Related Disorders, 2021
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Genome wide study of tardive dyskinesia in schizophrenia

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Authors	Keane Lim, Max Lam, Clement Zai, Jenny Tay, Nina Karlsson, Smita N Deshpande, BK Thelma, Norio Ozaki, Toshiya Inada, Kang Sim, Siow-Ann Chong, Todd Lencz, Jianjun Liu, Jimmy Lee
Publication date	2021/6/8
Journal	Translational Psychiatry
Volume	11
Issue	1
Pages	351
Publisher	Nature Publishing Group UK
Description	Tardive dyskinesia (TD) is a severe condition characterized by repetitive involuntary movement of orofacial regions and extremities. Patients treated with antipsychotics typically present with TD symptomatology. Here, we conducted the largest GWAS of TD to date, by meta-analyzing samples of East-Asian, European, and African American ancestry, followed by analyses of biological pathways and polygenic risk with related phenotypes. We identified a novel locus and three suggestive loci, implicating immune-related pathways. Through integrating *trans*-ethnic fine mapping, we identified putative credible causal variants for three of the loci. Post-hoc analysis revealed that SNPs harbored in *TNFRSF1B* and *CALCOCO1* independently conferred three-fold increase in TD risk, beyond clinical risk factors like Age of onset and Duration of illness to schizophrenia. Further work is necessary to replicate loci that are reported ...
Total citations	Cited by 16

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Scholar articles Genome wide study of tardive dyskinesia in schizophrenia
K Lim, M Lam, C Zai, J Tay, N Karlsson, SN Deshpande... - Translational Psychiatry, 2021
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FMR1 gene CGG repeat distribution among the three individual cohorts with intellectual disability, autism, and primary ovarian insufficiency from Tamil Nadu …

[PDF] from wiley.com
Full View

Authors Indhumathi Nagarathinam, Samuel S Chong, Thelma BK, Jeffrey Justin Margret, Viswanathan Venkataraman, Karthikeyen Natarajan Padmavathy, CR Srikumari Srisailapathy

Publication date 2021/6

Journal Advanced Genetics

Volume 2

Issue 2

Pages e10048

Publisher John Wiley & Sons, Inc.

Description Fragile X syndrome is the most common genetic cause of intellectual disability (ID) and is also well known to have a role in primary ovarian insufficiency (POI) and fragile X-associated tremor ataxia syndrome (FXTAS) that expresses across generations. The objective was to compare the CGG repeat variants in *FMR1* gene among three correlating cohorts of ID, autism and idiopathic POI. Thirty-six patients with ID, 12 with autism spectrum disorder (ASD) and 13 females with idiopathic POI were screened for *FMR1* CGG repeat size by fluorescent methylation-specific PCR and GeneScan analysis, irrespective of Hagerman checklist clinical scores. Among 29 males and seven females, 11 *FMR1* allelic variants ranging from 21 to >200 CGG repeats were observed. Three (CF2-3, 39-5, 44-2) out of 29 males had full mutation alleles accounting for a 10.34% incidence of FXS among idiopathic ID males. One of them was …

Prof. Thelma B.K

Correlation between an intronic SNP genotype and ARL15 level in rheumatoid arthritis

[HTML] from springer.com
Full View

Authors Anuj Kumar Pandey, Aishwarya Saxena, Sanjay Kumar Dey, Maumita Kanjilal, Uma Kumar, BK Thelma

Publication date 2021/10

Journal Journal of genetics

Volume 100

Issue 2

Pages 26

Publisher Springer India

Description ADP ribosylation factor like protein 15 (*ARL15*) was identified as a novel susceptibility gene for rheumatoid arthritis (RA) based on a genomewide association study in a north Indian cohort. Mechanism of its action and functional relevance in RA biology remain largely unknown. In this study, we aimed to establish (i) ARL15 protein level in sera samples of RA patients; and (ii) its correlation, if any, with the RA associated *ARL15* intronic single-nucleotide polymorphism (SNP) rs255758 (A > C). DNA, RNA and sera were isolated from blood samples of 117 RA patients and 25 age-matched healthy controls recruited at All India Institute of Medical Sciences, New Delhi with institutional ethical committee clearance. SNP rs255758 (A > C) was genotyped by Sanger sequencing; ARL15 RNA and protein levels were estimated by quantitative polymerase chain reaction (qPCR) and enzyme-linked immunosorbent assay ...

A brief summary of human molecular genetic techniques for clinical psychiatrists

Authors Chandra Bhushan Rai, Anirban Mukhopadhyay, Smita N Deshpande, BK Thelma

Publication date 2021

Source Open Journal of Psychiatry & Allied Sciences

Volume 12

Issue 1

Pages 55-61

Publisher Academy Publisher

Description Concerted and systematic efforts to understand genetics of human health and disease over the preceding 60 odd years have witnessed remarkable progress. The incremental gains through this journey were enabled by chromosomal analysis, recombinant deoxyribonucleic acid (DNA) techniques, notable discovery of single nucleotide polymorphisms following the Human Genome Project, consequent genome-wide variant-based studies, and now whole genome sequencing with ultimate diagnostic potential. Of note, success in prediction and prevention of chromosomal and single gene disorders comprising ~six to eight per cent each of all genetic disorders have been unprecedented but uncovering genetics of common complex disorders conferring ~60% of the genetic disease burden continues to pose a challenge and await new analytical paradigms - a mix of reductionist and organismal biology together with ...

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DOI: 10.1002/ddr.21883

DRUG DEVELOPMENT RESEARCH WILEY

RESEARCH ARTICLE

Exploration of novel TOSMIC tethered imidazo[1,2-a]pyridine compounds for the development of potential antifungal drug candidate

Pratibha Shukla[1,2] | Deepa Deswal[2] | Mansi Pandit[3] | Narayanan Latha[3] | Divyank Mahajan[4] | Tapasya Srivastava[4] | Anudeep Kumar Narula[1,2]

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Abstract

New candidates of imidazo[1,2-a]pyridine were designed by combining 2-amino pyridine, TOSMIC and various assorted aldehydes to explore their antioxidant and antifungal potential. The design of these derivatives was based on utilizing the antifungal potential of azoles and TOSMIC moiety. These derivatives were synthesized by adopting multi-component reaction methodology, as it serves as a rapid and efficient tool to target structurally diverse heterocyclic compounds in quantitative yield. The resulting imidazo [1,2-a]pyridine derivatives were structurally verified by ^{1}HNMR, ^{13}CNMR, HRMS, and HPLC. The compounds were analyzed for their antioxidant and fluorescent properties and it was observed that compound 15 depicted highest potential. The compounds were evaluated for their antifungal potential to highlight their medical application in the area of Invasive Fungal Infections (IFI). Compound 12 gave the highest antifungal inhibition against *Aspergillus fumigatus* 3007 and *Candida albicans* 3018. To elucidate the antifungal mechanism, confocal images of treated fungi were analyzed, which depicted porous nature of fungal membrane. Estimation of fungal membrane sterols by UPLC indicated decrease in ergosterol component of fungal membrane. In silico studies further corroborated with the in vitro results as docking studies depicted interaction of synthesized heterocyclic compounds with amino acids present in the active site of target enzyme (lanosterol 14 alpha demethylase). Absorption, distribution, metabolism, and excretion (ADME) analysis was indicative of drug-likeliness of the synthesized compounds.

KEYWORDS
ADME, antifungal, antioxidant, fluorescence, imidazo[1,2-a]pyridine, multicomponent reaction

1 | INTRODUCTION

The importance of heterocyclic compounds is directly associated with the structures that are frequently found in medicines (Jeong & Balwe, 2018). In the family of heterocyclic compounds, the nitrogen atom containing fused bicyclic or tricyclic scaffolds possess very high reactivity (Flick et al., 2017), which in turn considerably influences their interaction with the biological targets (Jordan & Roughley, 2009). The *N*-Heterocyclic frameworks are amenable chemical structures used as a "probe" and a "tool" to discover a new lead in medicinal chemistry. Imidazo[1,2-a]pyridines are one of the most widely used *N*-heterocyclics and have depicted significant biological activities (Tan & Wang, 2020) relevant to medicinal applications. Besides their biological application, the core also has many applications in electronic devices (Chen et al., 2017). Additionally, these *N*-heterocyclic often form a complex π-conjugated system and consequently serve as fluorophores (Benson et al., 2019). Therefore, owing to their robust applications, the development of Nitrogen-rich novel heterocyclic compounds is highly desirable.

Plant Cell Reports
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FOCUS ARTICLE

Engineering the AEG1 promoter from cotton to develop male sterile lines

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Received: 19 March 2021 / Accepted: 24 April 2021

Abstract

Keymessage A promoter expressing in anther and roots is made anther specific. The modified promoter is used to drive barnase gene and develop male sterile lines.

Tapetum specific promoters are key to develop *barnase* and *barstar* gene based male sterile and restorer lines for production of hybrid seeds (Mariani et al. 1992). The *Nicotiana tabacum* (tobacco) TA29 promoter has been used to develop male sterile and restorer lines in crops like *Brassica juncea* (Jagannath et al. 2001, 2002). To expand the technology for cotton, our laboratory identified the Anther Expressing Gene 1 (*AEG1*, Paritosh et al. 2018), which from a microarray-based comparative analysis of the transcriptome from different tissues was found to express in anthers from *Gossypium hirsutum*. In situ hybridization showed presence of *AEG1* transcripts in the tapetum. Cotton transgenic lines carrying 1.5 Kb region upstream of the open reading frame (URM, Upstream Regulatory Module) to drive an intron containing *β-glucuronidase* gene (Gi) as reporter confirmed GUS activity in tapetum. However, GUS activity was also observed in roots (Paritosh et al. 2018). This made the URM unsuitable to drive *barnase* gene, which expresses a cytotoxic protein and, therefore, expression in roots would be highly undesirable. Analysis of the 1.5 Kb URM for presence of different *cis*-elements showed that apart from elements like POLLEN1LELAT52 and GTGANT10 observed in genes expressed in anthers, it also contained multiple copies of the *cis*-element, ROOTMOTIFTAPOX1. This root motif with a consensus sequence of 'ATATT' is observed in the rolD promoter of *Agrobacterium rhizogenes*, which is strongly expressed in tobacco roots (Elmayan and Tepfer 1995). It is also present in promoter of the root-specific wheat peroxidase (Elmayan and Tepfer 1995) and *Arabidopsis glycosyltransferase* genes (Vijaybhaskar et al. 2008). A total of 12 motifs were observed, 9 of which were clustered between −285 and −452 bp region and three at −53, −97 and −237 positions of the URM (Fig. 1a).

Here, we engineered the wild-type URM of AEG1 [called AEG1(1.5)] to make its expression tapetum specific. We developed two different URMs: (i) AEG1(ΔB), wherein the cluster of nine root motifs in the −285 and −452 bp region were deleted by removing a DNA fragment flanked by *Pac*I sites at −242 and −631 bp and (ii) AEG1(ΔBmut), wherein the three proximal root motifs were mutated in the background of AEG1(ΔB), thus removing all the root motifs in AEG1(1.5) URM (Fig. 1a). The activity of these URMs was studied in transgenic tobacco lines using the Gi reporter or an intron containing *barnase* gene (Bi). Tobacco, rather than cotton was used because of ease in generating multiple transgenic lines in a shorter time. Further, Bi was used a reporter in addition to Gi as (i) the *barnase* gene gives a more sensitive read-out for tissue specificity (Sharma et al. 2018) and (ii) would allow testing the possibility of developing male sterile lines using the engineered URMs. Constructs having Gi under the control of CaMV 35S promoter (35S:Gi) and Bi under the control of tapetum specific promoter TA29 (TA29:Bi) were used as controls. Eight different expression cassettes were developed in the binary vector pPZP200N (Fig. 1b). Following *Agrobacterium*-mediated transformation the activity of the URM in the URM:Gi lines was monitored through histochemical and biochemical assay of

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Molecular Plant Pathology WILEY

ORIGINAL ARTICLE

Extra-large G-proteins influence plant response to *Sclerotinia sclerotiorum* by regulating glucosinolate metabolism in *Brassica juncea*

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Abstract

Heterotrimeric G-proteins are one of the highly conserved signal transducers across phyla. Despite the obvious importance of G-proteins in controlling various plant growth and environmental responses, there is no information describing the regulatory complexity of G-protein networks during pathogen response in a polyploid crop. Here, we investigated the role of extra-large G-proteins (XLGs) in the oilseed crop *Brassica juncea*, which has inherent susceptibility to the necrotrophic fungal pathogen *Sclerotinia sclerotiorum*. The allotetraploid *B. juncea* genome contains multiple homologs of three *XLG* genes (two *BjuXLG1*, five *BjuXLG2*, and three *BjuXLG3*), sharing a high level of sequence identity, gene structure organization, and phylogenetic relationship with the progenitors' orthologs. Quantitative reverse transcription PCR analysis revealed that *BjuXLGs* have retained distinct expression patterns across plant developmental stages and on *S. sclerotiorum* infection. To determine the role of *BjuXLG* genes in the *B. juncea* defence response against *S. sclerotiorum*, RNAi-based suppression was performed. Disease progression analysis showed more rapid lesion expansion and fungal accumulation in BjuXLG-RNAi lines compared to the vector control plants, wherein suppression of *BjuXLG3* homologs displayed more compromised defence response at the later time point. Knocking down *BjuXLGs* caused impairment of the host resistance mechanism to *S. sclerotiorum*, as indicated by reduced expression of defence marker genes *PDF1.2* and *WRKY33* on pathogen infection. Furthermore, BjuXLG-RNAi lines showed reduced accumulation of leaf glucosinolates on *S. sclerotiorum* infection, wherein aliphatic glucosinolates were significantly compromised. Overall, our data suggest that *B. juncea XLG* genes are important signalling nodes modulating the host defence pathways in response to this necrotrophic pathogen.

KEYWORDS

Brassica juncea, extra-large G-proteins (XLG), glucosinolates, plant defence, *Sclerotinia sclerotiorum*

Transgenic Res
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ORIGINAL PAPER

Expression of barley oxalate oxidase confers resistance against *Sclerotinia sclerotiorum* in transgenic *Brassica juncea* cv Varuna

Rashmi Verma · Jagreet Kaur

Received: 29 July 2020 / Accepted: 21 January 2021

Abstract *Sclerotinia* Stem Rot (SSR) caused by the oxalic acid (OA)-secreting necrotrophic fungal pathogen *Sclerotinia sclerotiorum,* causes significant yields losses in the crop *Brassica sps*. Oxalate oxidase (OxO) can metabolize OA to CO_2 and H_2O_2. Degradation of OA during the early phase of fungal–host interaction can interfere with the fungal infection and establishment processes. The present study demonstrates the potential of barley oxalate oxidase (*BOxO*) gene in conferring stable resistance against stem rot in a productive and highly susceptible *Brassica juncea* cv Varuna under field conditions. Four stable, independent, single-copy transgenic lines (B16, B17, B18, and B53) exhibited a significant reduction in the rate of lesion expansion i.e. 11–26%, 39–47%, and 24–35% reproducibly over the three-generation i.e. T_2, T_3, and T_4 respectively. The enhanced resistance in the transgenic lines correlated with high OxO activity, accumulation of higher levels of H_2O_2, and robust activation of defense responsive genes upon infection by *S. sclerotiorum.*

Supplementary Information The online version contains supplementary material available at (https://doi.org/10.1007/s11248-021-00234-1).

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Keywords Barley oxalate oxidase · *Brassica juncea* · *Sclerotinia sclerotiorum* · Oxalic acid · *Sclerotinia* stem rot (SSR)

Abbreviations

bp	Base pairs
bar	Bialaphos resistance
CaMV	Cauliflower Mosaic Virus
cDNA	Complementary DNA
SCF	*Sclerotinia* culture filtrates
cm	Centimeter
cv	Cultivar
DAB	3,3′-Diaminobenzidine
dpi	Days post infection
hpi	Hours post infection
L	Litre
mg	Milligram
O/N	Overnight
ROS	Reactive oxygen species
RT-PCR	Reverse transcription PCR
$T_1/T_2/T_3/T_4$	Transgenic generation 1,2,3,4
T-DNA	Transfer DNA
WT	Wild type
V/v	Volume/volume

Introduction

Sclerotinia stem rot (SSR) is a serious disease of oilseed mustard (*Brassica juncea)* reported from

MRX8, the conserved mitochondrial YihA GTPase family member, is required for de novo Cox1 synthesis at suboptimal temperatures in *Saccharomyces cerevisiae*

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ABSTRACT The synthesis of Cox1, the conserved catalytic-core subunit of Complex IV, a multisubunit machinery of the mitochondrial oxidative phosphorylation (OXPHOS) system under environmental stress, has not been sufficiently addressed. In this study, we show that the putative YihA superfamily GTPase, Mrx8, is a bona fide mitochondrial protein required for Cox1 translation initiation and elongation during suboptimal growth condition at 16°C. Mrx8 was found in a complex with mitochondrial ribosomes, consistent with a role in protein synthesis. Cells expressing mutant Mrx8 predicted to be defective in guanine nucleotide binding and hydrolysis were compromised for robust cellular respiration. We show that the requirement of Pet309 and Mss51 for cellular respiration is not bypassed by overexpression of Mrx8 and vice versa. Consistently the ribosomal association of Mss51 is independent of Mrx8. Significantly, we find that *GTPBP8*, the human orthologue, complements the loss of cellular respiration in Δ*mrx8* cells and GTPBP8 localizes to the mitochondria in mammalian cells. This strongly suggests a universal role of the *MRX8* family of proteins in regulating mitochondrial function.

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INTRODUCTION

Mitochondrial proteome is a composite of proteins encoded by its genome and the nuclear genome. Cells maintain at least two distinct translation systems to achieve this; one in the cytoplasm and one in the mitochondria. The cytosolic translation apparatus is responsible for the expression of the bulk of the mitochondrial proteome, while the mitochondrial translation apparatus is required for expression of only a small subset of open reading frames that are retained in the mitochondria (Ott *et al.*, 2016). In *Saccharomyces cerevisiae*, mitochondrial DNA (mtDNA) encodes eight polypeptides, of which seven are involved in oxidative phosphorylation (OXPHOS) and ATP synthesis and one is the component of the small ribosome (Kurland and Andersson, 2000). Components that make up the mitochondrial translation system, including ribosomal proteins, are encoded by a set of nuclear genes that are separate from those encoding the cytosolic protein synthesis apparatus (Amunts *et al.*, 2014; Desai *et al.*, 2017). These are translated in the cytosol and imported into the mitochondria, where they are assembled into macromolecular complexes in a coordinated manner to incorporate mitochondrially expressed rRNAs (15S and 21S) at the correct stoichiometry. This allows for the tight regulation of the mitochondrial gene expression machinery by the nuclear genome (Couvillion *et al.*, 2016).

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Author contributions: Y.V., U.M., D.K.P, and J.K. performed experiments. Y.V., S.S.J., and K.D. analyzed data. X.P.-M. created some strains. Y.V. and K.D. conceived the project, designed experiments, analyzed the data, and wrote the paper.

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Abbreviations used: CDS, coding sequence; EGFP, enhanced green fluorescent protein; UTR, untranslated region.

Prof. Thelma B.K

Human Heritable Genome Editing-Potential and Current Status for Clinical Use.

Authors Navneesh Yadav, BK Thelma

Publication date 2021/3/1

Journal Asian Biotechnology & Development Review

Volume 23

Issue 1

Description Medical genomics has moved significantly from human genome sequencing project uncovering millions of variations across the genome to identifying disease specific variants in a substantial number of human genetic disorders. Understanding the molecular basis of single gene disorders (SGDs) in particular, has opened up possibilities of i) notable prediction and prevention with powerful diagnostic tool development and ii) improved cure/treatment. The revolutionary Nobel prize winning CRISPR/Cas9 based genome editing tool to precisely correct a disease causing mutation in somatic or germ cells is the recent one in personalised medicine. This technology has immense applications across life sciences but its clinical use, in human heritable genome editing (HHGE) in particular combined with Assisted Reproductive Technology and Pre-implantation diagnostics should be tread with caution. Scientific evidence for its safety, specificity, efficacy; the consequences of potential off-targets; and more insights into human embryogenesis are essential for its clinical translation. In this paper, we address these issues and highlight the rare group of prospective parents with a SGD where HHGE is the only option to have a healthy biological (genetically related) child. A brief note on the current limitations and the accompanying ethical issues of this technology for clinical use is also added.

Prof. Thelma B.K

Association of g-quadruplex variants with schizophrenia symptoms

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Authors Upasana Bhattacharyya, Triptish Bhatia, Smita N Deshpande, BK Thelma

Publication date 2022/5

Journal Schizophrenia research

Volume 243

Pages 361

Publisher NIH Public Access

Description Schizophrenia is heterogenous, both genetically and in positive-negative symptom manifestation (Takahashi, 2013) as assessed by SAPS (Kumari et al., 2017) and SANS (Kumari et al., 2017) respectively. Genetic studies employing factor scores derived from symptom scales showed improved clinical homogeneity among cases with promising results (Xavier and Vorderstrasse, 2017). Genome-wide or candidate gene-based association studies with either the primary disease (Huo et al., 2019) or symptoms (Edwards et al., 2016; Fanous et al., 2012) revealed that many of the risk conferring loci are in noncoding regions. Associations of different classes of variants in or around such associated loci have been investigated, but one class of variants termed Quad-SNPs present in G-Quadruplex regions (G4) with a potential to impact gene expression through altered DNA secondary structure (Baral et al., 2012), remain …

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Genetic variations in evolutionary accelerated regions disrupt cognition in schizophrenia

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Authors Upasana Bhattacharyya, Triptish Bhatia, Smita N Deshpande, BK Thelma

Publication date 2022/8/1

Journal Psychiatry Research

Volume 314

Pages 114586

Publisher Elsevier

Description Cognition is believed to be a product of human evolution, while schizophrenia is ascribed as the by-product with cognitive impairment as it's genetically mediated endophenotype. Genomic loci associated with these traits are enriched with recent evolutionary markers such as Human accelerated regions (HARs). HARs are markedly different in humans since their divergence with chimpanzees and mostly regulate gene expression by binding to transcription factors and/or modulating chromatin interactions. We hypothesize that variants within HARs may alter such functions and thus contribute to disease pathogenesis. 49 systematically prioritized variants from 2737 genome-wide HARs were genotyped in a north-Indian schizophrenia cohort (331 cases, 235 controls). Six variants were significantly associated with cognitive impairment in schizophrenia, thirteen with general cognition in healthy individuals. These ...

RESEARCH ARTICLE

Editorial Process: Submission:06/17/2022 Acceptance:10/24/2022

SNP rs9387478 at ROS1-DCBLD1 Locus is Significantly Associated with Lung Cancer Risk and Poor Survival in Indian Population

Jonita Chongtham[1], Namita Pandey[1,2], Lokesh Kumar Sharma[3], Anant Mohan[4], Tapasya Srivastava[1]*

Abstract

Objective: Receptor tyrosine kinases (RTK) are relevant therapeutic targets in the treatment of lung cancer. Germline susceptibility variants that influence these RTKs may provide new insights into their regulation. rs9387478 is located in the genomic interval between two RTK-genes ROS1/DCBLD1, of which ROS1 alterations are implicated in lung carcinogenesis and treatment response while the latter remains poorly understood. **Materials and methods:** Venous blood was drawn from 100 control and 231 case subjects. Genotype was scored by restriction fragment length polymorphism (RFLP), PCR amplification followed by HindIII digestion. Logistic regression was applied to compare the association between variables. Survival curve was plotted to draw a correlation between the genotype and overall survival. Also, eQTL and chromatin state changes were analyzed and correlated with the survival of patients using available datasets. **Results:** In our population smoking correlated significantly with lung cancer [OR= 2.607] with the presence of the minor allele 'A' enhancing the nicotine dependence [CA (OR=3.23)]. Individuals with homozygous risk allele 'A' had a higher chance of developing lung cancer [OR=2.65] than individuals with CA/CC implying a recessive model of association. Patients with CC/CA genotype had better overall survival than patients with AA genotype [161 days/142 days vs 54 days, p=0.005]. The homozygous risk allele was significantly associated with increased DCBLD1 and ROS1 expression in lung cancer, with enriched active histone marks due to the polymorphism. Interestingly, increased DCBLD1 expression was associated with poor outcomes in lung cancer. **Conclusion:** Overall, our study provides strong evidence that rs9387478 is significantly associated with both nicotine dependence and lung cancer in our North Indian cohort. The association of the SNP with prognostic genes, DCBLD1 and ROS1 make rs9387478 a promising prognostic marker in the North Indian population. The results obtained are significant, however, the study needs to be performed in a larger sample size.

Keywords: Lung cancer- smoking- overall survival- rs9387478- ROS1- DCBLD1

Asian Pac J Cancer Prev, **23 (10)**, 3553-3561

Introduction

Lung cancer which accounts for 11.4% (one in 10 cancers diagnosed) of the total cancer incidence and 18% (one in 5 deaths) of the total cancer mortality is one of the most common malignancies in adults (Sung et al., 2021). According to GLOBOCAN 2021, India reported 1,324,413 new lung cancer cases and 851,678 mortalities (Sung et al., 2021). While a decline in lung cancer is seen globally (Islam et al., 2015), the incidence in India is increasing with most cases exhibiting an advanced disease state at the time of diagnosis explaining the high lung cancer morbidity in India (Mohan et al., 2020). The decrease in global lung cancer incidence can be attributed to the decline in overall tobacco use (WHO Global report) the highest risk factor for lung cancers. However, 14.8% of adults in Indian population use tobacco in different forms (WHO 2020), which along with other environmental factors such as pollution and lifestyle contribute to the growing burden of lung cancer in India. Various high-throughput genome-wide association studies (GWAS) of SNPs and candidate genes have powered our understanding of the genetic component of lung cancer (Stadler et al., 2010; Wang et al, 2017). Additionally, expression quantitative trait loci (eQTL) studies have shown the influence of SNP on gene expression and

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Stratification of rheumatoid arthritis cohort using Ayurveda based deep phenotyping approach identifies novel genes in a GWAS

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Authors Garima Juyal, Anuj Pandey, Sara L Garcia, Sapna Negi, Ramneek Gupta, Uma Kumar, Bheema Bhat, Ramesh C Juyal, BK Thelma

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Journal Journal of Ayurveda and Integrative Medicine

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Description Background and aim

Genome wide association studies have scaled up both in terms of sample size and range of complex disorders investigated, but these have explained relatively little phenotypic variance. Of the several reasons, phenotypic heterogeneity seems to be a likely contributor for missing out genetic associations of large effects. Ayurveda, the traditional Indian system of medicine is one such tool which adopts a holistic deep phenotyping approach and classifies individuals based on their body constitution/prakriti. We hypothesized that Ayurveda based phenotypic stratification of healthy and diseased individuals will allow us to achieve much desired homogeneous cohorts which would facilitate detection of genetic association of large effects. In this proof of concept study, we performed a genome wide association testing of clinically diagnosed rheumatoid arthritis patients and healthy controls, who were re ...

Total citations Cited by 1

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Scholar articles Stratification of rheumatoid arthritis cohort using Ayurveda based deep phenotyping approach identifies novel genes in a GWAS
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Prof. Thelma B.K

Genetic affinities and sub-structuring in Coorg population of Southern India

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Authors Anirban Mukhopadhyay, Lomous Kumar, Kiran Sran, Kumarasamy Thangaraj, BK Thelma

Publication date 2022

Journal bioRxiv

Pages 2022.07. 20.500704

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Description The Coorgs, also known as Kodavas, are one of the smallest religious and socio-culturally homogenous communities in the world, currently residing in the state of Karnataka, India. Due to a stark contrast with the surrounding subpopulations, their genetic architecture and population & demographic history have been a matter of debate for long. To better understand the population structure and demographic history of this caste group, we analysed the population, using high-resolution autosomal (n=70) as well uniparentally inherited markers (Y-chromosomal and mitochondrial DNA) (n=144). Our first ever findings elucidate that origin of Coorgs traces back to early or middle Bronze Age. We further found population substructure among Coorgs, which manifested as three distinct clusters in a Principal component analysis. One of these subgroups has undergone a rare and immense amount of population-specific drift but all three eventually admixed, both genetically and socio-culturally. The mtDNA analysis showed 40% South Asian-specific mitochondrial lineages among Coorgs; while the Y-chromosomal analysis revealed predominant presence of Eurasian, Middle-Eastern and Indian-specific haplogroups suggesting male-centric migration and eventual assimilation with local females. Our results for the first time identify these ancient and distinct genealogies that make up the contemporary Coorgs and may explain the socio-cultural differences with their immediate and distant neighbours in the country and the prevalent narrative history. In a wider context, the study also reveals an ancient, yet unknown, Middle Eastern source population that might …

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Research paper

When "No-Smoking" is not enough: Hypoxia and nicotine acetylcholine receptor signaling may drive lung adenocarcinoma progression in never-smokers

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ARTICLE INFO

Keywords:
Hypoxia
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Neversmokers

ABSTRACT

The question of how lung cancer progresses in never-smokers remains largely unanswered. In our analysis of data from 1727 lung cancer patients, we observed a difference of only 47 days in the overall survival between lung adenocarcinoma patients who were smokers vis-a-vis never-smokers - the disease has a poor prognosis irrespective of the smoking status, or gender. We have investigated the possible collaboration between the nAChR and hypoxia signaling pathway to explicate a mechanism of disease progression in never-smokers using patient-derived tumor cells. We found a previously unidentified increase in both acetylcholine and *nAChR-α7* levels in non-small cell lung cancer cells in hypoxia. A similar increase in ubiquitously expressed *nAChR-α7* transcripts was also observed in other cancer lines and primary tumor tissues. A direct binding of HIF-1α with the hypoxia-response element (HRE) present at −48 position preceding the transcriptional start site in *nAChR-α7* promoter region was established. Crucially, the increased acetylcholine levels in hypoxia drove a feedback loop via modulation of PI3K/AKT pathway to stabilize HIF-1α in hypoxia. Further, hypoxia-mediated metastasis and induction of HIF-1α in these cells was significantly reversed by bungarotoxin, an antagonist of *nAChR-α7*. The nAChR-AKT-HIF network needs to be further investigated to conclusively prove its mechanism and to explore its therapeutic potential. Our study gives a plausible explanation for the equally worse prognosis of lung adenocarcinoma in never-smokers wherein the *nAChR* signaling is enhanced in hypoxia by acetylcholine in the absence of nicotine.

1. Introduction

A perplexing gap in our understanding of lung cancer remains: how does the disease progress in never-smokers? In the case of lung adenocarcinoma, the patients were observed to have a more aggressive form of tumor at the time of diagnosis [1] and one that metastasized more often to the lung pleura [2]. Mirroring the global trend, there has been a considerable increase in the number of lung cancer - especially adenocarcinoma - cases among patients in India who do not, and have never, consumed tobacco [3]. The growing number of lung cancer cases in never-smokers, their unique molecular profile and response to therapy, prompted us to study non-tobacco related risk factors and the progression of the disease in them [4].

nAChRs are ubiquitously expressed [5] ligand-gated cation channels that form pentameric structures assembled from a family of subunits that include α1-α10 and β1-β4 encoded by the CHRNA gene family [6]. Importantly, they are activated in response to both endogenous neurotransmitter acetylcholine (ACh) and exogenous agonists, such as

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New druggable targets for rheumatoid arthritis based on insights from synovial biology

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Pages	834247
Publisher	Frontiers
Description	Rheumatoid arthritis (RA) is a multifactorial autoimmune disease characterized by chronic inflammation and destruction of multiple small joints which may lead to systemic complications. Altered immunity via pathogenic autoantibodies pre-date clinical symptom development by several years. Incompletely understood range of mechanisms trigger joint-homing, leading to clinically evident articular disease. Advances in therapeutic approaches and understanding pathogenesis have improved prognosis and likely remission. However, partial/non-response to conventional and biologic therapies witnessed in a subset of patients highlights the need for new therapeutics. It is now evident that joint disease chronicity stems from recalcitrant inflammatory synovial environment, majorly maintained by epigenetically and metabolically reprogrammed synoviocytes. Therefore, interference with effector functions of activated cell types seems a rational strategy to reinstate synovial homeostasis and complement existing anti-inflammatory interventions to mitigate chronic RA. Presenting this newer aspect of fibroblast-like synoviocytes and myeloid cells underlying the altered synovial biology in RA and its potential for identification of new druggable targets is attempted in this review. Major leads from i) molecular insights of pathogenic cell types from hypothesis free OMICS approaches; ii) hierarchy of their dysregulated signaling pathways; and iii) knowledge of druggability of molecular nodes in these pathways are highlighted. Development of such synovial biology-directed therapeutics hold promise for an enriched drug repertoire for RA.
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Computational insight into the three-dimensional structure of ADP ribosylation factor like protein 15, a novel susceptibility gene for rheumatoid arthritis

Authors Aditya Sharma, Manisha Saini, Suman Kundu, BK Thelma

Publication date 2022/6/21

Journal Journal of Biomolecular Structure and Dynamics

Volume 40

Issue 10

Pages 4626-4641

Publisher Taylor & Francis

Description The ARL15 gene (ADP ribosylation factor like protein 15) encodes for an uncharacterized small GTP-binding protein. Its exact role in human physiology remains unknown, but a number of genetic association studies have recognised different variants in this gene to be statistically associated with numerous traits and complex diseases. We have previously reported a novel association of *ARL15* with rheumatoid arthritis (RA) based on a genome-wide association study in a north Indian cohort. Subsequent investigations have provided leads for its involvement in RA pathophysiology, especially its potential as a novel therapeutic target. However, the absence of an experimentally determined tertiary structure for ARL15 significantly hinders the understanding of its biochemical and physiological functions, as well as development of potential lead molecules. We, therefore, aimed to derive a high quality, refined model of ...

Microhomology-mediated endjoining repair mechanism enables rapid and effective indel generations in stem cells

Authors	Navneesh Yadav, BK Thelma
Publication date	2022/12/10
Journal	Journal of Biosciences
Volume	47
Issue	4
Pages	72
Publisher	Springer India
Description	Functional characterization of gene(s) using a transgene approach in a human cell line or in an animal model generally poses limitations due to persistent transgene overexpression. Conversely, the CRISPR/Cas9 gene-editing technology enables precise variant(s) introduction in a gene, thus facilitating accurate characterization in human iPSC-derived target cell/tissue. Such editing is generally mediated by non-homologous end joining, the predominant and error-prone double-strand break repair mechanism which mostly results in gene knockout due to indel(s) generation. However, in most cases the best *in silico* predicted sgRNAs fail to generate indels especially in iPSCs, encouraging a revisit of DNA damage repair principles. Microhomology-mediated end joining (MMEJ) is another error-prone repair mechanism which relies on exposed microhomologous sequences flanking the broken ends to fix double …
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Transethnic analysis of psoriasis susceptibility in South Asians and Europeans enhances fine mapping in the MHC and genome wide

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Authors Philip E Stuart, Lam C Tsoi, Rajan P Nair, Manju Ghosh, Madhulika Kabra, Pakeeza A Shaiq, Ghazala K Raja, Raheel Qamar, BK Thelma, Matthew T Patrick, Anita Parihar, Sonam Singh, Sujay Khandpur, Uma Kumar, Michael Wittig, Frauke Degenhardt, Trilokraj Tejasvi, John J Voorhees, Stephan Weidinger, Andre Franke, Goncalo R Abecasis, Vinod K Sharma, James T Elder

Publication date 2022/1/13

Journal Human Genetics and Genomics Advances

Volume 3

Issue 1

Publisher Elsevier

Description Because transethnic analysis may facilitate prioritization of causal genetic variants, we performed a genome-wide association study (GWAS) of psoriasis in South Asians (SAS), consisting of 2,590 cases and 1,720 controls. Comparison with our existing European-origin (EUR) GWAS showed that effect sizes of known psoriasis signals were highly correlated in SAS and EUR (Spearman $\rho = 0.78$; $p < 2 \times 10^{-14}$). Transethnic meta-analysis identified two non-major histocompatibility complex (non-MHC) psoriasis loci (1p36.22 and 1q24.2) not previously identified in EUR, which may have regulatory roles. For these two loci, the transethnic GWAS provided higher genetic resolution and reduced the number of potential causal variants compared to using the EUR sample alone. We then explored multiple strategies to develop reference panels for accurately imputing MHC genotypes in both SAS and EUR populations and …

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A novel leaky splice variant in centromere protein J (*CENPJ*)-associated Seckel syndrome

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Authors Navneesh Yadav, Laxmi Kirola, Thenral S Geetha, Kirti Mittal, Jayarama Kadandale, Yuval Yogev, Ohad S Birk, Neerja Gupta, Prahlad Balakrishnan, Manisha Jana, Meena Gupta, Madhulika Kabra, Bittianda Kuttapa Thelma

Publication date 2022/9

Journal Annals of Human Genetics

Volume 86

Issue 5

Pages 245-256

Description Abstract

Primary microcephaly and Seckel syndrome are rare genetically and clinically heterogenous brain development disorders. Several exonic/splicing mutations are reported for these disorders to date, but ~40% of all cases remain unexplained. We aimed to uncover the genetic correlate(s) in a family of multiple siblings with microcephaly. A novel homozygous intronic variant (NC_000013.10:g.25459823T>C) in *CENPJ* (13q12) segregating with all four affected male siblings was identified by exome sequencing and validated by targeted linkage approach (logarithm of the odds score 1.8 at θ 0.0). RT-PCR of *CENPJ* in affected siblings using their EBV derived cell lines showed aberrant transcripts suggestive of exon skipping confirmed by Sanger sequencing. Significantly reduced wild type transcript/protein in the affected siblings having the splice variant indicates a leaky gene expression of pathological ...

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Mutation spectrum and enzyme profiling of G6PD deficiency in neonates of north India: a prospective study

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Authors Upasana Bhattacharyya, Preeti Deswal, Sunil Kumar Polipalli, Diksha Sharma, Manpreet Kaur, Seema Kapoor, BK Thelma

Publication date 2023/8/7

Journal Journal of Genetics

Volume 102

Issue 2

Pages 40

Publisher Springer India

Description Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common X-linked disorder with well-established clinical and allelic heterogeneity and ethnic disparity. With ~390,000 annual births with G6PD deficiency in India, it emerges as the most predictable and preventable inborn metabolic error. Disease prevalence and mutation spectrum have been reasonably reported from central, western and southern parts of India and are mostly retrospective studies. Although prevalence data from north India is available, there is paucity of data on the mutation spectrum and genotype–phenotype correlation (G×P). Thus, we aimed at establishing the clinical and mutation profiles for *G6PD*, as a part of a large prospective newborn screening study conducted between 2014 and 2016 across hospitals in Delhi, India. G6PD activity levels were measured at 24–48 h of life for ~200,000 neonates using Victor 2D and/or Genomic ...

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HLA-DP on Epithelial Cells Enables Tissue Damage by NKp44+ Natural Killer Cells in Ulcerative Colitis

Authors Martin E Baumdick, Annika Niehrs, Frauke Degenhardt, Maria Schwerk, Ole Hinrichs, Ana Jordan-Paiz, Benedetta Padoan, Lucy HM Wegner, Sebastian Schloer, Britta F Zecher, Jakob Malsy, Vinita R Joshi, Christin Illig, Jennifer Schröder-Schwarz, Kimberly J Möller, Alaa Akar, Cornelius Flemming, Markus Flosbach, Julia Jäger, Niklas Jeromin, Johannes Jung, Mareike Ohms, Konrad Reinshagen, Johann Rische, Adrian Sagebiel, Deborah Sandfort, Fenja Steinert, Christian Tomuschat, Jasmin Wesche, Maureen Martin, Yuko Yuki, Mikki Ozawa, Jürgen Sauter, Alexander H Schmidt, Daniel Perez, Anastasios D Giannou, Mary Carrington, Randall S Davis, Udo Schumacher, Guido Sauter, Samuel Huber, Victor G Puelles, Nathaniel Melling, Andre Franke, Shifteh Abedian, Clara Abraham, Jean-Paul Achkar, Tariq Ahmad, Rudi Alberts, Behrooz Alizadeh, Leila Amininejad, Ashwin N Ananthakrishnan, Vibeke Andersen, Carl A Anderson, Jane M Andrews, Vito Annese, Guy Aumais, Leonard Baidoo, Robert N Baldassano, Peter A Bampton, Murray Barclay, Jeffrey C Barrett, Johannes Bethge, Claire Bewshea, Joshua C Bis, Alain Bitton, BK Thelma, Gabrielle Boucher, Oliver Brain, Stephan Brand, Steven R Brant, Jae Hee Cheon, Angela Chew, Judy H Cho, Isabelle Cleynen, Ariella Cohain, Rachel Cooney, Anthony Croft, Mark J Daly, Mauro D'Amato, Silvio Danese, Naser Ebrahim Daryani, Lisa Wu Datta, Goda Denapiene, Lee A Denson, Kathy L Devaney, Olivier Dewit, Renata D'Inca, Hazel E Drummond, Marla Dubinsky, Richard H Duerr, Cathryn Edwards, David Ellinghaus, Pierre Ellul, Motohiro Esaki, Jonah Essers, Lynnette R Ferguson, Eleonora A Festen, Philip Fleshner, Tim Florin, Denis Franchimont, Yuta Fuyuno, Richard Gearry, Michel Georges, Christian Gieger, Jürgen Glas, Philippe Goyette, Todd Green, Anne M Griffiths, Stephen L Guthery, Hakon Hakonarson, Jonas Halfvarson, Katherine Hanigan, Talin Haritunians, Ailsa Hart, Chris Hawkey, Nicholas K Hayward, Matija Hedl, Paul Henderson, Georgina L Hold, Myhunghee Hong, Xinli Hu, Hailiang Huang, Jean-Pierre Hugot, Ken Y Hui, Marcin Imielinski, Omid Jazayeri, Laimas Jonaitis, Luke Jostins, Garima Juyal, Ramesh Chandra Juyal, Rahul Kalla, Tom H Karlsen, Nicholas A Kennedy, Mohammed Azam Khan, Won Ho Kim, Takanari Kitazono, Gediminas Kiudelis, Michiaki Kubo, Subra Kugathasan, Limas Kupcinskas, Christopher A Lamb, Katrina M de Lange, Anna Latiano, Debby Laukens, Ian C Lawrance, James C Lee, Charlie W Lees, Marcis Leja, Nina Lewis

Publication date 2023/7/15

Journal Gastroenterology

Publisher WB Saunders

Description Background & Aims

Ulcerative colitis (UC) is characterized by severe inflammation and destruction of the intestinal epithelium, and associated with risk of single nucleotide polymorphism in HLA class II. Given the recently discovered interactions between subsets of HLA-DP molecules and the activating natural killer (NK) cell receptor NKp44, genetic associations of UC and HLA-DP haplotypes and their functional implications were investigated.

Methods

HLA-DP haplotype and UC risk association analyses were performed (UC: n = 13,927; control: n = 26,764). Expression levels of HLA-DP on intestinal epithelial cells (IECs) in individuals with and without UC were quantified. Human intestinal 3-dimensional (3D) organoid co-cultures with human NK cells were used to determine functional consequences of interactions between HLA-DP and NKp44.

Results

These studies identified *HLA-DPA1*01:03-DPB1*04:01* (*HLA* ...

Scholar articles HLA-DP on Epithelial Cells Enables Tissue Damage by NKp44+ Natural Killer Cells in Ulcerative Colitis
ME Baumdick, A Niehrs, F Degenhardt, M Schwerk... - Gastroenterology, 2023
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RESEARCH PAPER

Downregulation of lncRNA *SNHG1* in hypoxia and stem cells is associated with poor disease prognosis in gliomas

Sanchit Gandhi[a,*], Ashish Bhushan[a,*], Unmesh Shukla[b], Amit Pundir[c], Sanjeev Singh[b], and Tapasya Srivastava[a]

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ABSTRACT

Gliomas are brain tumors associated with high morbidity, relapse and lethality despite improvement in therapeutic regimes. The hypoxic tumor microenvironment is a key feature associated with such poor outcomes in gliomas. The Hypoxia Inducible Factor (HIF) family of transcription factors are master regulators of cellular proliferation, high metabolic rates and angiogenesis via aberrant expression of downstream genes. Recent studies have implicated long non-coding RNAs (lncRNAs) as potential prognostic and diagnostic biomarkers. In this study, identification of hypoxia regulated lncRNA with a bioinformatic pipeline consisting of a newly developed tool "GenOx" was utilized for the identification of Hypoxia Response Element (HRE) and Hypoxia Ancillary Sequence (HAS) motifs in the promoter regions of lncRNAs. This was coupled with molecular, functional and interactome-based analyses of these hypoxia-relevant lncRNAs in primary tumors and cell-line models. We report on the identification of novel hypoxia regulated lncRNAs *SNHG12*, *CASC7* and *MF12-AS1*. A strong association of RNA splicing mechanisms was observed with enriched lncRNAs. Several lncRNAs have emerged as prognostic biomarkers, of which *TP53TG1* and *SNHG1* were identified as highly relevant lncRNAs in glioma progression and validated in hypoxia cultured cells. Significantly, we determined that *SNHG1* expression in tumor (vs. normal) is different from glioma stem cells, GSC (vs. tumors) and in hypoxia (vs. normoxia), positioning downregulation of *SNHG1* to be associated with worsened prognosis.

ARTICLE HISTORY
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KEYWORDS
LncRNA; hypoxia; SNHG1; RNA splicing; glioma; glioma stem cells

Introduction

Solid tumors develop in niche hypoxic regions that are often associated with poor prognosis in cancers. Hypoxic stress response manifests as changes in gene expression, metabolism, pluripotent state and chemoresistance [1]. Most cancers with hypoxic interiors undergo rounds of reperfusion, further exaggerating the poor outcome. Hypoxic interiors of glioblastoma have been widely studied to be associated with poor prognosis, and enrichment of glioma stem cells. As the glioma progresses from lower grade, its histology is transmogrified from non-angiogenic to leaky angiogenic rich tissue that attempts to keep up with the uncontrolled oncogenic proliferation of cells [2]. Concurrence of nutrient deficit and chaotic vascular support leads to hypoxic stress. Hypoxia orchestrates the adaptive response by stabilizing the transcription factors of the Hypoxia Inducible Factor (HIF) family. Hypoxia utilizes HIF, the master regulator, to accomplish the perturbations in the downstream genes and thus alterations in various processes at cellular level. The promoter region is an indispensable region for a gene located upstream to the transcription start site (TSS). It consists of core, proximal and distal regions, proximal in the middle and core upstream to TSS [3]. Under hypoxic conditions, the HIF stabilizes and translocates into the nucleus. It then interacts with Hypoxia Response Element (HRE) motifs in the promoter region of the genes and affects its transcription. The localization of HREs is not limited to the promoter region but is also found in the enhancers. The proximity of HREs to TSS is of profound importance for transcriptional control of HIF transcription factors [4]. The presence of Hypoxia Ancillary Sequence (HAS) downstream in the

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Significance of an altered lncRNA landscape in schizophrenia and cognition: clues from a case–control association study

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Authors Anirban Mukhopadhyay, Smita N Deshpande, Triptish Bhatia, BK Thelma

Publication date 2023/4/3

Journal European Archives of Psychiatry and Clinical Neuroscience

Pages 1-15

Publisher Springer Berlin Heidelberg

Description Genetic etiology of schizophrenia is poorly understood despite large genome-wide association data. Long non-coding RNAs (lncRNAs) with a probable regulatory role are emerging as important players in neuro-psychiatric disorders including schizophrenia. Prioritising important lncRNAs and analyses of their holistic interaction with their target genes may provide insights into disease biology/etiology. Of the 3843 lncRNA SNPs reported in schizophrenia GWASs extracted using lincSNP 2.0, we prioritised $n = 247$ based on association strength, minor allele frequency and regulatory potential and mapped them to lncRNAs. lncRNAs were then prioritised based on their expression in brain using lncRBase, epigenetic role using 3D SNP and functional relevance to schizophrenia etiology. 18 SNPs were finally tested for association with schizophrenia ($n = 930$) and its endophenotypes—tardive dyskinesia ($n = 176$ ...

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Spray-Induced Gene Silencing of *SsOah1* and *SsCyp51* confers protection to *Nicotiana benthamiana* and *Brassica juncea* against *Sclerotinia sclerotiorum*

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Department of Genetics, University of Delhi, South Campus, Benito Juarez Marg, New Delhi- 110021, India

ARTICLE INFO

Keywords:
Brassica juncea
Cyp51
Oah1
RNAi
Sclerotinia sclerotiorum
SIGS

ABSTRACT

Brassica juncea is a major oilseed, vegetable and condiment crop in the Indian subcontinent. Its yields are compromised by the aggressive broad host range Ascomycete *Sclerotinia sclerotiorum*, which causes Sclerotinia Stem Rot (SSR). The limited effectiveness of fungicides, the rapid development of resistance to fungicides, and the long-term viability of sclerotia in the soil are crucial bottlenecks in controlling the disease. The discovery of the uptake of environmental RNA by fungal pathogens has opened up avenues for exploiting Spray-Induced Gene Silencing (SIGS) as a tool for mitigating plant diseases. We studied the impact of SIGS-based knockdown of *S. sclerotiorum SsOah1* (SS1G_08218) and *SsCyp51* (SS1G_04805), involved in virulence and fungal development, respectively, on two hosts- *N. benthamiana* and *B. juncea*. A knockdown of the two genes delayed disease initiation, reduced lesion development, and slowed disease progression within *B. juncea*. However, this silencing was concentration and host-dependent. Further, it also altered fungal hyphal morphology and growth, indicating its utility as a functional genomics tool. Our results identify *SsCyp51* as a novel and viable target for SSR control along with *SsOah1* and corroborate SIGS as a robust method for crop protection against broad-host-range fungal pathogens.

1. Introduction

Globally, agricultural losses caused by pests and pathogens necessitate extensive use of pesticides. However, their broad spectrum activity, persistent nature, and indiscriminate use have led to chemical pollution and adverse effects on non-target species. The European Commission's Farm-to-Fork strategy aims to reduce agricultural inputs such as pesticides to achieve greater sustainability in agriculture [1]. It hopes to consolidate integrated pest management strategies, artificial intelligence, precision agriculture and reduced usage of pesticides to ensure crop protection while reducing biodiversity loss. Globally, efforts to develop target-specific, environmentally conscious, and sustainable alternatives are the need of the hour.

RNA Interference (RNAi) has been proposed as a robust strategy to control fungal pathogens [2]. Host-Induced Gene Silencing (HIGS), the generation of stable transgenic crops expressing dsRNA against pests and pathogens, is favoured due to the transmittance of resistance to the progeny. However, the commercial release of transgenics has been hindered by negative public perception and associated regulatory blockages. Alternatively, Spray-Induced Gene Silencing (SIGS) is a non-transformative and environment-friendly pest and pathogen management strategy. Here, naked or nanomaterial-bound dsRNA targeting candidate genes are applied exogenously on hosts. They are taken up by pathogens [3,4] and degrade the target pathogen mRNA. The success of SIGS rests upon the ability of the pathogens to take up exogenous dsRNA, an efficient pathogen RNAi machinery, the essentiality of the gene targeted, and the length, dosage, and stability of dsRNA applied [2]. Despite a few limitations, SIGS-based anti-fungal strategies hold great promise. They can bypass several existing regulatory roadblocks and potentially reduce excessive chemical usage in agriculture. The approach has been tested in several agronomically important crops including barley, tomato, lettuce, grape, and rapeseed [3,5,6].

Sclerotinia Stem Rot (SSR) caused by the notorious generalist fungal pathogen *Sclerotinia sclerotiorum* (Lib) de Bary affects over 600 dicotyledonous plants. Indian mustard (*Brassica juncea* (L.) Czern & Coss) is aggressively attacked by *S. sclerotiorum*, with severe infections leading to 10–90% losses [7]. Infection initiates during cold and humid conditions when ascospores dispersal coincides with the onset of host flowering. The pathogenic success of *S. sclerotiorum* rests on the foundation of a complex pathogenesis strategy and secretion of an assortment of Cell

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Effect of rs1108580 of *DBH* and rs1006737 of *CACNA1C* on Cognition and Tardive Dyskinesia in a North Indian Schizophrenia Cohort

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Authors Toyanji Joseph Punchaichira, Prachi Kukshal, Triptish Bhatia, Smita Neelkanth Deshpande, BK Thelma

Publication date 2023/7/26

Journal Molecular Neurobiology

Pages 1-14

Publisher Springer US

Description Genetic perturbations in dopamine neurotransmission and calcium signaling pathways are implicated in the etiology of schizophrenia. We aimed to test the association of a functional splice variant each in *Dopamine β-Hydroxylase* (*DBH*; rs1108580) and *Calcium voltage-gated channel subunit alpha1 C* (*CACNA1C*; rs1006737) genes in these pathways with schizophrenia (506 cases, 443 controls); Abnormal Involuntary Movement Scale (AIMS) scores in subjects assessed for tardive dyskinesia (76 TD-positive, 95 TD-negative) and Penn Computerized Neurocognitive Battery (PennCNB) scores (334 cases, 234 controls). The effect of smoking status and SNP genotypes on AIMS scores were assessed using ANOVA; health status and SNP genotypes on three performance functions of PennCNB cognitive domains were assessed by ANCOVA with age and sex as covariates. Association with Positive and Negative ...

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Celiac disease-associated loci show considerable genetic overlap with neuropsychiatric diseases but with limited transethnic applicability

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Authors Nidhi Sharma, Pratibha Banerjee, Ajit Sood, Vandana Midha, BK Thelma, Sabyasachi Senapati

Publication date 2023/1/10

Journal Journal of Genetics

Volume 102

Issue 1

Pages 16

Publisher Springer India

Description Clinical and public health research has revealed the co-occurrence of several neuropsychiatric diseases among patients with celiac disease (CD). The significant presence of CD-specific autoantibodies in patients with neuropsychiatric diseases and vice versa are often reported. To explain the genetic basis of such frequent disease co-occurrence and investigate the underlying common pathways/processes, we performed an extensive cross-disease association study followed by supporting *in silico* functional validation of the leads. Genomewide association study (GWAS) data for CD and eight commonly co-occurring neuropsychiatric diseases from Caucasian populations were analysed, and the shared loci were determined. We performed Immunochip-based fine mapping of these overlapping association signals in an independent European CD data and tested their cross-ethnic transferability using CD ...

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Expression of Arabidopsis *NPR1* (*AtNPR1*) in *Brassica juncea* var Varuna confers significant resistance against *Sclerotinia sclerotiorum* and *Alternaria brassicae*

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ARTICLE INFO

Keywords:
Alternaria brassicae
Brassica juncea
Disease resistance
Non-expressor of PR genes (NPR1)
Sclerotinia sclerotiorum

ABSTRACT

The productivity of *Brassica juncea*, a major oilseed crop grown widely in South Asia, is limited by two major fungal pathogens: *Sclerotinia sclerotiorum*, and *Alternaria brassicae*. Currently, no effective resistance against these pathogens has been identified in the *B. juncea* germplasm. To improve the resistance against these fungal pathogens, Non-expressor of *PR1* (*NPR1*) from *Arabidopsis* was expressed in the mega variety Varuna via *Agrobacterium*-mediated transformation. A total of 129, independent transgenic events were generated. Segregation analysis for Basta resistance and subsequent Southern hybridization identified six single-copy transgenic lines (PN23, 42, 60, 72, HN30, and HN32) which were taken forward for disease assays over two generations. Transgenic lines challenged with *S. sclerotiorum* exhibited a significant reduction in stem lesions ranging from 13 to 42% in the T_3 generation and 4 to 31% in the T_4 generation. We also observed a reduced infection against *A. brassicae* in the transgenic lines which developed smaller and fewer necrotic lesions as compared to untransformed lines. A correlation between the upregulation of defense marker genes and enhanced tolerance was observed in the transgenic lines upon *S. sclerotiorum* infection.

1. Introduction

Brassica juncea (Indian mustard) is an important edible oilseed crop grown in diverse agroecological zones across the world. In India, *B. juncea* is grown by small landholders under rainfed and low input regimens resulting in lower average yields of around 1245 kg/ha versus the global yield of 1994 kg/ha [1]. Additionally, its productivity is challenged by fungal pathogens mainly *Albugo candida* (causing white rust), *Alternaria brassicae* (causing Alternaria leaf blight), and *Sclerotinia sclerotiorum* (causing stem rot). Among all the fungal diseases stem rot has emerged as a major threat to oilseed mustard productivity across all agronomic zones in the last decade, causing yield losses ranging from 5 to 100% depending upon the severity of the disease [2]. *A. brassicae* on the other hand is more prevalent and destructive in the well-irrigated regions of North India, causing 10 to 70% yield losses in the areas where the weather is cool and humid [3,4].

Genetic resistance against stem rot and Alternaria leaf blight has not been identified in *B. juncea* germplasm. As opposed to *B. juncea*, field-level partial tolerance to stem rot has been reported in *B. napus* cultivar Zhongyou 821, Zhongshuang 9, and pre-breeding lines J7005, ZY004, and 0663792 from several research groups [5–9]. Tolerance to *Sclerotinia* has also been reported in the C genome harbouring *Brassicas: B. carinata, B. incana, B. villosa,* and *B. oleracea* [10–13]. However, the introgression of resistance to *B. juncea* from related species is limited due to cross-hybridization barriers. Moreover, resistance against these pathogens shows low to moderate heritability and is governed by multiple genes making it difficult to implement traditional breeding approaches for crop improvement [14,15]. To bridge the gap between attainable and realized yields of *B. juncea*, the development of broad-spectrum disease-resistant varieties through Genetic engineering (GE) is an achievable option for these two diseases. Several antifungal genes like chitinases, glucanases, lectins, and defense-related genes like WRKYs, MAPKs, GDSLs, PGIPs, and OXO have been tested for their effectiveness in providing tolerance against *S. sclerotiorum* and

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Deletion induced splicing in *RIC3* drives nicotinic acetylcholine receptor regulation with implications for endoplasmic reticulum stress in human astrocytes

[PDF] from archive.org

Authors Navneesh Yadav, BK Thelma

Publication date 2023/5

Journal Glia

Volume 71

Issue 5

Pages 1217-1232

Publisher John Wiley & Sons, Inc.

Description Nicotinic acetylcholine receptor (nAChR) dysregulation in astrocytes is reported in neurodegenerative disorders. Modulation of nAChRs through agonists confers protection to astrocytes from stress but regulation of chaperones involved in proteostasis with pathological implications is unclear. Resistance to inhibitors of cholinesterase 3 (*RIC3*), a potential chaperone of nAChRs is poorly studied in humans. We characterized *RIC3* in astrocytes derived from an isogenic wild-type and Cas9 edited "del" human iPSC line harboring a 25 bp homozygous deletion in exon2. Altered *RIC3* transcript ratio due to deletion induced splicing and an unexpected gain of α7nAChR expression were observed in "del" astrocytes. Transcriptome analysis showed higher expression of neurotransmitter/G-protein coupled receptors mediated by cAMP and calcium/calmodulin-dependent kinase signaling with increased cytokines ...