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Table of Contents

IX. *Design and Implementation of an assay for genetic variants associated with Non deletion Alpha Thalassemia in a cohort of Sri Lankan population.*
By: Wickramarathne N., Sri Lanka

X. *The impact of common TMPRSS6 gene variants on iron status of pregnant women from rural Gambian.*
By: Momodou W. J., et al, USA

XI. *Diagnosis rate of Clinical Exome Sequencing and Whole Exome Sequencing in rare diseases: A comparative approach*.
By: Lagos, C., et al, Chile

XII. *Impact of Genetic Relatedness of Parents on Reproductive Outcomes.*
By: Lynch M., et al, USA

XIII. *Temple syndrome as a differential diagnosis in Chilean population with suspected Silver Russell syndrome.*
By: Martin F., et al, Chile

XIV. *The Dravet Prediction tool: predicting patient's phenotypic outcome by combined modeling of SCN1A genetic effects with clinical features.*
By: Pérez-Palma, E., et al, Chile

XV. *A descriptive study of the genetic aetiology of rare undiagnosed disorders in a cohort of Sri Lankan patients.*
By: Poorni, F., et al, Sri Lanka

XVI. *Proposed algorithm for Primary Immunodeficiency Disorders diagnoses.*
By: Rey-Jurado, E., et al, Chile

XVII. *Rapid whole genome sequencing in the neonatal intensive care unit of Brazilian hospitals.*
By: Sobreira, J., et al, USA

XVIII. *Regions of Homozygosity: Finding the Needle in the Haystack Efficiently & Effectively.*
By: Tise, C., et al, USA

XIX. *Ethical Concerns About in Utero Gene Editing for People with Hemophilia.*
By: Vasquez-Loarte T, et al, USA

XX. *The importance of the clinical reanalysis of whole exome sequencing data: discovery of a pathogenic variant in the SETD1A gene.*
By: Zavala M. J., et al, Chile

Title of Abstract

Therapeutic trajectories of patients and families with rare diseases: a narrative literature review

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Background & Objectives

Rare diseases (RD) are a large group of highly heterogeneous disorders, defined according to incidence. Given their rarity and complex manifestations, the patient and family experiences are unique. Research on patients´ therapeutic trajectories is important to understand these experiences and improve health care. Research on therapeutic trajectories from the perspective of patients and families has grown in the past decade, yet studies on RD are limited and diverse. Our objective was to develop a narrative synthesis of existing scientific evidence in order to answer the question: which are the most frequent therapeutic trajectories and/or odysseys of patients and families (or caregivers) with RD, according to existing scientific evidence?

Method (s) and Results:

We conducted a narrative literature review. The search was performed in PubMed (May 2021), including studies with trajectories of RD patient and their families or caregivers, without filters. Of the 574 titles identified, 53 studies met the inclusion criteria and were selected for the narrative review. Most studies were from Europe (n=20), case study (n=23) and cross-sectional (n=16). Twenty were quantitative and 27, qualitative and 6 mixed studies. We identified six main themes: diagnosis, treatment, cost, quality of life, key informant, and technology contributions. The main topics are time, diagnosis, information, new diagnosis, and treatment strategies.

Conclusions (Significance and Impact of the Study):

Findings from this narrative review suggests that understanding patients and families therapeutic trajectories could help recognize effective time-to-diagnosis, treatments, and the responsiveness of healthcare systems at point of care. Findings indicate that the perspective of patients and families with RD must be included as part of the research and policy agenda, as their experience is vital to shed light on global healthcare quality and equity goals. Generating this information in other countries and contexts is relevant to develop public policies for rare diseases, from the experience of patients and.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: rare disease, patient trajectory, patient odyssey, health system.

Estimating the global burden of Inborn Errors of Metabolism

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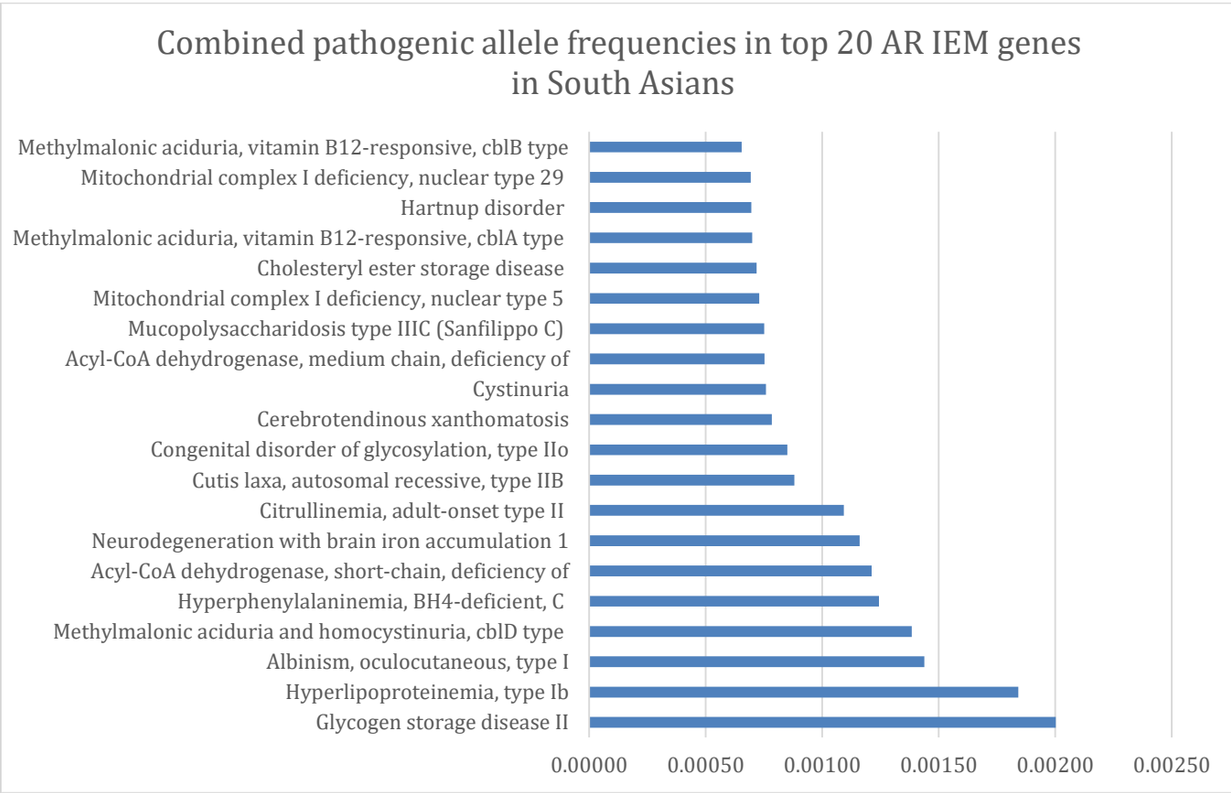
Background & Objectives: For the developing nations it is always a challenge to allocate resources for rare diseases due to high prevalence of infectious and emerging lifestyle diseases. Estimation of the rare disease burden therefore would provide critical data for deciding allocation of scarce resources. Here we wanted to estimate gene specific combined minor allele frequency of pathogenic variants for different ethnicities from the gnomAD dataset for 235 genes associated with Inborn Errors of Metabolism (IEM) phenotypes in OMIM.

Method (s) and Results: We retrieved population specific carrier frequencies for 1,72,829 variants in 235 AR IEM genes from gnomAD v2.1 dataset. Out of these 7200 variants were probable loss of function (plof) and 60345 variants were missense / inframe deletion. We classified these variants based on plof status, ClinVar annotation, allele frequency of <0.005 and InterVar annotation. We therefore narrowed down to 7,256 pathogenic variants in 217 AR IEM genes.



Conclusions (Significance and Impact of the Study): We estimated Hyperlipoproteinemia, type Ib to be the second commonest IEM (carrier frequency 4/1000) in South Asians and Citrullinemia, adult-onset type II to be the commonest IEM (carrier frequency 31/1000) in East Asians. Overall for South Asians we estimated 84 out of 1000 are carriers for at least one AR IEM disease and at least 30 out of a million conceptions have an AR IEM. These are much lower than the estimates for East Asians (275/434) and African Americans (260/228). Whether these observations have some biological reasons or due to inadequate capture of rare alleles needs to be elucidated. We now have a starting point for designing a newborn screening study to validate our findings.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: Inborn Error of Metabolism, gnomAD, ClinVar, Birth prevalence, Carrier frequency

Design and implementation of a novel assay for a selected *SERPINC1*gene variant in a cohort of Portal Vein Thrombosis patients in the Sri Lankan population.

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Background & Objectives: Portal vein thrombosis (PVT), is a thromboembolic disorder with a genetic etiology. In developing countries, 40% of portal hypertension are attributed to PVT. Anti-thrombin (AT) deficiency is a major risk factor for venous thromboembolic disorders. The AT precursor is encoded by the *SERPINC1* gene. A comprehensive literature review revealed that a variant of the *SERPINC1* gene (rs2227589, g.5301G>A), is associated with an increased risk of thrombosis in South Asian populations. The objective of this study was to design and implement an assay for determining the presence of the *SERPINC1* g.5301G>A gene variant in the Sri Lankan population.

Method (s) and Results: This retrospective study comprised of 80 individuals clinically diagnosed with PVT, who had been referred to the Human Genetics Unit, Faculty of Medicine, University of Colombo, for genetic screening after obtaining written informed consent for future studies. A novel tetra-primer amplification refractory mutation system-polymerase chain reaction (T-ARMS-PCR) assay was designed and optimized to genotype the variant rs2227589, in the *SERPINC1* gene. The optimized protocol was validated by Sanger sequencing. The allele frequency for the benign variant (G/G) and the heterozygous for the pathogenic variant (G/A) was 62.4% and 31.2%, respectively. No homozygotes for the pathogenic variant were identified. The minor allele frequency for the g.5301G>A genotype was 0.01 (chi squared = 0.98) according to the Hardy Weinberg equilibrium.

Conclusions (Significance and Impact of the Study): The designed T-ARMS-PCR assay can be implemented to genotype the rs2227589 variant of the *SERPINC1* gene. This assay can be introduced as a sensitive, specific, and simple diagnostic technique for testing genetic variants associated with PVT.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: PVT, Thrombosis, *SERPINC1*, Anti-thrombin, T-ARMS PCR

Identification of genetic variants associated with Deep Vein Thrombosis in the Sri Lanka population.

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Background & Objectives: Deep Vein Thrombosis (DVT) is a major preventable cause of morbidity and mortality worldwide. DVT is a multi-factorial disorder and occurs due to various acquired conditions, and inherited genetic risk factors. Genetic risk factors include mutations in the *Factor V*, *prothrombin* and *MTHFR* (5, 10- methylenetetrahydrofolate reductase) genes. Apart from these established genetic risk factors, studies have implicated various other candidate genes that might be involved in DVT pathogenesis. The aim of this study was to identify novel genetic variants associated with DVT in the Sri Lankan population.

Method (s) and Results: The study population comprised of 110 individuals diagnosed with DVT, who were referred to the Human Genetics Unit, University of Colombo, for genetic screening retrospectively following ethical clearance. Through literature search, globally studied genetic variants were identified, which were shown to be associated with DVT in various populations. Two gene variants were identified through literature review to be associated with DVT in South Asian populations, *CYP4V2* c.775C>A **(**rs13146272) and *Factor 5* (*F5*) c.2573A>G (rs4524). A T-ARMS-PCR assay was designed and optimized to genotype extracted patient DNA. Genotyping results were validated by Sanger sequencing. For the *CYP4V2* variant, the ancestral (C) allele frequency was 0.3045 and variant (A) allele frequency was 0.6955 at Hardy Weinberg's equilibrium. For the *F5* variant, the allele frequency was 0.6651 and 0.3349 for ancestral (A) allele and variant (G) allele, respectively. The allele frequencies of both gene variants in the Sri Lankan population were consistent with other South Asian populations.

Conclusions: The optimized T-ARMS-PCR assay protocol that was developed in this study can be introduced to genotype the CYP4V2 c.775C>A variant and F5 c.2573A>G variant, in DVT patients. Our findings suggest that CYP4V2 c.775C>A variant and F5 c.2573A>G variant maybe new possible candidate genetic risk factors for DVT in the Sri Lankan population.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: Deep Vein Thrombosis, Sri Lankan population, T-ARMS PCR, *CYP4V2*, *Factor 5*

SCREENING OF *PCSK9* GENETIC VARIANTS IN FAMILIAL HYPERCHOLESTEROLEMIA (FH) PATIENTS IN A COHORT OF SRI LANKAN POPULATION

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ABSTRACT

Background:

A hereditary predisposition for elevated serum levels of low-density lipoprotein cholesterol (LDL-C) leading to cardiovascular disease is a typical Familial hypercholesterolemia (FH) which affects approximately 1 in 250 individuals. In excess of thousand low-frequency variants in *LDLR, APOB,* and *PCSK9* have been implicated in **FH**, but only few studies have been conducted at the population level. The discovery of proprotein convertase subtilisin/kexin type 9 *(PCSK9),* a secretory protein that posttranscriptionally regulates levels of low density lipoprotein receptor (LDLR) by inducing its degradation, has opened a new era of pharmacological modulation of cholesterol homeostasis. Nevertheless, certain mutations of the *PCSK9* genes appear to hinder the expected results in certain patients. Thus, this study was aimed at designing of a novel PCR assay for the identification of *PCSK9* genetic variants in a cohort of patents in Sri Lanka diagnosed with FH.

Method:

A comprehensive literature review was followed by designing of an allele specific PCR assay to genotype a total of 18 unrelated patients with a clinical diagnosis of familial hypercholesterolemia at the Human Genetics Unit, Faculty of Medicine, University of Colombo, Sri Lanka. The assay designed for the SNP *rs11591147* G>T variant was validated using Sanger sequencing.

Results:

The expected band sizes at 428bp, 285bp and 188bp indicated the wild type allele, heterozygous allele and the homozygous allele for the pathogenic variant respectively. Out of the 18 patients tested, no heterozygotes or homozygotes the pathogenic variant was detected.

Conclusions:

This study is first of its kind to screen the PCSK9 genetic variants in FH patients in Sri Lanka. However, no pathogenic variations were identified which shows *PCSK9* gene variants may be less significant in our population. Nevertheless, the designed assay will allow the application of precision medicine which will serve as paradigms for the prevention of premature atherosclerotic cardiovascular disease in all at-risk patients and families.

Key words

Familial Hypercholesterolemia, PCSK9, allele, genotype

Abstract Template

Approaching Clusters of Mucopolysaccharidoses in Latin America with Population Medical Genetics Tools

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Background & Objectives The Mucopolysaccharidoses (MPS) are rare genetic disorders caused by deficiency of lysosomal enzymes resulting in the accumulation of undegraded glycosaminoglycans (GAGs). The combined incidence of the MPS subtypes in the general population is estimated as 1:25,000 live births. Clusters of these diseases have been identified in areas with high consanguinity rates and/or founder effect associated to endogamy. **Method (s) and Results:** The MPS Brazil Network, associated to the Brazilian Institute of Population Medical Genetics (INAGEMP), identified several MPS clusters in Latin America and investigated them by biochemical and molecular analyses. Three clusters were confirmed in Brazil, of MPS IIIC (state of Paraíba), MPS IVA (state of Paraíba) and MPS VI (state of Bahia). Two clusters were identified in Ecuador: MPS IIIB (state of Manabi) and MPS IVA (state of Pastaza). A cluster of MPS VI was also identified in the Dominican Republic. Other clusters are being investigated in Haiti (MPS VI), Panamá (MPS IVA), and Brazil (MPS IIIB, Minas Gerais state). Haplotype analyses are underway, and results already available for the clusters of MPS IVA and MPS VI in Brazil indicate founder effects with common ancestors. As one example of the benefits of cluster identification, a newborn screening program for MPS VI was implemented in the specific Brazilian region to provide early

identification and treatment. Measures to increase awareness of the community, to provide training to health care personnel, as well as genetic counseling and prenatal diagnosis, could also be offered. **Conclusions (Significance and Impact of the Study):** Examples of MPS clusters were identified in Latin America, and likely, several others are still unreported. The identification and characterization of MPS clusters provides a better understanding about how they were originated and it also enable preventive and management measures to the affected communities.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: Population medical genetics, mucopolysaccharidoses, clusters, lysosomal storage disorders, inborn errors of metabolism.

A study of the clinically important *CYP2C19* gene variants in the Sri Lankan Population

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Background & Objectives: *CYP2C19* is the most polymorphic gene belonging to cytochrome P450 superfamily of drug metabolizing enzymes. *CYP2C19* catalyzes the metabolism of a range of clinically important drugs such as anti-epileptics (diazepam, phenobarbitone), antidepressants (amitriptyline clomipramine), the antiplatelet drug clopidogrel, and anti-ulcer proton pump inhibitors (omeprazole, lansoprazole). Three of its variants, *CYP2C19*2*, *CYP2C19**3 and *CYP2C19*17*, are considered to be clinically important. *CYP2C19*1* is the wild type allele and individuals homozygous for this allele exhibit the normal metabolizer phenotype, with a normal enzyme activity. Phenotypically, *CYP2C19*2* and *CYP2C19*3* are associated with poor metabolizers (PM) and *CYP2C19*17* is associated with ultra-rapid metabolizers (UM). The objective of the study was to determine the frequency of these alleles in the Sri Lankan population.

Method (s) and Results: Peripheral blood samples were collected from individuals (n = 100) referred to the Human Genetics Unit, University of Colombo, for genetic screening retrospectively following ethical clearance. Genotyping was achieved by the T-ARMS-PCR method. Results were confirmed by PCR-RFLP assays and validated by Sanger Sequencing. The observed and expected frequencies were calculated using Hardy-Weinberg equation. Genotype analysis revealed that the allele frequencies of *CYP2C19*2*, *CYP2C19*3* and *CYP2C19*17* in the Sri Lankan population were 0.3, 0.01 and 0.2, respectively. Out of the 100 subjects, 30% were normal metabolizers (*CYP2C19*1/*1* genotype); while 37% were intermediate metabolizers *(*1*2, *2*/17, *3*/17*), 12% poor metabolizers *(*2/*2*), 19% rapid metabolizers *(*1/*17*), and 2% were ultra-rapid metabolizers *(*17/*17*). The expected frequencies of *CYP2C19* genotypes in Sri Lankan population had no significant deviation from the Hardy-Weinberg equilibrium ($p>0.05$).

Conclusions: We can predict from this data that 70% of patients would require consideration of alternative treatment or dose adjustment based on their genotype, for the aforementioned drug classes. Therefore, we recommend that testing for these alleles be started in Sri Lanka.

Conflict of interest disclosure: No conflicts of interest.

Keywords: *CYP2C19*, variants, Sri Lankan population, T-ARMS-PCR, pharmacogenomics

RBBP5 protein is associated with poor survival in breast invasive carcinoma through desregulation of DNA damage genes.

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Background & Objectives: In women, breast cancer is one of leading cancer-related cause of disease. Even when advance in detection and therapy have been development, still remains as most lethal cancer worldwide, therefore, it's urgent to identify new molecular target to increase patients survival.

Method (s) and Results: In order to study gene expression throughout the illness, we analized transcriptional levels associated at each cancer stages (T1 – T4), using cbioportal database. Our data show that levels of RBBP5 (Retinoblastoma-binding protein 5) signficantly increase as well the disease progresses. In arround 9% of patients (89 patients) RBBP5 gen was found amplified and 24% (238 patients) have high levels of the transcript. Interesly, high RBBP5 levels correlationed with a poor survival (Logrank P =0.0142). Functional protein association assay, using String database, reveled that RBBP5 interact with different member of Histone-lysine N-methyltransferase family (KMT2A, KMT2C, KMT2D) and MLL1/MLL complex (WDR5) to bound at differents DNA sites. Predict protein-DNA interaction assay (Chip-atlas database) showed 7633 RBBP5'targets genes, which are mostly enriched in DNA repair category (by ontology assay).

Conclusions: Our data suggest that RBBP5 interact with several methyltransferase to modulate DNA repair-associated genes expression, which drive an decrease in survival in patients with breast invasive carcinoma.

This Work was financially supported by ANID PIA/Anillo ACT-172101 grant and ANID-FONDECYT Postdoctoral grant 3190396.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: RBBP5, breast cancer, DNA damage, methyltransferase, predict genes expression.

Design and Implementation of an assay for genetic variants associated with Non deletion Alpha Thalassemia in a cohort of Sri Lankan population

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Background & Objectives

Non-deletion variants are a rare cause of alpha thalassaemia. These Non-deletional variants of alpha thalassemia includes missense and point variants that alters the genomic regions of the α-globin genes that are critical for the normal expression. *Hb Quong Sze* and *Hb Adana* were found to be the commonest types of non-deletion alpha thalassemia within the South East Asian population. The present study was undertaken to design an allele specific PCR of selected non-deletion variants and to detect the presence of these novel variants in Sri Lankan population.

Method (s) and Results

Novel single variant tetra primer-amplification refractory mutation system (T-ARMS) polymerase chain reaction (PCR) assays were designed for the *HBA2:c.377 T>C* (rs41397847) and *HBA2:c.179 G>A* (rs28928878) variants. The optimum annealing temperatures, where 61.8^{0}C for the *HBA2:c.377 T>C* and 68.3^{0}C for *HBA2:c.179 G>A*. *HBA2:c.377 T>C* variant was further optimized, validated by Sanger sequencing. Implementation by genotyping for the variants were performed by using an existing blood sample collection. A total of 100 samples were genotyped.

Among the 100 samples genotyped, the genotype frequency for the homozygous variant (C/C) was 0.88%, heterozygotes (T/C) frequency was of 0.04% and homozygous wild type (T/T) was 0.08%. The respective variant allele frequency was (0.1%) and ancestral allele frequency was (0.9%). Out of the 100 samples genotyped, no variant allele samples were detected for this variant. The allele frequency was 0% respectively.

Conclusion

The *HBA2:c.377 T>C* variant was optimized and implemented. T-ARMS PCR was used to Genotype the HBA2 α-globin gene. The minor alleles of the *HBA2:c.377 T>C* variant were identified in the genotyped cohort in the heterozygous form. Optimization on *HBA2:c.179 G>A* for non-deletion alpha thalassemic patients' needs to be further developed. T-ARMS PCR can be used as a low-cost assay for detecting non-deletion alpha thalassemic variants.

Keywords: T-ARMS PCR, Non-deletion Alpha-thalassemia, *HBA2:c.377 T>C, HBA2:c.179 G>A,*

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Abstract title:

The impact of common TMPRSS6 gene variants on iron status of pregnant women from rural Gambian

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Background

Anaemia is a global health problem that has a significant impact on women of reproductive age in low-and middle-income countries. Nutritional deficiencies, infection and genetic risk factors are the major drivers. However, the role of genetic factors particularly in settings where the prevalence of anaemia is high, has not been fully investigated. Genome-wide association studies have identified numerous single nucleotide polymorphisms in the TMPRSS6 gene which are linked to impaired iron status in non-African populations. However, the impact of these SNPs on the risk of anaemia in West African populations have not been fully investigated.

Objectives

To investigate the effects of *TMPRSS6* rs2235321, rs4820268 and rs855791 on iron status biomarkers in pregnant Gambian women.

Methods

We analyse data from a cohort of pregnant (18 to 49 years, N=364), with genotype data on *TMPRSS6* rs2235321, rs855791 and rs4820268, and on iron biomarkers (serum iron, unsaturated iron binding capacity (UIBC), transferrin, ferritin soluble transferrin receptor (sTfR), transferrin saturation (TSAT) and total iron binding capacity (TIBC) and hepcidin) and hematology traits. We investigated the effects of genotype on these iron status indicators.

Results

The *TMPRSS6* rs223521 is associated significantly with reduced hepcidin levels (F ratio = 6.16, P=0.00235). The carriers of the minor allele (A) had decreased hepcidin concentration compared to GG carriers; AA vs GG = [mean (SE) 3.28 ng/mL (1.11) vs 5.44 ng/mL (0.62), P=0.0004]. Similarly, *TMPRSS6* rs4820268 significantly influenced serum iron levels (F = ratio = 3.58, P = 0.0289). Carriers of the rs4820268 minor alleles (GG) had decreased serum iron concentrations compared to AA

genotype carriers; GG vs AA = [mean (SE) 10.77 μmol/L (1.40) vs 13.56 μmol/L (3.13)]. No other iron phenotype was influenced by any of these two SNPs and no effect of rs855791 was observed on any phenotype.

Conclusion

TMPRSS6 rs2235321 may modulate hepcidin levels in pregnancy, whereas rs2235321 may predispose pregnant women to low iron status. Analysis of a larger dataset with more genetic markers associated with iron status may provide further insight into the functional effects of genetic variants within the iron regulatory genes on the risk of anaemia in African women of reproductive age. This may enable the development of genomic medicine approaches for the treatment and prevention of anaemia and iron related pathologies.

Keywords:

TMPRSS6 SNPs, Iron biomarkers, Pregnant women, Anemia

Diagnosis rate of Clinical Exome Sequencing and Whole Exome Sequencing in rare diseases: A comparative approach

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Rare Diseases (RD) are a large group of highly heterogeneous disorders, defined according to incidence. Given their rarity and complex manifestations, many patients remain undiagnosed for several years. These are considered Rare Undiagnosed Diseases (RUDs). To generate discoveries on novel causes of RUDs in the context of a country with limited genomic resources, we developed a pilot program for patients with unknown diagnoses.
In this report compared the diagnostic yield of proband-only NGS alternatives, including Clinical Exome Sequencing (CES) (approximately 5000 known disease-causing genes) and Whole Exome sequencing (WES), vs WES in family trio strategy using commercially available bioinformatics analysis algorithms. These processes were followed by multidisciplinary team variant interpretation.
To date, a total of 39 patients with RUD have participated in the study; 15 patients had CES, 25 had WES (10 with previous CES testing) and 9 patients had WES trio family analysis. The global rate of variant detection was 53.8%. These preliminary results twice higher diagnostic yields for WES (50% overall) compared to CES (26%) in this group of patients. The yield of WES trio family analysis was higher than WES- and CES-proband only (67, 44 and 26%, respectively). A predominance of *de novo* variants in the diagnosed cases was observed. The results show the feasibility of developing a local undiagnosed diseases program in Chile.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: Genetic testing, Rare variants, Exome

Impact of Genetic Relatedness of Parents on Reproductive Outcomes

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Background & Objectives: Genetically isolated populations that have arisen due to recent bottleneck events have reduced genetic variation that reflects the common set of founding individuals. Members of such populations share increased genetic relatedness and are often enriched for recessive disorders that are rare in the general population. In this report, we evaluate, in the Lancaster Amish community, the impact of genetic relatedness of couples on reproductive health outcomes.

Method(s) and Results: We first identified 234 highly penetrant recessive conditions with known variants segregating in the community (Plain Insight Panel [PIP]) and used exome sequencing data to identify couples who are carriers for a PIP variant in the same gene. Reproductive outcomes were assessed by questionnaire. In addition, we evaluated whether genetic relatedness of parents across the genome, assessed by kinship coefficient (R), was associated with reproductive health outcomes. We found 300 out of 1824 (16.4%) couples at risk of producing a child with an autosomal recessive disorder. Carrier couples were more likely to report stillbirths (8.3% vs. 4.8%, p=0.02) although the number of children (6.3 vs. 6.4, p=0.8) or number of pregnancies (7.7 vs. 7.6, p=0.4) did not differ between groups. The mean R coefficient (± SD) between spouses in the Amish is 0.073 ± 0.017, a larger value compared to randomly mating outbred populations (R <0.005). We found that a higher relatedness between spouses was positively correlated with number of children (p <0.0001), pregnancies (p <0.0001), and stillbirths (p=0.03), although not with the number of miscarriages (p=0.4).

Conclusions: We assessed the impact of known highly penetrant recessive variants on reproductive outcomes and the association of pregnancy outcomes with overall relatedness between parents. These results highlight a complex association between relatedness of parents and reproductive health outcomes in founder communities.

Conflict of interest disclosure: Megan T. Lynch, Kristin A. Maloney, Toni I. Pollin, Elizabeth A. Streeten, Erik G. Puffenberger, Kevin A. Strauss and Braxton D. Mitchell declare that they have no conflict of interest. Alan R. Shuldiner is an employee of Regeneron Pharmaceuticals, Inc. and receives compensation as salary and stock options.

Keywords: [Reproductive Health] [Kinship] [Genetic Association] [Founder Effect] [Recessive Disorders]

Temple syndrome as a differential diagnosis in Chilean population with suspected Silver Russell syndrome

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Background: Temple Syndrome (TS14) is a rare imprinting disorder secondary to alterations at the 14q32 imprinted locus. One of its main differential diagnoses is Silver Russell Syndrome (SRS) caused by aberrations of the imprinted 11p15 region or by maternal Uniparental Disomy of chromosome 7 (matUPD7) in most cases. Both TS14 and SRS share within their phenotypes delayed growth associated with feeding difficulties during childhood.

Objective: To identify patients with TS14 in individuals with a negative molecular study result of the imprinted region of chromosome 11p15 with clinical suspicion of SRS.

Methods: We studied 20 individuals with a negative result of MS-MLPA BWS / SRS with clinical suspicion of SRS, previously analyzed at the INTA Molecular Cytogenetics laboratory between the years 2017 and 2021, using MS-MLPA UPD7-UPD14.

Results: The diagnosis of TS14 was confirmed in 1 individual (5%) with 0% methylation in the three probes that analyze the imprinted 14q32 locus, without alteration in copy number in the region. This result is compatible with an epimutation or matUPD14 at the locus. No other molecular alterations were identified with this MS-MLPA salsa in the rest of the studied individuals.

Conclusion: TS14 is probably underdiagnosed, and the molecular study of the imprinted region 14q32 in patients with suspected SRS with a normal study of the imprinted region 11p15 should be considered in the diagnostic algorithm, given their phenotypic overlap.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: Temple syndrome, Silver Russell syndrome, MS-MLPA, 14q32, UPD14

The Dravet Prediction tool: predicting patient's phenotypic outcome by combined modeling of *SCN1A* genetic effects with clinical features.

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Background: Mutations in the voltage-gated sodium channel gene (*SCN1A)* are associated with a spectrum of epileptic phenotypes, ranging from 'milder' forms such as genetic epilepsy with febrile seizures plus (GEFS+) to the 'severe' Dravet syndrome (DS) with 30% mortality. With limited performance seizure onset is commonly used as an informal predictor. Currently, there is no systematic predictor for *SCN1A* trajectories and early diagnosis of DS improves prognosis. To date, systematic analysis of genetic variants effects in addition to seizure onset have not been formally addressed.

Methods and Results: Collaborations partners from all around the world help us build the largest set of genetic and clinical data for *SCN1A* patients. A total of 745 *SCN1A* mutation-positive DS (n = 616) and GEFS+ (n=129) patients were included in the analysis. We generated a *SCN1A-specific* genetic score by combining paralog conservation of the affected amino acids with the physicochemical properties of the exchange observed. Next, we trained a generalized linear model using *SCN1A* genetic score and seizure onset as predictors of DS and GEFS+. The *SCN1A* genetic score was positively associated with DS outcome (p-value=4.88×10^{-27}) while seizure onset had a negative significant effect (p-value=3.69×10^{-36}). Taken together the model was effectively able to separate both outcomes (AUC=0.89). We used an additional blind cohort of 277 cases (209 DS and 68 GEFS+) to validate the model. A total of 207 DS cases were correctly predicted, achieving a 90.06% accuracy. We deployed the model into an online tool designed to evaluate any given *SCN1A* patient. The Dravet prediction tool will calculate patient's probability (%) of developing milder GEFS+ or severe DS.

Conclusion: The Dravet prediction tool effectively combines clinical and genetic data to predict the phenotypic spectrum of *SCN1A* variants. Broad collaboration coupled with cost effective computational methods allows the development of novel models with direct clinical applications. Our results can be accessed by doctors from all around the world who can further characterize the expected outcome of S*CN1A* patients and begin treatment.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: Dravet syndrome, *SCN1A*, GEFS+, clinical genetics, Neurodevelopmental disorders.

Abstract

A descriptive study of the genetic aetiology of rare undiagnosed disorders in a cohort of Sri Lankan patients.

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Background & Objective: Today it is possible to detect the underlying genetic aetiology of rare undiagnosed disorders using Whole Exome Sequencing (WES) without the need to sequence genes separately reducing the time from presentation to diagnosis. The objective of this study was to report the genetic aetiology of patients with rare undiagnosed disorders undergoing WES in our unit.

Method and Results: A database of patients tested in our unit consisting of phenotype and genotype data was maintained prospectively from 13th November, 2014 to 26th March, 2021 and analysed retrospectively.
123 patients were sequenced. 75 (61%) were male. Age ranged from 14 days to 18 years. The genetic aetiology was confirmed in 58 (47.2%). 27 (22%) had *novel* variants. The systems affected, the total number and percentage of patients, the number of patients diagnosed and the percentage and the total number with *novel* variants in each system respectively were: neurological, 66 (53.7%), 30 (45.5%), 17; musculoskeletal, 16 (13.0%%), 7 (43.8%), 2; multisystem, 16 (13.0%), 5 (31.3%), 2; eye, 7 (5.7%), 6 (85.7%), 3; metabolic, 7 (5.7%), 5 (71.4%), 2; blood and lymphoreticular, 4 (3.3%), 0 (0%), 0; cardiovascular, 3 (2.4%), 2 (66.7%), 0; skin, 2 (1.6%), 2 (100%), 1; gastrointestinal, 1 (0.8%), 1 (100%), 0 and renal, 1 (0.8%), 0 (0%) 0.
In those with a definitive diagnosis, a pathogenic variant related to an autosomal dominant condition was found in 30 (51.7%); an autosomal recessive condition in 23 (39.7%); an x-linked dominant condition in 2 (3.4%) and an x-linked recessive condition in 3 (5.2%).

Conclusions (Significance and Impact of the Study): The use of WES has made it possible to arrive at the genetic aetiology in nearly half of the patients with rare undiagnosed disorders tested in our unit. It has led to early diagnosis, accurate prognostication and appropriate treatment of these patients.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: Rare undiagnosed disorders, Whole Exome Sequencing, *novel* variants.

Proposed algorithm for Primary Immunodeficiency Disorders diagnoses

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Background & Objective: Primary immunodeficiency disorders (PIDD) are genetic defects of the immune system. PIDD comprise a heterogeneous group of phenotypes and genotypes, hence the management of each individual disease is challenging. Immunological workup together with genetic studies is important to establish diagnosis. However, low and middle-income countries might have difficulties to have access to all these studies. Hence, decisions for which and when immunological and genetic studies need to be performed is a paramount for diagnoses of PIDD in low and middle-income countries. We aimed to provide an algorithm for PIDD diagnoses that can be used in low and middle-income countries.

Methods: A systematic search was performed in PIDD diagnoses guidelines and next generation sequencing for suspected PIDD in Web of Science and online tools available for genetic analysis.

Results: We proposed the following algorithm for PIDD diagnoses (**Figure 1**). For PIDD diagnosis, immunological testing together with clinical manifestations is required to evaluate which cells are affected and this should be correlated with genetic studies to establish molecular diagnoses. Genetic panels for known PIDD-associated genes are available. In most scenarios, next-generation sequencing is considered if panel testing does not result in a diagnosis and a monogenic cause is clinically suspected. After genetic testing, whether no relevant gene is found, diagnosis should be reconsidered. Finally, if genetic tests arise variants of uncertain significance in a PIDD phenotype-related gene or novel variant, functional studies should be performed in clinical or research setting.

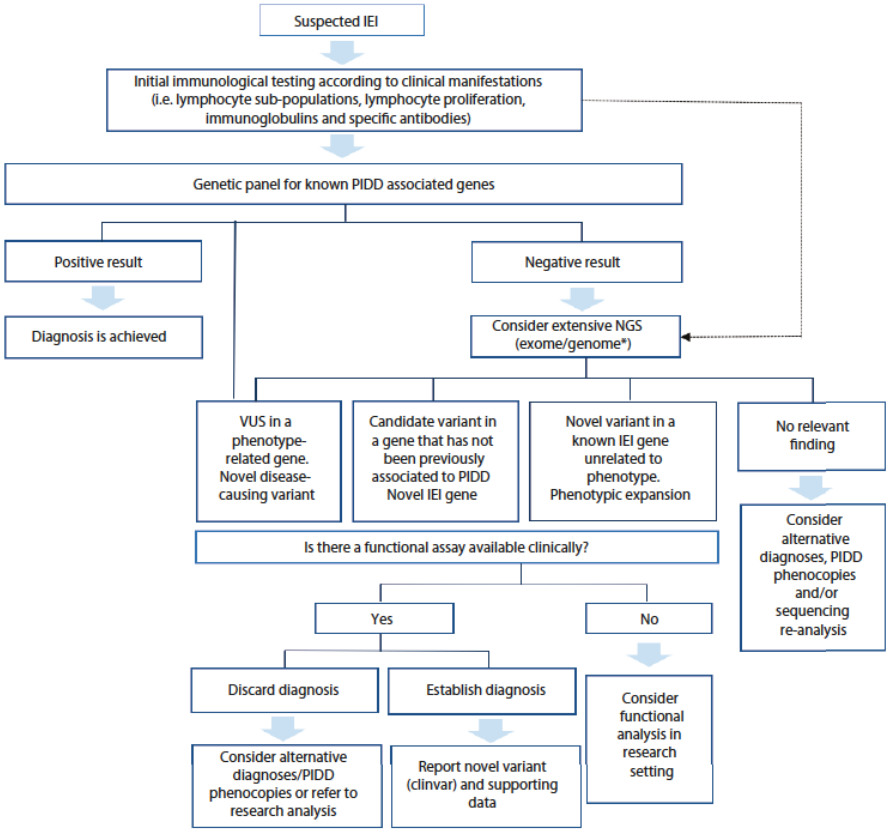

Figure 1. Algorithm for primary immunodeficiency disorders (PIDD). NGS: Next generation sequencing. VUS: variant of uncertain significance. IEI: inborn errors of immunity.

Conclusions: Extensive exome or genome sequencing, functional studies and alternative diagnoses whether no molecular diagnosis is achieved should be considered for PIDD diagnoses.

Conflict of interest disclosure: The authors declare no potential conflicts of interest.

Rapid whole genome sequencing in the neonatal intensive care unit of Brazilian hospitals.

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Background & Objectives: Rare Mendelian diseases can be caused by a variety of variant types what makes the molecular diagnosis of Mendelian diseases a challenge because many investigation methods may be used for the identification of disease-causing variants. Traditionally, a series of genetic tests are used step wise for the cytogenetic or molecular diagnosis of these diseases. Mainly in low- and middle-income countries, the access to these tests is difficult, they are very expensive and the results are frequently delayed. Because of that precise timely diagnoses are not made and opportunities for prevention, anticipatory guidance, and treatment are missed or delayed.

Method (s) and Results: To address these difficulties related to performing multiple genetic tests we will perform rapid whole genome sequencing (WGS) on 100 neonatal patients (and their parents) being treated in the intensive care units of Brazilian hospitals with suspected rare Mendelian diseases that fit a pre-stablished selection criteria. WGS libraries will be sequenced on the NovaSeq 6000 platform at DASA laboratory. The final report will be returned in 15 days and will include the analysis of CNVs, indels, SNVs and a number of selected non-coding variants known to cause rare diseases.

Conclusions (Significance and Impact of the Study): With this project we expect to decrease the time for precise diagnosis of neonatal patients with rare Mendelian disease and in critical medical conditions. Precise timely diagnoses may improve management and treatment of these patients and decrease the costs to the health care system in general.

Conflict of interest disclosure: The authors are employees of the DASA laboratory.

Regions of Homozygosity: Finding the Needle in the Haystack Efficiently & Effectively

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Background & Objectives: In addition to identifying copy number variants, single nucleotide polymorphism chromosomal microarray technology allows for the identification of regions of homozygosity (ROH) in individuals. Analysis of ROH can be particularly helpful in developing a differential diagnosis when an autosomal recessive condition is suspected. Presented below are two illustrative cases.

Method (s) and Results: ROH were analyzed using Franklin (https://franklin.genoox.com) with incorporation of phenotypic features based on clinical evaluation by Medical Genetics.

Case 1: A two-week-old Mexican (Guerrero) boy is evaluated for intrauterine growth retardation, hypotonia, and poor feeding. Postnatal microarray reveals several ROH, including a region of chromosome 6 containing *PEX6*, identified to have the strongest genotype-phenotype relation. Newborn screening on day of life 19 is positive for elevated C26 without an identified variant in *ABCD1*, concerning for Zellweger spectrum disorder (ZSD). Molecular testing reveals a homozygous likely-pathogenic variant in *PEX6* (c.1409G>C, p.G470A), consistent with a diagnosis of ZSD. Biochemical testing further supports the diagnosis and the variant is later reclassified as pathogenic.

Case 2: A five-week-old Guatemalan (Chiquimula) boy with negative prenatal infectious screening and negative postnatal urine cytomegalovirus testing is evaluated for microcephaly, bilateral cataracts and hearing impairment, and neonatal cholestasis. Postnatal microarray reveals a 29.9 Mb interstitial ROH on chromosome 19 containing *ERCC2*, identified to have the strongest genotype-phenotype relation. Molecular testing reveals a homozygous likely-pathogenic variant in *ERCC2* (c.1997G>A, p.R666Q), consistent with a diagnosis of *ERCC2*-related disorder.

Conclusions (Significance and Impact of the Study): Analysis of ROH is a resourceful tool for developing a narrow list of genes for further molecular analysis in individuals suspected to have an autosomal recessive condition, particularly when broad-based genetic testing is inaccessible. Analysis of ROH has the potential to decrease time to diagnosis and lead to the identification and/or reclassification of rare disease-causing variants.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial, and/or personal.

Keywords: regions of homozygosity (ROH), chromosomal microarray, autosomal recessive, homozygous variant, diagnosis

The importance of the clinical reanalysis of whole exome sequencing data: discovery of a pathogenic variant in the *SETD1A* gene

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Background & Objectives: As the number of genes analyzed by commercial sequencing diagnostic tests increases, interpretation of the results becomes more challenging for clinical geneticists. These studies have the potential to detect new genetic variants and their analysis is a dynamic process. In a significant proportion of cases no results are found in a first instance analysis, but if the sequencing data is re-analyzed in a certain amount of time, it is possible to encounter new findings. We present the case of a 5-year-old male patient with healthy non-consanguineous parents. He was referred to clinical genetics with a history of delayed psychomotor development, hypotonia, and dysmorphia. He has a 46,XY karyotype and a panel of 21 microdeletions without alterations. Given the suspicion of Opitz-Frias syndrome, whole exome sequencing (WES) was requested which showed a variant of uncertain significance in the *KMT2C* gene associated with Kleefstra syndrome, a phenotype that did not fit the patients' phenotype.

Method (s) and Results: We reanalyzed the VCF file from the WES performed by the commercial laboratory a year later from the initial report in the local clinical setting using free access tools. Through this exercise we found a new pathogenic variant in the *SETD1A* gene. Recent studies suggest that loss-of-function variants in *SETD1A* cause a variety of neurodevelopmental disorders that match the patient's phenotype.

Conclusions: This began as an exercise in our training process as clinical geneticists to learn how to analyze sequencing raw data, and ended up highlighting the importance of the reanalysis of the data in cases where the first report did not show conclusive findings. The study of human Mendelian diseases is ongoing and approximately 250 novel gene–disease and 9200 novel variant–disease associations are reported each year. Reexamination of sequencing data is cost-effective and may benefit patients and their families.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: Reanalysis, exome, sequencing, variant of uncertain significance

ETHICAL CONCERNS ABOUT IN UTERO GENE EDITING FOR PEOPLE WITH HEMOPHILIA

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Background & Objectives: Hemophilia is an inherited lifelong debilitating disease for which current treatment is non-curative. While gene therapy, and gene editing are explored as potential curative alternatives, there is a need to evaluate the bioethical concerns that they implicate. In this study, we explored the ethical concerns about these new technologies in patients with hemophilia and their relatives in order to bring up important questions before the technologies are implemented.

Method (s) and Results: This qualitative study used semi-structured interviews on 22 patients with hemophilia A or B and their relatives across the U.S. Grounded theory was used to analyze the data. We had 21 participants between 18 and 67 years old, 19 of them had severe hemophilia. The themes about Genetic identity and Trustworthy Science were brought up when the participants talked about gene therapy (GT) and gene editing (GE). However, gene editing only brought up quotes about Respect for Persons (eugenics and the right for child of self-determination) and Transnational Cooperation to control the use of gene editing.

Conclusions (Significance and Impact of the Study): Ethical concerns are common in the hemophilia community regarding gene therapy and editing. While the results of clinical trials from gene modification therapies will clarify most concerns, gene editing elicits more ethical concerns compared to gene therapy and is less likely to be accepted among the community.

Conflict of interest disclosure: The authors disclose no conflicts of interest during the execution of this study.

Keywords: [gene therapy, gene editing, bioethics, hemophilia]