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ABSTRACT BOOKLET

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Implementation of a genotyped virtual African population cohort: A feasibility study in the Western Cape Province, South Africa

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Background and Objectives:
There is limited knowledge on genetic drivers of disease in African populations, largely because of the prohibitive cost of genomic research in Africa. We present a proof-of-concept study demonstrating the creation of a cost-effective, scalable population cohort which is feasible in low-resource settings and can address genomic questions. This is achieved by linking genotype data from consenting participants to routine health records that can be updated prospectively.
Methods and Results:
Using a tiered informed consent model, we prepared DNA from both buccal swabs and peripheral blood samples for genotyping using the Infinium™ H3Africa Consortium Array V2. Disease phenotypes were derived from routine health data of the participants. We demonstrated the feasibility of running nested case control genome wide association studies (GWAS) with these data using type 2 diabetes mellitus (T2DM) and severe COVID-19 as distinct outcome phenotypes. We characterized 2267346 single nucleotide polymorphisms (SNPs) in 459 participants of which 1782023 (78.6%) SNPs and 343 (74%) samples passed quality control. We characterized 31 known COVID-19-associated variants, observing no significant difference between cases and controls. Similarly, 43 known T2DM variants were identified and 3 (rs12742393, rs2466293 and rs9581943) occurred with significantly higher frequency in T2DM cases than controls.
Conclusions:
We show that routine health data can be effectively linked with genotype data to create a virtual genotyped cohort, which may be used as a disease-agnostic resource that can address multiple disease outcomes in both hypothesis-generating and hypothesis-testing research. We are confident that the design and implementation are appropriate to scale up this cohort to a size where novel health discoveries can be made through nested case-control studies for a variety of phenotypes, and where follow-up of participant phenotypes over their life course may be undertaken virtually by accessing their routine health data.
Conflict of interest disclosure:
None
Keywords (5): Africa, GWAS, H3Africa chip, routine health data, genotyped cohort

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Unravelling the molecular basis of rare skeletal dysplasias using trio exome sequencing: A case series study

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Background & Objectives
Skeletal dysplasias are a diverse group of rare genetic disorders characterized by abnormal bone and cartilage tissue development. The diagnosis of skeletal dysplasias is often challenging due to the wide range of clinical features and overlapping phenotypes. However, exome sequencing and other

advanced genetic techniques have enabled identifying rare genetic defects that underlie many cases of skeletal dysplasias. The purpose of this study was to report our experience in identifying the genetic aetiology of three previously uncharacterized cases of skeletal dysplasias using a standard diagnostic strategy.

Methods and Results:
Three cases with features suggestive of skeletal dysplasia were referred for genetic evaluation. All probands were male and aged 1.5 to 4 years. Trio whole exome sequencing revealed a molecular diagnosis in all of the cases. The first case involved an atypical presentation of pycnodysostosis with craniosynostosis. Compound heterozygous variants in the CTSK gene were found in the proband, with carrier status established in both parents. In case 2, a next-generation sequencing (NGS) based CNV analysis identified a large pathogenic copy number variant involving the GLI3 gene that caused 7p14.1 microdeletion and Greig cephalopolysyndactyly syndrome. The CNV was confirmed by chromosome microarray analysis. In our 3rd case, the proband and mother had comparable phenotypes. A variant of uncertain significance was detected in the COL2A1 gene in both patients. In two out of three cases, the diagnosis could not be suspected accurately without genetic testing.

Conclusions
The utilization of NGS-based CNV analysis can be a valuable tool in resource-limited settings to screen for large CNVs. Our study emphasized the importance of obtaining a molecular diagnosis for rare skeletal dysplasias with atypical clinical presentations, as they are frequently misdiagnosed clinically. Thus, early and accurate diagnosis is essential to ending the diagnostic odyssey.

Keywords: Skeletal dysplasia, Rare disorders, Whole exome sequencing, Trio sequencing, Sri Lanka.

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Genotypic spectrum of limb-girdle muscular dystrophy (LGMD) in Sri Lanka - Case Series

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Background and objectives
LGMD is the fourth most prevalent muscle disease worldwide. Next-generation sequencing based (NGS) whole exome sequencing (WES) has enabled detection of several genes implicating in this phenotype. Hence, the genotypic and phenotypic diversity of LGMD continue to expand. Existing evidence suggest significant genotypic diversity in different ethnicities. However, data is lacking on the genetic spectrum of LGMD in underrepresented populations like Sri Lankans. The aim of this study is to present a case series of Sri Lankan patients with LGMD phenotype with their genotypic spectrum.

Methods
We included 6 patients with LGMD according to clinical evaluation supported by investigations including neurophysiology studies who underwent WES between January 2015 and December 2022.Their data were maintained prospectively in a database and analyzed retrospectively. NGS data were subjected to bioinformatics analysis and variants were classified according to American College of Medical Genetics and Genomics guidelines. Their clinical and investigation findings were also recorded in the database. Informed written consent is obtained from all participants.

Results

There were 2 male (33.3%) and 4 female (66.7%) patients in the series. The youngest patient was aged 11 years and the eldest was 38 years old. CAPN3 gene variants were detected in 4/6 (66.7%) while ANO5 and DYSF gene variants were detected in 1/6 (16.7%) each. The variants detected in the CAPN3 were c.1342C>T:p.Arg448Cys (pathogenic; homozygous), c.1662C>A:p.Tyr554* (pathogenic; heterozygous), c.427delC: H143Tfs*36 (likely pathogenic; homozygous), c.245C>T: p.Pro82Leu (likely pathogenic; heterozygous). Other variants detected were ANO5: c.*112_*113delTT (variant of uncertain significance; homozygous), DYSF:c.1717C>T: p.Arg573Trp (pathogenic; homozygous). None of them had affected family members or proven involvement of respiratory or cardiac muscles.

Conclusion

CAPN3 variants were common in Sri Lankan patients with LGMD, though existing data indicate them to be rare in Asian populations in which DYSF is known to be the commonest gene implicated.

Keywords : LGMD, Sri Lankan, CAPN3, DYSF, ANO5

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Sri Lankan experience of a low-cost genetic test for diagnosing mitochondrial disorders -Leber hereditary optic neuropathy (LHON) and Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes syndrome (MELAS)

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Background and objectives

Mitochondrial disorders are heterogeneous with overlapping clinical features. Genetic confirmation is of paramount importance for therapeutic decision making. Diagnosing primary mitochondrial DNA variants are challenging in low-income countries due to lack of facilities and financial constraints faced in sequencing the mitochondrial genome. Some mitochondrial disorders such as LHON and MELAS are caused by few common mitochondrial mutations in 95% of cases. Implementing a targeted Sanger sequencing technique to detect these common mutations is beneficial considering its adequate coverage and low cost. We are presenting a case series of Sri Lankan patients suspected of LHON and MELAS in whom genetic confirmation was obtained by this low-cost method.

Methods

Two unrelated patients suspected of LHON, and one patient and his mother suspected of MELAS after proper clinical evaluation and investigations including serum and cerebrospinal fluid (CSF) analysis and standard neuroimaging were included in the study. Genetic test was performed using Sanger sequencing on their extracted mitochondrial DNA to detect the three common mutations in LHON MT-ND4:m.11778G>A, MT-ND6:m.14484T>C, MT-ND1:m.3460G>A and the three common mutations in MELAS MT-TL1:m.3243A>G, m.3271T>C and m.3252A>G based on clinical suspicion.

Results

Two patients suspected of having LHON were males of 15 and 21 years of age presenting with painless progressive bilateral sequential visual impairment developed over 1 year duration without positive family history or consanguinity. Both harbored MT-ND6:m.14484T>C with heteroplasmy confirming LHON. The male patient and his mother suspected of having MELAS presented at 11 years and 36 years of age, respectively with partial seizures, infarcts on neuroimaging and elevated serum and CSF lactate. Both were found to be harboring MT-TL1:m.3243A>G confirming MELAS. The proband was heteroplasmic while the mother was homoplasmic.

Conclusion

Targeted Sanger sequencing for common mitochondrial mutations in suspected LHON and MELAS is a cost-effective method of genetic confirmation.

Keywords : LHON, MELAS, low-cost genetic test, Sanger sequencing, common mitochondrial mutations

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Mapping the evolving dynamics of genomic and immune interactions during initiation and progression of oral squamous cell carcinoma from precancerous lesions

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Background & Objectives:
Oral cancer is a major public health burden in south-east Asia. Oral cancer often progresses from precancerous lesions, such as leukoplakia, in a small fraction (<10%) of individuals. The stepwise molecular basis of this transformation is poorly understood. In this study we sought to understand dynamics of molecular evolution from normal oral epithelium to squamous cell carcinoma through a precancerous-state (leukoplakia).

Method(s) & Results:
We jointly analysed multi-omics-data from normal, leukoplakia and tumour tissue-triads from same oral cancer patients (N=28). Substantial sharing (16.4-94.1%) of somatic mutations were observed in leukoplakia with concomitant tumour pairs. We reconstructed the most-probable sequential events during malignant transformation of leukoplakia. We identified somatic alterations in CASP8-gene to occur early in a leukoplakia-state (54.5% cases) and matched transcriptome data showed enhanced gene-expression favouring survival and intra-epithelial-migration of the mutant cells. In a validation cohort of 20 patients, we have validated the early appearance of CASP8-alteration. Further, in-vitro pan-caspase-inhibition-assay in patient-derived oral cancer cell-line resulted in significantly enhanced migration. Our integrative multi-omics-analysis constructed a stepwise model of tumour evolution as follows, after initiation of tumorigenesis in precancerous tissue, tumours additionally acquired - (a) higher mutation rate - often contributed by increased APOBEC activity, (b) additional pathogenic somatic mutations in driver genes and (c) increased chromosomal instability. We identified evolving immune dynamics - sequential depletion of cytotoxic T-cells and concomitant increase in inflammation - during malignant progression. Genomic alterations that appeared early in a leukoplakia-state (e.g.,CASP8-alterations) and propagated to tumour showed to harbour immune-escape capabilities.

Conclusions:

We show that the selection and clonal expansion of mutant cells from precancerous lesions to tumour is a resultant of a tradeoff between the pathogenicity of mutation and its immune escape potential.

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

Keywords: Oral precancer, progression, CASP8, immune-escape, evolution

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Indirect Genotyping Techniques: a Valuable Tool for Limited-Resource Settings

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Background & Objectives

Genetic study of several diseases in Tunisia has shown the presence of founder mutations. Genotyping them using Sanger Sequencing is costly. Our goal was to develop indirect cost-effective genotyping techniques.

Methods and Results:
Linkage analysis:
Microsatellite homozygosity mapping was used to unravel the causative gene. Due to the lack of information for certain families and the inability to interpret the haplotypes, we have abandoned this technique.
RFLP
We have applied this strategy for genetic variants that are associated with the creation or the abolition of restriction sites. Taken the required time added to its limitation to a certain number of variants, this technique was left aside.
ASO
This technique requires 2 assays per individual performed by 2 different forward primers. A direct analysis of the gel can reflect the genotype of the tested individual. It was considered time and cost-effective. However, it was not always enough sensitive.
HRM
It is based on the differentiation of the genotypes according to their melting curve shape.
This technique was reliable only for substitutions but not applicable for deletions or insertions.
KASPR
Based on the same principle as ASO, with the use of fluorescent primers, this technique was useful in diagnosing several genetic variants in an automatically, rapid, and middle-throughput way. However its cost added to its limited applications to approved variants was behind leaving this technique.
ASO-GO
A derivative from ASO with the detection being performed by fluorescence measurement after adding graphene oxide, an advanced material, in order to increase the revelation sensitivity. With this technique, we were able to reduce the cost by 5 and the time by 3.

Conclusions:

Among the above techniques, we retained ASO-GO as the most reliable. We are actually working on optimizing a specific biosensor for molecular biology techniques, generally and for genotyping, specifically.

Keywords: Indirect genotyping, cost-effective, ASO-GO

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Rare spastic paraplegia: First case report from Nepal

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Introduction: Autosomal recessive spastic paraplegia-57 is an extremely rare and complex genetic disorder that causes progressive muscle weakness, primarily in the legs. The condition is caused by a mutation in the TFG gene and is inherited in an autosomal recessive pattern. This case report aims to describe a newly identified case of autosomal recessive spastic paraplegia-57 in Nepal.
Case Report: The report describes a 10-year-old girl with a history of abnormal cervical curvature, muscle weakness, spastic paraparesis, and hyperactive reflexes. Genetic testing identified a homozygous missense mutation in the TFG gene (c.317G>A; p.Arg106His), confirming the diagnosis of SPG57. The diagnosis of SPG57 is challenging due to its rarity and complexity, and genetic testing is crucial for its identification. The identified mutation in the TFG gene is predicted to be disease-causing and has a low frequency in the general population. This case report highlights the importance of genetic testing in diagnosing rare genetic disorders.
Conclusion: Autosomal recessive spastic paraplegia-57 is a rare and complex genetic disorder primarily affecting the legs' muscles. This case report demonstrates that genetic testing is crucial in diagnosing this condition. Further research is needed to understand the underlying mechanisms of SPG57 and develop effective treatments for patients.

Keywords: Rare Disease, Spastic, Paraplegia, Genetic Disorder, Autosomal Recessive

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Breast cancer and smell: Hints from epigenetic and functional alteration of the olfaction

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Background & Objectives: Olfactory receptors are G protein coupled surface receptors (GPCRs) of which their ectopic expression is currently of mounting interest to the development and metastasis of malignancies. These genes having a direct contact with the environment may probably be stimulated by various factors which can bring about methylation aberrations, including DNA hypo and hyper-methylation. Here we gather clues from epigenetic and phenotypic data in order to further our understanding of the potential association of the olfaction with oncogenesis.
Method(s) and Results: Whole methylome dataset of breast cancer series generated by Illumina Infinium Human Methylation 450 Bead Chip was interrogated for differentially methylated genes and further subject to network analysis using various bioinformatic tools. Analysis of putative phenotypic trait in olfaction function was performed using smell detection and smell identification tests and data were analysed using Mann-Whitney test.

Sixty-eight differentially methylated ORs were enriched mainly on chromosomes 1q23, and 11p15, specifically 1q44 (P value 6.867e-20). Amongst the disease signatures of these hypomethylation events was breast cancer itself (P value 0.004437). Network analysis suggests the interaction of differentially hypo and hyper methylated olfactory receptor genes might be pivotal in stimulating several important biological pathways including circadian genes and pathways potentially associated with metastasis. Phenotypic smell test shows a generalised impairment of smell capability in breast cancer patients as compared to controls (Mann-Whitney Test P=0.0001), an effect that is independent of chemotherapy.

Conclusions: In nutshell the olfaction appears as a crucial element and feature of carcinogenesis, evident by both phenotypic and genotypic (epigenetic) data in a well characterized breast cancer subset.

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

Keywords: Breast cancer, Gene networks, Hypomethylation, Olfactory receptors, Smell test.

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Exploring factors contributing towards competencies of medical sciences laboratory technicians and recommendations for plausible improvement: A case study of a Scientific Innovation Laboratory based in a resource constraint setting focusing on genomics.

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Background & Objectives: Research in Africa is booming, seeing an increase in projects taken up. In fields that are constantly advancing and evolving, like genomic medicine, it is essential to diligently and reproducibly conduct research and services, this will sustainably build capacity in Africa. There are four main categories that impede growth of capacity. I will focus on the educational barrier as it builds on the competency needed to create quality outputs that attract funding and business to resolve the other three monetary related categories. In order to produce quality outputs, it is important to ensure that there is competency, that is, the necessary knowledge is applied when designing and implementing solutions.

Method(s) and Results: I conducted a study that recruited technicians, their direct managers (senior scientists) and senior management. I conducted focus groups, survey (technicians and managers) and safe-to-fail experiment (senior management). Technicians are key as they complete core functions that directly affect outcomes. I used Educational Theories to elucidate how adults in this environment learn. To better understand the complexity of my case study's system, I used Systems Theory. There were 7 theme findings: communication, contextual factors, education, hierarchy, interpersonal, leadership, operational systems, and organizational climate/culture. The themes were selected as they were described to directly affect outcomes.

Conclusions (Significance and Impact of the Study): The emergence of these themes was directly or strongly indirectly influenced by management. In conclusion, there is a need to rethink management strategies and recommendations were made. That is to better manage organisations in fields like genomic medicine that are ever evolving. In particular, an organisation that has prevailing resource constraints due to being based in a low and middle income country.

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

Keywords: Adult learning, Genomic medicine, Systems theory, Resource constraint, Medical Sciences and Management.

Differential expression of inflammatory-related genes in healthy long-term meditators: A case-control study

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Background and objectives: The effectiveness of meditation in enhancing both mental and physical health is well supported by data, although the molecular mechanisms behind these beneficial effects are still poorly understood. It is hypothesized that the expression of stress-induced inflammatory-related genes is downregulated by practising long-term meditation. Hence, this study aims to investigate the differences in the expression of a selected set of inflammatory-related genes in healthy long-term meditators and non-meditators.

Methods and results: In this case-control study, RNA was extracted from peripheral venous blood samples collected from 30 long-term meditators and 30 age- and gender-matched non-meditators after obtaining informed consent. Gene expression of a selected set of inflammatory pathway genes: IFN-ɣ, IL-6, CCL-2, CCR-7, TNF-α, NF-ĸB, CXCL1, and COX-2 were performed by reverse transcription quantitative polymerase chain reaction relative to the house-keeping gene, GAPDH. Mean relative gene expression for both groups were compared using independent sample t-test. Relationship between duration of meditation practice and the relative gene expression of the above genes were analysed by Pearson correlation. The average age (±SD) of the participants was 43.83 ± 9.92 years, and 19 out of the 30 (63.34%) participants in each group were males. The meditators had been practicing meditation for an average of 6.80 ± 3.27 years, and they had averaged 5.82 ± 3.45 hours per day. Mean relative gene expression of IFN-ɣ (Fold change (FC)=3.6,p=0.013), IL-6 (FC=3.6,p=0.045), TNF-α (FC=2.7,p=0.038), NF-ĸB (FC=3.2,p=0.048), CXCL1 (FC=3.3,p=0.023), and COX-2 (FC=3.8,p=0.045) genes were significantly lower in the long-term meditators compared to the non-meditators. Further, relative gene expression of IFN-ɣ (p=0.005), IL-6 (p<0.001), TNF-α (p<0.001), and NF-ĸB (p<0.001) showed significant down-regulation with increasing duration of meditation practice.

Conclusion: The significant differential expression observed between meditators and non-meditators indicate that practising long-term meditation may promote down-regulation in expression of some inflammatory pathway genes leading to reduced inflammation in the body.

Keywords: meditation, gene expression, inflammation, long-term meditators, case-control

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Genetic and Molecular Study of Congenital Myopathies and Congenital Muscular Dystrophies in Morocco

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Background & Objectives: Congenital neuromuscular diseases, in particular congenital muscular dystrophies (CMD) and congenital myopathies (CM) are a group of rare pathologies of genetic origin, characterized by the complexity of their diagnosis due to their clinical and genetic heterogeneity. There are very few genetic studies on CMD and CM in the Moroccan population, which explains the absence of molecular epidemiology data for these diseases. This work focuses on the genetic and molecular study of 21 unrelated Moroccan families affected by early-onset neuromuscular diseases.

Methods and Results: The diagnostic approach that we followed is Next-Generation Sequencing (NGS) analysis in the probands using two types of approaches: targeted gene panel sequencing, oriented by clinical features, and clinical exome sequencing. These two strategies allowed us to identify 16 mutations in 17 families including four novel pathogenic mutations in LAMA2 and TTN genes. We also showed, for the first time, the association of a known LMNA mutation with a CMD phenotype that has never been previously reported in the literature. NGS technology allowed us to aset the precise diagnosis of congenital myasthenic syndrome in another Moroccan family (Family 22) with identification of a novel mutation in COLQ gene.

Conclusions: We emphasize, through our work, the interest of NGS in the precise diagnosis of these heterogeneous diseases in order to reduce wandering and diagnostic impasse, to adapt patient care, and to provide appropriate genetic counseling to relatives at risk. Our results enrich the molecular epidemiology data in our population, and to expand the phenotypic and mutational spectrum of these diseases. This work also opens perspectives for other subsequent studies, in particular on genotype-phenotype correlations and on diagnostic strategies with the best cost-benefit ratios.

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

Keywords: Congenital Muscular Dystrophy, Congenital Myopathy, Congenital hypotonia, Next-Generation Sequencing, Moroccan patients

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Designed and Implementation of a T-ARMS-PCR Assay to Genotype Genetic variants Associated with Retinoblastoma in a cohort of Sri Lankan Population

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Background

Retinoblastoma (RB) is the most common intraocular malignancy, characterized by high mortality if not detected early and treated promptly. Due to its familial and sporadic occurrence has led to the identification of the first tumor suppressor gene RB1. The rare childhood malignancy retinoblastoma serves as one of the most important models in modern cancer genetics and is the most common ophthalmic malignancy in children under five years in developing countries. Mutations screening is important for risk assessment in future siblings and offspring of RB patients.

Objective
To design and implement a novel genetic assay to identify genetic variants associated with Retinoblastoma in a cohort of Sri Lankan Patients.

Method

A prospective descriptive study was carried out with 59 patients referred to the Eye unit of the lady Ridgeway hospital, Colombo, Sri Lanka. Genomic DNA of 59 patients were genotyped using primers designed for Tetra-primer amplification refractory mutation system PCR (T-ARMS-PCR).

Results

The median age at diagnosis was 2 year and 7 months. Female to male ratio was 3:2. Out of which, 63% had unilateral retinoblastoma and 36% had bilateral retinoblastoma. Family history of RB was seen in 6.78 % patients. Most cases were advanced group D at presentation. All patients tested homozygous for the ancestral allele for both rs587776789 and rs121913305 variants of the RB1 gene.

Discussion

The discovery of germ-line mutations in unilateral patients is valuable since they can be segregated based on their mutational status, and this will impact the genetic counseling given to them as they age.

Conclusion

This assay can be introduced as a sensitive, specific and simple diagnostic technique for screening related genetic variants for Retinoblastoma in the Sri Lankan population.

Declaration of Conflicts of Interests

The research team declares that they have no conflicts of interests in relation to this study.

Key words: Retinoblastoma, Novel variants, RB1 gene mutation, genotype, Allele frequency

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Engagement in a UK South-Asian ancestry community to support pharmacogenomics clinical implementation and research.

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Background:

South-Asian ancestry populations are underrepresented in genomic studies and therapeutics trials. British South-Asians suffer from multi-morbidity leading to polypharmacy. Our objective was to elucidate British South-Asian ancestry community perspectives on pharmacogenomic implementation, and potential barriers to sharing pharmacogenomic clinical data for research.

Methods and Results:

Four focus groups were conducted consisting of 9-12 participants per group. Two groups were mixed gender, while one group was male only and one was female only. Simultaneous interpretation was available to participants in Urdu and Bengali. Focus groups were recorded and abridged transcription and thematic analysis were undertaken.

There were 42 participants, 64% female. 26% were born in the UK or Europe. 52% were born in Bangladesh and 17% in Pakistan. 36% reported university level education.

Main themes that emerged common to both clinical implementation and sharing clinical data for research were: benefits, trust, education, and data sharing.

Pharmacogenomics was perceived to be beneficial to individuals but pose a risk of overburdening resource limited systems, and research from this data was felt to be beneficial to the community with some risks to the individual privacy. Trust was a central theme in clinical implementation and essential to sharing clinical pharmacogenomic data for research. Feeding back research results was crucial to trust. There was consensus that pharmacogenomic testing with education, outreach, and communication would facilitate trust, and that where there was trust there was a higher chance of people both taking their medication as prescribed and sharing data for research. Data sharing was desirable if the researchers did not have a financial stake, and benefits would be shared.

Conclusions (Significance and Impact of the Study):
Pharmacogenomics implementation with appropriate education and communication has the potential to enhance trust and contribute to increased medication compliance. Trust drives data sharing.

Conflict of interest disclosure: None to declare.

Keywords: Pharmacogenomics, Special Populations, Pharmacotherapy, Clinical Service Development, Research engagement

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Exome sequencing and an in-house bioinformatic pipeline as a diagnostic tool in pediatric epilepsy and other neurological disorders

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Background & Objectives: Among the possible known hereditary factors that can cause epilepsy, many of them are point mutations in a large group of known genes. This may lead to a run of different time consuming tests to intent to reach a diagnostic result. Here, we present a next generation sequencing approach combined with a bioinformatic pipeline to improve diagnostic yield, comparing to conventional tests.
Methods: Sixty five paediatric patients with different types of epilepsies and related neurological disorders where tested for point mutations in selected genes using a novel bioinformatic gene panel approach. Participants where patients from the paediatric division of the Neurological clinic Fleni in Argentina from December 1, 2017, to December 1, 2019; final follow-up was March 1, 2020. Gene panels where designed according to patients symptoms to improve diagnostic accuracy. Re-analysis of genomic sequencing results was available upon medical request.
Results: Among 65 patients that where studied (mean age, 7 years; [54%] males, [46%] females), we were able to identify 45 sequence alterations in known disease-causing genes; one was founded through gene panel re-analysis. Identified variants led to a diagnostic result in 22 patients (34%). Gene panel re-analysis resulted in the genetic diagnose of one initially unsolved case.
Conclusions: Our results using a next-generation-sequencing approach combined with bioinformatics tools exhibit a diagnostic yield of 34%, which is considerably higher than most mutation detection rates achieved with conventional tests (18-29%). This massive approach enables the possibility for possible re-analysis of inconclusive and non-diagnosed cases to further determine the definitive cause of the disease, without additional costs and minimizing diagnostic time compared to conventional genetic tests. Overall, our results demonstrate that this is a powerful diagnostic tool when it comes to diseases with a wide or unclear genetic etiology like epilepsies.

Keywords: Genetics, NGS, Argentina, Neurology, Diagnosis

Impact of donor CYP3A5 genotype on pharmacokinetics of tacrolimus in South African paediatric liver transplant patients

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Optimal therapeutic blood levels of the immunosuppressant, tacrolimus, are critical for preventing solid organ rejection, especially in paediatric liver transplant recipients. The cytochrome P450 3A5 isoenzyme (CYP3A5) is primarily responsible for hepatic tacrolimus metabolism. Pharmacogenetic research, although limited in South Africa, attributes CYP3A5 single nucleotide polymorphisms (SNPs) to variable inter-patient tacrolimus concentration dose ratios (CDR). The rs776746 T>C SNP (CYP3A5*3 defining variant) results in a splice defect and a non-functional enzyme. Clinically, to reach the same tacrolimus CDR, patients with at least one copy of the *1 allele (expressors) require a higher tacrolimus dose than *3 homozygotes (non-expressors).

Blood samples from 46 living liver donors were collected, gDNA extracted, and CYP3A5 rs776746 T>C genotype established (PCR, RFLP analysis and Sanger sequencing validation). The relationship of donor and recipient characteristics with the mean CDR over the first 15 days of tacrolimus immunosuppression was analysed by a general linear model. Non-confounding significant variables were included in a multiple regression model.

This study showed that all expressor donors genotyped as CYP3A5*1 homozygotes are of Black African self-reported ethnicity. The graft-to-recipient weight ratio and the CYP3A5 donor genotypes were independent factors that significantly ($p<0.05$) impacted the mean tacrolimus CDR over the first 15 days of immunosuppression. Donor CYP3A5 expressors (*1/*1 and *1/*3) have significantly lower recipient mean tacrolimus CDRs post-transplant and therefore, require higher tacrolimus doses, in comparison to non-expressors, to reach the same therapeutic target range. Whilst aspects of this study have been previously published, this is the first dataset in a liver transplant cohort to have predominant representation of homozygous CYP3A5 expressors, prevalent in the African population, with associated clinical data. These findings suggest that a stratified tacrolimus dose algorithm incorporating CYP3A5 genotype could be developed, which would better inform immunosuppression treatment, especially in patients of African ancestry undergoing solid-organ transplantation.

Precision Medicine, Tacrolimus, Liver Transplant, CYP3A5, Pharmacokinetics

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Investigating KRAS and BRAF mutations as a means of distinguishing sporadic from hereditary forms of colorectal cancer

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Colorectal cancer (CRC) is the third most prevalent malignancy and mutations affecting tumour-suppressor genes, proto-oncogenes, and genes involved in DNA repair pathways are the root causes. CRCs can be categorised as hereditary or sporadic depending on the source of the mutation. Microsatellite instability (MSI) is one pathogenic process that may result in CRC, while gene mutations

affect key pathways in CRC. Therefore, mutated genes can be employed as prognostic and predictive markers. This study aimed to resolve the unknown case status of CRC. The mismatch repair (MMR) status and mutational status of the KRAS and BRAF genes in each patient (n=47) were determined to infer disease heritability. Objectives: i) Selection of CRC patients from the UCT Anatomical Pathology database based on deficient MMR, proficient MMR with mucinous tumours, and high tumour infiltrating lymphocytes, ii) Selection of specific KRAS and BRAF mutations, iii) Isolation of DNA from formalin fixed paraffin-embedded tissue, iv) Sanger sequencing to detect mutations in KRAS and BRAF, v) Correlation of mutational changes and pathology in patients with an observed mutation, vi) MSI testing, vii) Finalising the decision on each patient's unknown case status (sporadic, hereditary, or to remain unresolved). All patients whose samples were successfully amplified were wild-type for each of the six mutations (BRAFV600E, KRASG12D, KRASG13D, BRAFK601E, BRAFG469A and BRAFG466V). MSI testing found 23 patients to be MSI-High while two patients were found to be microsatellite stable. Sanger sequencing and MSI testing helped partially resolve the unknown case status of CRC. These results are an indication that 45 patients' CRC is likely inherited while in two patients the disease is likely sporadic. However, further work is needed to confirm these results such as resequencing BRAFV600E and germline mutation testing in MMR genes.

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

Keywords:Hereditary colorectal cancer; Lynch Syndrome; Sporadic colorectal cancer; Sequencing; Cancer genetics

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Phenotype-Genotype correlation of chromosome 22q11.2 deletion: clues for a better clinical suspicion in a resource limited setting

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Background & Objectives
DiGeorge Syndrome is the commonest human chromosomal deletion syndrome, caused by deletion in Chromosome 22q11.2 region (DiGeorge Critical Region), namely LCR22A-H. Deletions involving LCRA-D and A-B are classified as proximal, LCRB-D, C-D are classified as central and those beyond LCRD, classified as distal deletions. Studies have shown phenotype genotype correlation. This study aimed to describe the phenotype of a Sri Lankan cohort of children against genotype.
Method(s) and Results:
Sixteen children with features suggestive of DiGeorge syndrome were recruited. The phenotypic features were gathered by obtaining history, examination and investigation findings from clinical records. Genotyping was done using Multiplex Ligation Probe Amplification (MLPA) targeting the 22q11.2 region; SALSA MLPA Probemix P250 DiGeorge.
Six(37.5%) had deletions. All(100%) were in the 22q11.2LCRA-D region. Ages ranged from 3 weeks to 18 years. Four(66.66%) were females. All had microcephaly, developmental delay, prominent nose with squared nasal root and abnormally folded ears and congenital heart defects [VSD:4(66.67%), ASD:3(50%), right-sided aortic arch:2(33.34%), tetralogy of Fallot:1(16.67%), double aortic arch: 1(16.67%)]. Five(83.33%) had short stature, hyper-nasal speech, and micrognathia. Four(66.67%) had hypocalcemia, absent thymic gland in 3(50%) and small in 2(33.37%). Three(50%) had gastrointestinal abnormalities [hernia:2(33.34%), duodenal atresia:1(16.67%), vestibular anus:1(16.67%)]. Two(33.34%) had ophthalmological abnormalities [posterior embryotoxon:1(16.67%), tortuous retinal vessels:1(16.67%)].
Conclusions

Congenital heart disease and certain dysmorphic features such as prominent nose with squared nasal root and abnormally folded ears were recognized as most consistent features in children with proximal deletion of chromosome 22q11.2 region. Other features seems to be variable. Clinical examination in view of dysmorphic features in children with congenital heart disease will be useful clues to suspect chromosome 22q11.2 deletion syndrome, thereby utilize the limited resources for genetic confirmation, in a low resource setting.

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

Keywords: DiGeorge, chromosome 22q11.2, proximal deletion, genetics, LCR (Low copy repeats)

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Participants and Stakeholders views on feedback of Genetics Research Findings of the H3Africa Kidney Disease Research Network, Ghana

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Genetics and genomics research raise important ethical issues, particularly those related to obtaining valid consent, engaging with relevant communities in the implementation of research and feedback of research findings.

There is evidence that variants of the Apolipoprotein L1 gene in Africans and people of African descent increase the risk of developing chronic kidney disease (CKD). A study carried out by the H3Africa Kidney Disease Research Network showed that 28.2% of study participants carried 2 APOL1 high-risk variants. It is also known that relatives of subjects with CKD may be at increased risk of developing CKD. Should participants and their relatives be informed about their risk of developing CKD? What findings should be given and who should be involved in the feedback process? The aim of this study was to seek the views of kidney disease research participants, families and stakeholders on feedback of genetic research findings. An exploratory qualitative approach was used for data collection. The study explored views of genomic researchers, participants, families and members of research ethics committees on what count as good ethical practice in deciding what, who and how to return genetic research findings through in-depth interviews, focus group discussions and deliberative workshops. Data was coded and structured with NVivo software and thematically analysed.

There was a consensus that relevant individual and aggregate genetics results should be fed back to participants and communities. Most participants preferred to receive their personal results from a doctor or a research scientist.

There is an ethical imperative to return validated clinically relevant individual genetic research results to the kidney disease research participants and families and aggregate results to communities. We recommend the Kidney Disease Research Network to educate participants and families on the concept of APOL1 risk variants, train Genetic Counselors and explore innovative strategies to support the feedback process.

Key words: Feedback, genetics, kidney disease, Africa, Ghana

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Phenotypic and Genotypic Landscape of a Cohort of Sri Lankan Individuals with Inherited Kidney Disease (IKD)

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Background & Objectives:
Inherited kidney diseases (IKDs) are mainly caused by rare pathogenic variants in the mendelian genes and about 10% of adults and most children with chronic kidney disease suffer from an IKD. As part of the workup, genetic testing should be considered following risk assessment for an IKD, which will provide crucial information on management and prognosis. This study was done to determine the clinical and genetic characteristics of patients who underwent genetic testing on the suspicion of an IKD.

Method(s) and Results:
All patients referred to the Human Genetic Unit for the evaluation of a renal disorder over a period of six years were included in this retrospective observational study; which amounted to 4% of all referrals. The diagnostic yield of Whole Exome Sequencing was 80%. Clinical diagnosis matched the genetic diagnosis in 75% of the cases. It ranged from Gitelman Syndrome to X-linked Alport Syndrome-1, Nephrotic Syndrome Type 2 & 24, Dent Disease 1 & 2, Primary Hyperoxaluria Type 1, Renal Hypouricemia-2, Renal Glucosuria and Nephrogenic Diabetes Insipidus. Roughly two third were paediatric patients. Three families were consanguineous and one third had a family history of renal disease. A total of nineteen variants in sixteen genes was detected. 90% were likely pathogenic or pathogenic variants and one third were novel variants.

Conclusions (Significance and Impact of the Study):
Deep clinical phenotyping in a low resource setting such as Sri Lanka has contributed to a high diagnostic yield. The detected novel variants adds insight into the genetic landscape of the Sri Lankan population.
This study highlights the importance of genetic testing in IKDs and these results may be used to develop a national registry for IKDs in Sri Lanka.

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

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Towards pharmacogenomics-guided tuberculosis (TB) therapy. N-acetyltransferase-2 genotypes among TB-infected Kenyans of mixed ethnicity

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Background and Objectives Pharmacogenetics is essential in driving personalised healthcare. Genetic polymorphisms of drug-metabolising enzymes such as N Acetyltransferase 2 (NAT2) are understudied among Africans. Towards pharmacogenomics-guided tuberculosis (TB) therapy, from among TB-infected Kenyan volunteers of mixed ethnicity, we identified the prevalent NAT2 single nucleotide polymorphisms (SNPs). We inferred their potential effects on enzyme function. The heterogeneity of this population and the possibility of recombination among the SNPs were evaluated. Methods We isolated genomic DNA from cryopreserved Peripheral Blood Mononuclear Cells of 79 volunteers with TB infection. We amplified the protein-coding region of the NAT2 gene by polymerase chain reaction (PCR) and sequenced PCR products using the Sanger sequencing method. Sequencing data were mapped and aligned to the NAT2 reference sequence using the Geneious software (Auckland, New Zealand). The R statistical software was used to infer the Linkage Disequilibrium (LD) and test for Hardy-Weinberg Equilibrium (HWE). Results Five genetic variants of the NAT2 gene 282C>T (NAT2*13), 341T>C (NAT2*5), 803A>G (NAT2*12), 590G>A (NAT2*6) and 481C>T (NAT2*11) were detected with allele frequencies 29.1%, 17.7%, 6.3%, 6.3%, and 3.8% respectively. The most frequent haplotypes were the wildtype NAT2*4 (39.0%) and NAT2*13A (29.1%). According to the bimodal distribution of acetylation activity, the predicted phenotype of this population was 75.9% rapid and 24.1% slow. All SNPs displayed similar levels of LD and were in HWE except the NAT2*5 represented variant 341T>C (D′ = 0.77, r2 = 0.47, p=0.04). Conclusion Our study confirms the known diversity in African populations. The high frequency of the rapid-encoding NAT2 haplotypes among Kenyan volunteers with TB infection may translate to an altered therapeutic efficacy of isoniazid during TB treatment. This information helps advance the development of relevant pharmaco-diagnostic tools for TB infection. We recommend continued genotyping of African populations and genotype-phenotype studies towards pharmacogenomics-guided TB therapy.

Keywords acetylation; N-acetyltransferase 2 (NAT2); genetic variants; tuberculosis; pharmacogenetics

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Imatinib resistance: The role of pharmacogenetic variability in a South African chronic myeloid leukemia cohort

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Background & Objectives
Drug-resistant cancers are often associated with poor patient outcomes. Chronic Myeloid Leukemia (CML) serves as a disease model for studying cancer drug resistance, specifically to Imatinib, a tyrosine kinase inhibitor. Approximately 20-30% of patients become resistant to Imatinib. Variability in patient drug response could be due to single nucleotide variants (SNVs) in genes that encode for Imatinib-metabolizing enzymes and transporters. The aim of the present study was to determine whether selected SNVs located within genes CYP3A4/3A5, SLCO1A2, SLC22A4, and SLC22A1 that encode selected drug transporters, contribute to an alternative mechanism leading to Imatinib resistance.

Methods and Results:

A maximum of 45 samples from Imatinib-resistant and 44 samples from Imatinib good responders CML patients were analysed using PCR-based genotyping assays. Baseline allelic and genotypic frequencies within our CML cohort were determined and compared between Imatinib good responders and Imatinib-resistant groups.

There were differences in allele frequencies for the following SNVs in genes SLCO1A2, CYP3A4, and CYP3A5 when compared to the global and African frequencies. Furthermore, obtained results showed that the observed and expected genotype frequencies were comparable for genes SLC22A1, SLC22A4, and SLCO1A2, however, it was different for the following genes SLCO1A2, CYP3A4, and CYP3A5.

Interesting findings include SNV rs35191146 which was linked to poor Imatinib treatment outcome, however, the simultaneous presence of SNV rs628031 circumvented this effect. The detrimental genotype was not observed in our cohort. Furthermore, the coincidental findings of variants SLC22A4 rs11568500 (c.616_617delinsCC), and SLC22A1 rs35191146 (c.1258_1260delATG and g.160139876_160139883delGTAAGTTG), will be explored in future studies.

Conclusions:
Even though the selected SNVs do not affect Imatinib resistance in our cohort, our study adds to the body of knowledge. This in turn highlights the need for future studies focusing on larger cohorts, with a larger selection of SNVs at more healthcare institutions across South Africa and Africa.

Pharmacogenetics, Imatinib, Drug resistance, Chronic Myeloid Leukemia, Single Nucleotide Variants

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VARIATION IN DIAGNOSTIC REQUESTS AND OUTCOMES FOR HEREDITARY THROMBOPHILIA - OVER TESTING AND UNDER TESTING

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Heritable thrombophilia is a multiple gene disorder with high mortality and morbidity. Genetic risk factors associated with Venous Thromboembolism have been linked to mutations in the genes of the coagulation/anticoagulation system. The more prevalent inherited risk factors are the gain-of-function mutations in coagulation factors V and II, namely factor V-Leiden (FVL and/or F5G1691A (FVR506Q,)) and prothrombin/Factor II (FII) F2G20210A. The epidemiology of the FVL and FII mutations has not been well studied within either the South African or African context.

Therefore, a retrospective audit was conducted to determine the total number of FVL and FII tests requested by clinicians and the prevalence of FII mutations in our setting at Tygerberg Hospital for an 11-year period. (2007-2017). In addition, 50 of these patients' samples was selected randomly for the screening of a novel gain of function mutation Prothrombin Yukuhashi c.1787G>T in exon 14 of FII gene. Peripheral blood samples were received, by the NHLS Molecular Haematology diagnostic laboratory from clinicians requesting the FII and FVL assay. Exon 14 of the FII gene was amplified using reference primers and verified by PCR followed by Bidirectional sequencing to identity the presence of the mutation. Statistical analysis of all data was performed with the help of a statistician.

For the audit, 80.4% of the requests were for FVL, 3.8% were for FII and 15.8% of the requests were for FVL and FII together. The most tests were requested during 2013 when the implementation of a multiplex assay occurred. The mutational frequency for FVL was shown to be 3.3%, compared to FII which was 6.9%.

The frequency of the FII mutation was more than double that of the FVL mutation, despite more than 80% of requests being for FVL alone. The study also showed that the Prothrombin Yukuhashi mutation was not prevalent in our cohort.

Hereditable Thrombophilia, Coagulation Factors, Variant Screening, Test Requests, FII, FVL

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Screening and characterisation of BCR::ABL1 kinase domain mutations in Chronic Myeloid Leukaemia patients at Tygerberg Hospital – Secondary mutations, drug resistance and associated problems

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We use Chronic Myeloid Leukaemia (CML) as a disease model to explore the type of potential drug resistant causing mutations at Tygerberg Hospital (TBH). The underlying genetic abnormality is a translocation and fusion between the Breakpoint Cluster Region gene and the Non-Receptor Tyrosine Kinase Abelson gene (BCR::ABL), t(9::22).

A retrospective audit was conducted on a CML cohort from 2013-2020. 20 of these participants were recruited for detection of KD mutations within ABL1 oncogene. Peripheral blood from routine diagnostic screening by the NHLS Molecular Haematology diagnostic laboratory were obtained for the mutation detection assay via bidirectional Sanger Sequencing. Identified variants were subjected to various bioinformatics tools to investigate protein and consequent pathway effects.

165 patients with confirmed CML treated at TBH was captured. 46.1% of CML patients were female, and 53.9% were male. The patients were from 69 different areas in the Northern district of Western Cape. The youngest patient was two years old and the oldest was 88 years old, $\bar{x} = 45$-46 years. Of interest's sake, 104 of the initial 164 patients who were diagnosed were still undergoing treatment, with the remainder being Lost-To-Follow up. A total of 57 patients presented with possible resistance. 20 participants samples were screened for variants with a mortality rate of 20%, with a relative survival rate of less than five years. Sequence analysis showed potential interesting variants in Exon 4 and 9 of the ABL gene. However, bioinformatic analysis alludes to the fact that these variants are not likely to play a role in resistance.

In conclusion, the TBH CML cohort has a younger age at presentation which puts a greater strain on the public sector, and a great number of patients are loss to follow up. More so, the age relative to CML deaths, as well as relative survival greatly differs from literature.

CML, Drug Resistance, BCR::ABL1 dependent, Secondary Mutations, Fusion Genes

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A study on genetic variants associated with Sarcoidosis in the Sri Lankan population

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A study on genetic variants associated with Sarcoidosis in the Sri Lankan population.

Background and Objective

Sarcoidosis is a granulomatous disorder that affects multiple organs, primarily the lungs and the skin. Previous research has identified that environmental and genetic factors are highly associated with disease prevalence. HLA and non-HLA gene polymorphisms have been linked to the onset of this disease and are significant markers for Sarcoidosis susceptibility. BTNL2 and HLA-DQB1 are the most commonly associated genes with Sarcoidosis. The objective of this study is to determine the genetic variants associated with a cohort of Sarcoidosis patients in the Sri Lankan population.

Methods and Results

A cohort of 15 clinically suspected Sarcoidosis patients were selected for this study and DNA were extracted. The primers were designed to selected variants to perform T-ARMS polymerase chain reaction. The PCR protocol was optimized and validated by Sanger sequencing.
Granuloma formations were identified in 93.3% and the lungs were the highest affected organ, followed by the eyes. All patients had homozygous ancestral allele for rs1049130 and about 20 % had heterozygous mutant allele for rs2076530 who presented with symptoms affecting their eyes and granulomas in the lungs. Sanger Sequencing results confirmed the presence of heterozygous mutant allele for rs2076530.

Conclusion

As genetic research regarding Sarcoidosis has not been previously conducted in Sri Lanka, this study is an important step toward further understanding the genetic variants in our population. This study has developed a cost effective assay for the detection of variants rs1049130 and rs2076530 associated with Sarcoidosis. A replication of the study with a larger population is essential to develop biomarkers for early detection of the disease.

Key words

Sarcoidosis, Allele, Granulomatous disorder, Genetic variations, Polymerase chain reaction.

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Utilizing Population Pharmacogenomic Data for Priotorizing Drug Choice

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Utilizing Population Pharmacogenomic Data for Priotorizing Drug Choice
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Genomic variations dictate a significant proportion of interindividual drug response and toxicity differences. Population pharmacogenomic data, including variations in actionable pharmacogenes, can be used for optimizing drug choices in the same population. In the current work, we illustrated the application of this paradigm in the Emirati population.
First, we used targeted next-generation sequencing to examine 100 important pharmacogenes in 100 healthy individuals. The results revealed that 93% of healthy Emiratis could benefit from pharmacogenetic testing results for better and safer use of drugs. Pharmacogenetic variants interacting with cardiovascular medications, including warfarin, clopidogrel, and statins, were the most prevalent variants that alert to the possible suboptimal use of these medications in this population.
Second, three genes (SLCO1B1, ABCG2, and CYP2C9), known to affect the safe use of statins, were examined deeply. Re-analysis of whole exome sequencing data from 242 Emirati individuals enabled extracting the three genes' genotypes, haplotypes, diplotypes, and predicted phenotypes. The results

illustrated a 29.8% and 5.4% frequency of SLCO1B1 decreased and poor function alleles, respectively. The high frequency of these impaired function alleles alerts of the possible unsuitability of simvastatin and lovastatin use in this population. In contrast, the low frequency of ABCG2:rs2231142 (6%) indicates that rosuvastatin can be used more safely in Emiratis.

The application of genome-based precision medicine is sought as cost-effective practice in the long term. Our work highlighted how population-specific pharmacogenomic data could predict safer drugs for the same population. The illustrated paradigm can be used for middle and low-income countries as soon as pharmacogenomic data is available for their populations.

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Developing an integrated risk score for cardiovascular disease for African populations

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Background & Objectives: Cardiovascular diseases (CVDs) are a leading cause of morbidity and mortality in African populations. Polygenic scores (PGS) can provide a measure of an individual's genetic susceptibility to CVD and enhance risk prediction beyond traditional risk factors. This study aimed to develop and assess risk models that integrate genetic and non-genetic data to predict cardiometabolic traits in individuals of African ancestry.

Method(s) and Results: Summary statistics from the Uganda Genome Resource Genome-wide Association study (n=14,126) was used to derive PGSs for 14 cardiometabolic traits in the AWI-Gen target sample (n=10,603). Regression analysis assessed the relationship between each PGS and corresponding cardiometabolic traits and seven CVD outcomes (CVD, heart attack, stroke, diabetes mellitus, dyslipidaemia, hypertension, and obesity). The predictive utility of the genetic data was determined by deriving and evaluating elastic net models containing multiple PGS and reference-projected principal components (PCs) of ancestry. An integrated risk prediction model incorporating genetic and conventional risk factors was developed. Our African-specific PGS displayed significant but variable within and cross- cardiometabolic trait prediction (max. R^2 = 6.8%, p=1.86×10^{-173}). PGS were significantly associated with dyslipidaemia (DLD) (max. logOR (SE) = -0.25 (0.02), p=8.02×10^{-29}), hypertension (HTN) (max. logOR (SE) = 0.15 (0.04), p=8.34×10^{-4}), and obesity (OBS) (max. logOR (SE) = max. logOR (SE) = 0.13 (0.03), p=2.22×10^{-5}). Elastic net models combining PGS and reference-projected PCs significantly improved prediction over PGS scores alone. Furthermore, models including genetic data and non-genetic risk factors significantly improved risk prediction over non-genetic factors (DLD: R^2 increase= 1.8% p= 1.22×10^{-296}, HTN: R^2 increase= 1.5% p= 6.68×10^{-263}, OBS: R^2 increase = 2.3%, p= $>1.00 \times 10^{-300}$).

Conclusion - This study demonstrates the importance of considering genetic factors, including PGS and projected PCs of ancestry, when developing CVD risk prediction models in African populations,

and that combining these factors with conventional CVD risk factors, can enhance prediction models over conventional non-genetic CVD risk factors alone.

Conflict of interest disclosure: Cathryn M. Lewis is a member of the Research and Development SAB at Myriad Neuroscience. The remaining authors declare no potential conflicts of interest, whether scientific, financial, or personal.

Keywords: African populations, Cardiovascular diseases, Polygenic scores, Risk stratification, Integrated models

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Analysis of Genomic Data in Chilean Pediatric Patients with Drug-Resistant Epilepsy

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Background & Objectives:
The diagnosis of drug-resistant epilepsy (DRE) in pediatric patients with unresolved etiology is challenging, particularly in countries with non-European or admixed populations. In this study, we aimed to 1) increase our diagnostic capacity by implementing exome sequencing coupled with bioinformatic analysis in Chilean DRE patients, and 2) to identify novel monogenic causes, expand our clinical knowledge of pediatric DRE, and generate a rich phenotypical database of Chilean DRE patients.

Method(s) and Results:
We recruited 20 Chilean pediatric DRE patients between 0-18 years old who had a prior genetic epilepsy panel with negative results or variants of unknown significance. Exome sequencing was performed using the Agilent SureSelect V6 library and variant calling was carried out with the GATK2 protocols. Bioinformatic annotation and variant interpretation was performed following the American College of Medical Genetics (ACMG) criteria. We identified three novel pathogenic variants (CSNK2B, SCN1A, ALDH7A1) and nine likely pathogenic variants. The remaining three cases carried only variants of uncertain significance. Our approach detected pathogenic and likely pathogenic variants in 80% of cases.

Conclusions (Significance and Impact of the Study):
Our study shows the increased diagnostic yield of exome sequencing over epilepsy panels in pediatric DRE patients with unresolved etiology in Chile. The identification of novel pathogenic and likely pathogenic variants expands our clinical knowledge of pediatric DRE and provides potential targets for personalized treatment. The rich phenotypical database generated in this study can be used for future research and may lead to improved outcomes for patients with DRE. Finally, the development of an in-house bioinformatic pipeline for variant interpretation will accelerate diagnosis in Chile.

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

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Advancing Genomic Literacy: Implementing an Interactive Family Health History Resource in At-Risk Communities

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Background/Objectives:
Chronic diseases place significant burden on families and communities worldwide. Identifying genomic risks associated with chronic disease allows for earlier prevention and intervention, leading to improved health outcomes and a reduction in health disparities. Family health history (FHH) is a cost-effective genomic tool that allows families to identify their risk for common complex conditions. However, knowledge about personal FHH and the link between FHH and complex disease risk is not equitable across communities.

The Families Sharing Health Assessment and Risk Evaluation (SHARE) toolkit is an educational resource developed to improve families' understanding of FHH and chronic disease risk. Building upon the existing collection of Families SHARE tools, the objective of this project is to expand genomic literacy in at-risk communities via an interactive video resource.

Methods/Results:
Participants self-identifying as Black/African American were recruited from low-income neighborhoods of Washington, D.C. After providing informed consent, they watched an interactive video (available in multiple languages), designed to be a companion to the existing Families SHARE workbook. The video is interactive and personalized to a) assess participants' understanding of FHH and genetic risk, and b) allow participants to customize the video experience to their unique interests and knowledge gaps.

Preliminary data shows that 72% of participants with lower genomic literacy improved throughout the video on all knowledge check questions, suggesting the video resource is an effective education tool for FHH. Additionally, nearly all participants following video completion indicated they felt comfortable discussing FHH with family members and providers.

Conclusions:
FHH is an powerful educational tool for improving FHH knowledge across health disparities while reducing chronic disease prevalence. Ensuring accessibility to FHH tools through interactive formats is imperative to advance genomic literacy and promote health conversations within communities.

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

Keywords: genomic literacy, chronic disease, risk, equity, accessibility

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Precision Medicine course for Medical Residents in Rwanda: assessment of knowledge and satisfaction.

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Introduction

As genomic data are becoming part of patients' health records; there is a challenge to physicians to use this information, because current teaching methods rarely prepare medical graduates in a manner that enables them to discuss complex issues with their patients or help patients reach their own decisions.

This study assessed the impact and resident's satisfaction of an e-learning precision medicine short course at the University of Rwanda (UR).

Methods

PM course was developed and created in the e-learning management system, and was provided through blended learning approach during a period of 1 months in the academic year of 2022. The first 2 weeks consisted of online self-directed learning in the Moodle system, one week of face to face and one last week of online assignment. The course evaluation consisted of (1) a pre-course survey on Medical Residents perspectives on Precision Medicine, (2) Quasi experimental methods using 50-question pre-test and post-test knowledge assessment on Genetic and Genomic and (3) a post course satisfaction survey in year 1 medical residents (Internal Medicine, Gynecology & Obstetrics and Dermatology)

Results

Among the 28 residents who participate in the course: 20 (71%) completed the pre-course survey on perspectives on PM, both pre-post MCQs tests and the post-course satisfaction evaluation survey. Pre- and post-tests assessed residents' knowledge and change in knowledge was assessed using paired t-tests, with improvement of knowledge of 48% in pre-post MCQs upon completion. Medical residents showed satisfaction with the PM course, and were willing to use genomic information in their future practice however they still found content of genomic very complex.

Conclusions

The course was effective in improving resident's knowledge in precision medicine and residents found these lectures to be beneficial.

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

Keywords: Medical Residents, Precision Medicine, Blended learning, Genomics, Rwanda.

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Preparedness of Nigerian Medical Students for an Era of Precision Medicine – A Multi-center Cross-Sectional Survey in Lagos, Nigeria

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Background

Advances in precision medicine in Nigeria call for a need to improve genomics education and competency among healthcare practitioners to facilitate clinical translation. Due to the paucity of

research in this area, this study aimed to assess the preparedness of Nigerian medical students to integrate precision medicine into their clinical practice.

Methods

This was an institution-based cross-sectional study of 300 4th to 6th-year medical students attending the two fully-accredited colleges of medicine in Lagos, Nigeria recruited by convenience sampling between April and October 2022. The survey used an adapted tool administered via Google Forms and assessed awareness, perceived knowledge, ability, and attitudes toward precision medicine as well as ethical concerns and perceptions about their education in precision medicine. Collated data were analyzed using Stata/ MP-17.0. Univariate associations were carried out using Spearman's rank correlation, Independent t-tests, one-way ANOVA and Chi-square tests. P value < 0.05 was considered statistically significant.

Results

Awareness of precision medicine terminologies was high (92.0%). Respondents had slightly above-average median knowledge and ability scores and high median attitude scores. There was a strong positive significant correlation between knowledge and ability scores (r = 0.72, p < 0.001) and a weak negative significant correlation between knowledge and attitude scores (r=-0.14, p = 0.02). Respondents expressed concerns mostly about the misuse of genomic data by governments and corporate bodies (35.7%) and the possible consequent widening of socioeconomic disparities (34.0%). Although respondents thought that it is important to learn about precision medicine (65.0%), only 11.3% felt that their education had adequately prepared them and only 10.3% (n = 31) respondents felt their professors have encouraged the use of precision medicine.

Conclusion

These findings highlight gaps in preparedness for precision medicine and the consequent need to improve precision medicine education among Nigerian medical students.

Keywords

Precision Medicine, Personalized Medicine, Medical Genomics, Medical Education, Nigeria.

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Prevalence of Tuberculosis among health care seekers in Dangisharan, Dang

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Tuberculosis (TB) is a significant public health concern in Nepal, with high mortality rate due to its chronicity and multisystem complications. In 2018/19, the National TB Control Centre (NTCC) of Nepal estimated that approximately 0.44% of people in Nepal suffer from TB, with 0.26% new cases registered annually and 0.06% resulting in mortality. This study aims to determine the prevalence and risk factors associated with TB among individuals residing in Dangisharan, Nepal. A cross-sectional study was conducted at the Shreegaun Primary Health Centre between July 2022 and March 2023. Individuals aged 15 years and above, with a cough lasting for more than 14 days, were included. Symptomatic individuals were screened using chest X-ray (CXR), and sputum samples were collected

for microscopy and Xpert MTB/RIF. Informed consent was obtained from all participants, and the study was conducted in accordance with guidelines of NTCC. A total of 428 patients were screened for TB, of whom 20 (4.67%) were diagnosed with TB. The median age of individuals diagnosed with TB was 51.5 years. The prevalence of TB was higher in non-smokers as compared to smokers (5.13% vs 3.67%). In terms of gender, TB prevalence was higher in females than in males (6.63%vs 3.01%). Analyzing TB cases in terms of ethnicity , the overall prevalence of TB was higher among Brahmins (6.95%), Adivasis and Janjatis (4.49%, N=178) as compared to Dalits (2.29%) and Dasnami (4.16%). Individuals aged 45 years and above had a higher prevalence of TB than those aged 15-44 years (5.01% vs. 3.87%). This study highlights the prevalence of TB and associated risk factors including smoking status, age, gender, and ethnicity. Prevalence of TB was higher among non-smokers, females, the elderly, and non-Dalits. Ensuring better screening and diagnostic tools such as CXR, Xpert MTB/RIF are of importance for early case detection and treatment.

Keywords: Prevalence, tuberculosis, Xpert MTB/RIF, microscopy, sputum samples

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Clinicians' perceptions towards Precision Medicine tools for Cardiovascular disease risk stratification in South Africa

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Background/Objectives: Cardiovascular disease (CVD) risk stratification in African populations could improve with the inclusion of genetic risk to develop a clinically relevant precision medicine (PM) approach. African genetic data are scarce and current stratification approaches remain unvalidated. Clinicians are critical to PM adoption, and thus, this study explores clinicians' knowledge, perceptions, and confidence towards implementing a PM tool for CVD risk stratification in the South African public health setting.

Methods: Electronic self-administered questionnaire was provided to clinicians in public hospitals in Johannesburg. Knowledge, perception, and confidence towards PM-based CVD risk stratification and perceived barriers were evaluated. Bivariate analysis assessed the effect of clinical speciality, practice level, research involvement, postgraduate study, clinical experience, exposure to genetics training and traditional CVD risk stratification on mean scores.

Results: Of the 109 respondents, fewer than a third of respondents use clinical genetic testing, and 16% have formal genetics training. 80% had a low mean knowledge score, with higher scores associated with genetic training (p<0.0005) and research involvement (p<0.05). Despite limited knowledge and resources, 76% perceived PM approaches positively, with screening approaches tailored to African populations being the most valued benefit. 55% felt confident in applying the PM-based approach, with those already undertaking CVD risk stratification more confident (p<0.001). High cost and limited access to genetics services were considered the greatest barriers to implementation.

Conclusion: Integrating genetic information into established clinical tools will likely increase confidence in using PM approaches. Addressing the genetics training gap and investment into the country's genomics capacity is needed to advance PM in South Africa.

Conflict of interest disclosure: Cathryn M. Lewis is a member of the Research and Development SAB at Myriad Neuroscience.

A Comparative Analysis of Public versus Private Access to Genomic Medicine in Two Upper-Middle Income Countries, Malaysia and South Africa

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Background & Objectives:
Access to genomic medicine is generally both limited and variable even within high countries and is furthermore sometimes dependent on whether a patient has private health insurance or not. This is even more so the case within middle and low income countries. The purpose of this analysis was firstly to compare and contrast access to genomic medicine in general within two geographically distinct upper-middle income countries, Malaysia and South Africa, mainly from the perspective of oncology and rare diseases. A further analysis was performed for each country, comparing access within each country to genomic medicine based on whether individuals held private health insurance or were relying solely on publicly funded healthcare.

Method(s) and Results:
Data was obtained via a variety of primary and secondary data collection methods. From a primary perspective, genomics experts were interviewed within each country (e.g. clinicians, academics) as well as experts from industry (e.g. executives from insurance companies and private genomic laboratories). From a secondary data collection perspective, publicly available data such as insurance policy documentation, academic papers and national reports were also reviewed and analysed for each market / country.

Conclusions:
It was found that in general individuals in both South Africa and Malaysia have limited access to genomic medicine, both for oncology and rare disease patients, compared to high income countries, regardless of whether individuals held private health insurance or not. This inequality was however found to be further compounded based on whether individuals within these countries possessed private health insurance or not, as in recent years insurers in both countries are increasingly filling the protection gap for the provision of genomic medicine, especially for oncology but also for rare diseases.

Keywords: Insurance, Public, Private, Malaysia, South Africa

Chilean Population Genomic Variability: A Crowdsourcing Database

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Background & Objectives: The massive growth of sequencing technologies has led to unprecedented developments over the last decade. Consequently, several databases of common human genetic variation have been established (e.g., 1000 Genomes and GnomAD). As of now, few studies of genetic variation in the admixed Latin American, and more specifically, Chilean population have been

performed. These have primarily focused on relatively well-known variants, and the data is not readily available to the scientific community. In response to this, we have created an aggregated database of genomic variation of the Chilean population at the exon level. This database was generated through a collaborative crowdsourcing effort, collecting sequencing data produced by local genomic projects.

Methods and Results: A total of 386 unrelated samples of Chilean people were sequenced, 354 by whole exome sequencing (WES) and 32 clinical exomes (CES, about 5000 genes). Ancestry and relatedness between samples were calculated with Somalier v0.2.16 and variant calling was performed following the GATK v3.8 Best Practices. Finally, the allelic frequency was calculated using PLINK v1.9. Principal component analysis of global ancestry showed subjects with high percentage of European and admixed American ancestry. After a stringent filtering approach, 251,800 variants within 18,281 genes were identified, including single nucleotide variants and small insertions and deletions. The estimation revealed 84,168 (33.4%) common variants with a minor allele frequency (MAF) ≥ 1% and 167,632 (66.6%) rare variants with a MAF < 1%. 27,171 (10,7%) of these variants were not present in the 1000 Genomes (v2015) and gnomAD v2.1.1 datasets. We identified 492 variants classified as pathogenic or likely pathogenic, according to Intervar.

Conclusions: This database proves to be a valuable resource for understanding the genetic variability of the Chilean population. It holds significant potential for research and clinical applications, such as gaining insights into the genetics of diseases, personalizing medical treatments, and contributing to precision medicine efforts.

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