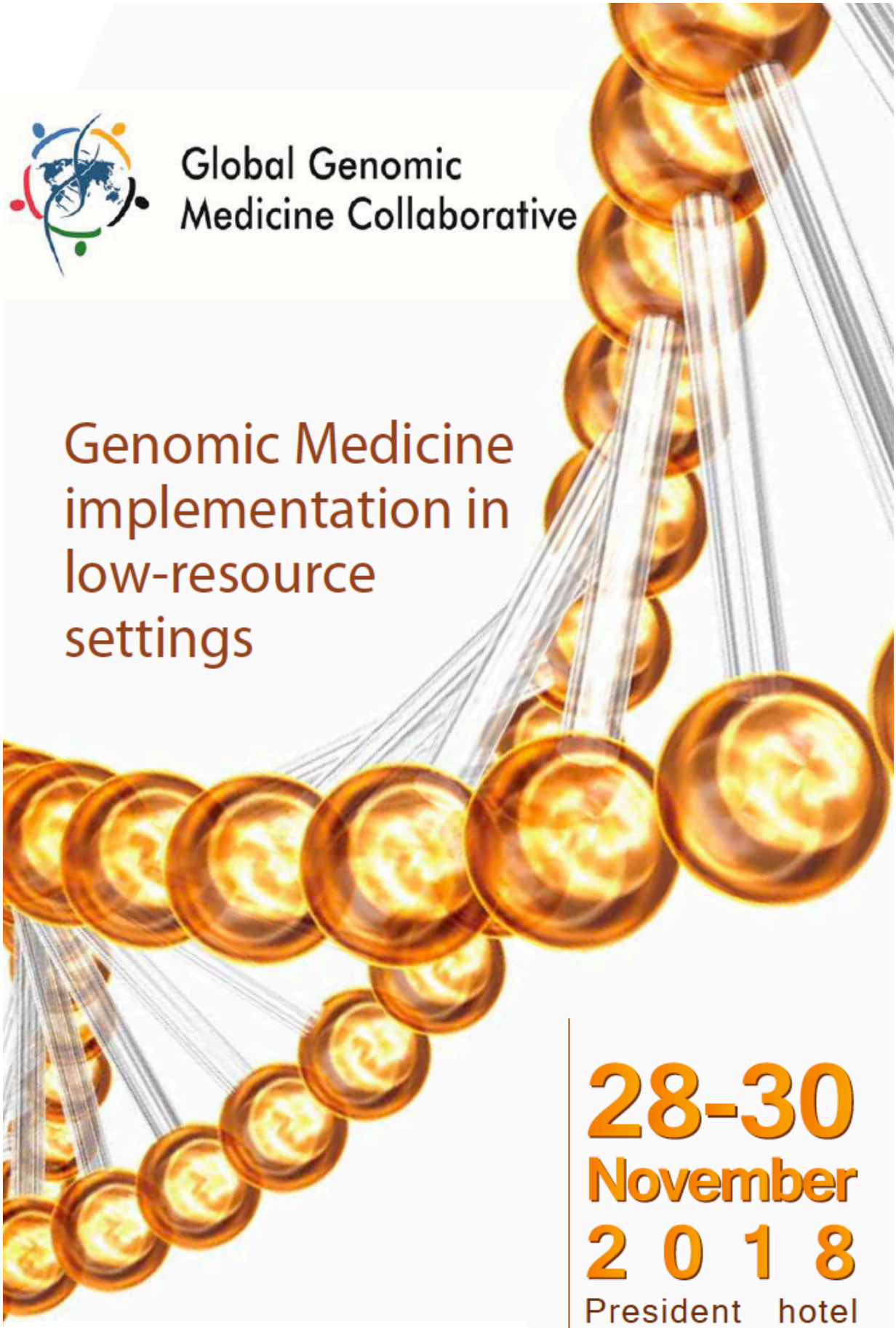

Global Genomic Medicine Collaborative

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Young Investigators Forum - Abstracts

Development of oriC-plasmid for use in Mycoplasma hyorhinis

Hassan Z. A. Ishag[1,2], Qiyan Xiong1, Maojun Liu[1], Zhixin Feng[1] & Guoqing Shao[1]

[1] *Institute of Veterinary Medicine, Jiangsu Academy of Agricultural Sciences, Key Laboratory of Veterinary Biological Engineering and Technology, Ministry of Agriculture, National Research Center for Engineering and Technology of Veterinary Bio-products, Nanjing, 210014, China*
[2] *College of Veterinary Science, University of Nyala, Nyala, Sudan*

Correspondence e-mail: hassan8377@yahoo.com

Mycoplasma hyorhinis (M. hyorhinis) is an opportunistic pig pathogen, belonging to the class Mollicutes. It causes polyserositis, arthritis and cancers in vitro, increasing attention of the researchers. Currently, there is no available genetic tool to manipulate its genome. This study describes a development of oriC-plasmids harboring either large (pGEMT-LoriC) or minimum (pGEMT-MoriC) origin of replication (oriC) of M. hyorhinis along with tetracycline resistance marker. These plasmids were successfully transformed into M. hyorhinis with average transformation frequency of 1.5 × 10−4 and 2.0 × 10−5 transformants/CFU for pGEMT-LoriC and pGEMT-MoriC respectively and were integrated at the chromosomal oriC as well as remained freely replicating. We also constructed a Mini-oriC-HT1 targeting plasmid by inclusion of hlyC arms and was used to inactivate hlyC at average frequency of 50%. The efficiency of hlyC inactivation was further improved (by 90%) when Mini-oriC-HT2 that contains E. coli recA was used. In both cases, hemolysin mutant bacteria diminished the ability to lyse mouse RBCs compared to wild-type (P 0.001). OriC-plasmids described in this study may, therefore open the way for functional genomics in M. hyorhinis. Furthermore, this is a first study demonstrated the gene associated with a hemolytic phenotype in mycoplasmas.

Using computational methods to map multigenic disease phenotypes: an ALS toolbox

Styliani Papadaki[1], Raphael Siakavaras[1], Constantina Chalikiopoulou[1], Aggeliki Balasopoulou[1], Stephania Koutsilieri[1], Clint Mizzi[2,3], Anne John[4], Bassam R. Ali[4], Theodora Katsila[1], George P. Patrinos[1,4]

[1] Department of Pharmacy, School of Health Sciences, University of Patras, Patras, Greece; [2] Erasmus University Medical Center, Faculty of Medicine and Health Sciences, Department of Bioinformatics, Rotterdam, The Netherlands; [3] University of Malta, Faculty of Medicine and Surgery, Department of Physiology and Biochemistry, Malta; [4] Department of Pathology, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE

Correspondence e-mail: stelpapha@gmail.com

Objectives and study: Precision medicine aims at optimal disease management and patient stratification and, in this perspective, mapping of phenotype-to-genotype association becomes vital. Considering the complexity of multigenic disease phenotypes and inter-individual variability, better-informed decisions need valid datasets. Herein, whole genome datasets were explored to reveal genomic variants of interest.

Methods: Following extensive bio- and chemo-informatics analyses coupled to R (programming language), we focused on genomic variants that were unique a) per disease phenotype (Behcet's vs. ALS vs. spastic paraparesis), b) in autoimmune disease phenotypes of interest (Behcet's plus ALS plus spastic paraparesis), c) in neurodegenerative disease phenotypes of interest (amyotrophic lateral sclerosis plus spastic paraparesis) and/ or metabolic disorders (Behcet's disease). In total, 260,671 genomic variants from Caucasian patients were assessed.

Results: Our findings demonstrate the existence of significant genomic consistency among the disease phenotypes in question, with 12,612 genomic variants being in common. Interestingly, these genomic variants are predominantly found in chromosomes 7, 8 and 11. Moreover, genomic variants unique to ALS and/ or spastic paraparesis and/ or Behcet's disease have been highlighted.

Conclusion: Our approach may serve as a paradigm to reveal the "actionable genome" and empower data reliability in multigenic disease phenotypes.

High utility of active tuberculosis case finding in prisoners

Y. Merid, Y. Woldeamanuel, M. Abebe, D. G. Datiko,T. Hailu, G. Habtamu, G. Assefa, R. R. Kempker, H. M. Blumberg, A. Aseffa

[1] Armauer Hansen Research Institute, Addis Ababa, Addis Ababa University, Addis Ababa, Hawassa University, Hawassa; [2] Addis Ababa University, Addis Ababa; [3] Armauer Hansen Research Institute, Addis Ababa; [4] REACH Ethiopia, Hawassa, Ethiopia, Liverpool School of Tropical Medicine, Liverpool, UK; [5] Emory University School of Medicine, Atlanta, Georgia, USA

Correspondence e-mail: gethabt2014@gmail.com

SETTING: Hawassa Prison, Southern Region of Ethiopia.

OBJECTIVE: To determine the burden of pulmonary tuberculosis (TB) using active case finding among prisoners.

DESIGN: In this cross-sectional study, prisoners were screened for TB using a symptom screen. Those with cough of ≥2 weeks had spot and morning sputum samples collected for acid-fast bacilli (AFB) smear microscopy and molecular diagnostic testing (Xpert® MTB/RIF).

RESULTS: Among 2068 prisoners, 372 (18%) had a positive cough screen. The median age of these 372 persons was 23 years, 97% were male and 63% were from urban areas. Among those with a positive symptom screen, 8 (2%) were AFB sputum smear-positive and 31 (8%) were Xpert-positive. The point prevalence of pulmonary TB at the prison was 1748 per 100 000 persons. In multivariate analysis, persons with cough >4 weeks were more likely to have TB (OR 3.34, 95%CI 1.54–7.23).

CONCLUSION: A high prevalence of TB was detected among inmates at a large Ethiopian prison. Active case finding using a cough symptom screen in combination with Xpert had high utility and has the potential to interrupt transmission of Mycobacterium tuberculosis in correctional facilities in low- and middle-income, high-burden countries.

Diabetes genetic susceptibility: Family disease awareness

Lucia Y. Ojewale and Oyenihun A. Oluwatosin.

Department of Nursing, University of Ibadan

Correspondence e-mail: luciayetunde@gmail.com

Introduction: Globally, the incidence of Diabetes mellitus, (DM), is on the increase and the greatest increase is expected in low and middle income countries. Genetics and environmental factors play a role in the development of the condition causing a variability in the susceptibility of offsprings of People Living With Diabetes (PLWD). Both offspring and spouses of affected individuals ought to be aware of the causes, prevention and management of the disease so as to modify their lifestyle and if possible undergo genetic susceptibility test, when available. However, to the best of our knowledge, there is no study in Nigeria that has examined family members' knowledge of DM or provided interventions to improve awareness. This is the impetus for the study.

Aim: To determine the effect of an educational intervention on DM awareness among family members of PLWD

Methods: A Pre- test post -test two - group intervention design was utilized. Control group (CG) consisted of 99 family members of PLWD and Intervention Group (IG) consisted of 98 family members. The study took place in two tertiary hospitals in south west Nigeria. Baseline (P1) data were obtained using Diabetes Knowledge Test (DKT). IG received educational intervention while CG did not, although some family members who attended diabetes clinic with PLWD continued to be passive observers. Post intervention data was collected immediately after the education. Data were entered into Statistical Package for Social Sciences (SPSS), version 20. Analysis was done using chi-square test, independent t-test, paired t-test at 0.05 level of significance.

Results: Family members were mostly female (62.9%) with 52.8% aged ≤ 40 years and 53.8% had tertiary education. Diabetes knowledge was below average in both groups at baseline. There was no significant difference in diabetes knowledge, ($p > 0.05$), at baseline. At post intervention, there was a significant difference between knowledge of family members in intervention group and control group, (CG 5.8; IG 8.6, p 0.01).

Conclusion: Family education can increase awareness of family members about DM and should be encouraged in all diabetes management settings. This can effectively reduce the incidence of the disease and impact uptake of diabetes susceptibility testing, when available.

Targeted Next-Generation Sequencing Identifies Novel Variant

Oluwafemi G. Oluwole [1], Helena Kuivaniemi [1], Shameemah Abrahams [1], William L. Haylett [1], Alvera Vorster [3], Carel Van Heerden [3], David L. Tabb [1,4], Michael B. Fawale [6], MSc, Taofiki Ajao Sunmonu [7], Matthew O. Olaogun [5], Jonathan Carr [2], Owen A. Ross [8], Morenikeji A. Komolafe [6], Gerard Tromp [1,4], Soraya Bardien [1]

[1] Division of Molecular Biology and Human Genetics, [2] Department of Biomedical Sciences, and Division of Neurology, Faculty of Medicine and Health Sciences, [3] DNA Central Analytical Facility, [4] Centre for Bioinformatics and Computational Biology, Stellenbosch University, South Africa; [5] Stellenbosch University, South Africa; Department of Medical Rehabilitation (MOO), [6] College of Health Sciences, and Neurology Unit, Department of Medicine, Faculty of Clinical Sciences, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria; [7] Neurology Unit, Department of Medicine, Federal Medical Center, Owo, Ondo State, Nigeria, [8] Parkinson's Disease Laboratory, Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA

Correspondence e-mail: femi@sun.ac.za

Background: The prevalence of Parkinson's disease (PD) is increasing in sub-Saharan Africa, but little is known about the genetics of PD in these populations. Due to their unique ancestry and diversity, sub-Saharan African populations have the potential to reveal novel insights into the pathobiology of PD.

Methods: We recruited 33 black South African and 14 Nigerian PD patients, and screened them for mutations in 751 genes using an Ion AmpliSeq™ Neurological Diseases panel. We used bcftools to assess the data quality and to filter the variants. Sequence variants with mapping quality score > 100 and a minimum read depth > 40 were selected for follow-up. We used annovar utility software for the annotation. We removed variants with minor allele frequency ≥ 0.01 in any of the frequency databases. We also assessed how often each variant was found in common among samples. Pathogenic variants were selected based on the prediction scores by MetaLR and MetaSVM as these two showed the best performance on curated data sets. We generated radar plots of these selected pathogenic variants to illustrate the overall pathogenicity prediction.

Results: The mean age at onset of PD in the South Africans and Nigerians was 48 ± 8 and 63 ± 13 years, respectively. Sequence data from all samples passed quality control criteria. We identified a total of 8210 unique variants. Among the 33 South African patients, we found 6525 substitutions, 276 deletions and 79 insertions. Among the 14 Nigerian patients, we identified 1224 substitutions, 74 deletions and 32 insertions. Only 12 substitutions, 189 deletions and 110 insertions were shared between the two study groups. Altogether 60 variants in 44 genes were prioritized based on MetaLR and MetaSVM scores for future follow-up studies. These included seven novel mutations in three known PD genes ATP13A2 (S960R), PRKN (P153R and D245E) and PINK1 (S73L, S228F, S284Y and P305A).

Conclusions: We identified variants predicted to be pathogenic in genes not previously known to harbour mutations in PD patients. We also identified novel mutations in known PD genes. Further studies are required to ascertain the biological functions of these variants.

A report of Williams-Beuren syndrome in South Africa

I. Crous, C. Tekendo-Ngongang, T. Ruppelt, K. Fieggen

[1] Division of Human Genetics, University of Cape Town; [2] The National Health Laboratory Service (NHLS), Groote Schuur Complex

Correspondence e-mail: ilse.crous@uct.ac.za

Introduction: Williams-Beuren syndrome (WBS) is a well described genetic disorder that includes typical cranio-facial features, a specific behavioral profile, congenital heart defects (CHD) and hypercalcemia. Diagnosis is based on the detection of a 7q11.23 contiguous gene deletion that includes the elastin gene (ELN). Gene deletion can be detected by fluorescent in situ hybridization (FISH), and by molecular microdeletion/duplication analysis including Multiplex Ligation-dependant probe Amplification (MLPA) and Chromosomal Microarray. Early diagnosis has been shown to significantly reduce morbidity and mortality. Cases from Sub-Saharan Africa have seldom been reported in literature. Recent case reports on patients from Cameroon recommend that clinical suspicion should be based on cardiac defects and behavioral phenotype as the craniofacial phenotype was found to be less distinctive when compared to the normal population features than that described in cohorts with predominantly European ancestry. Recognition that population differences influence the phenotypic expression of common genetic syndromes has led to projects such as the NIH Atlas of Human Malformation Syndromes in Diverse Populations in which photographic resources from worldwide collaborators aim to aid the early diagnosis of genetic disease in patients of non-European ancestry. Here we report our experience of diagnosing WBS in the South African setting.

Material and Methods: Retrospective analysis of a cohort of 19 patients diagnosed with Williams Beuren syndrome that presented to genetic clinic at Red Cross War Memorial Children's Hospital, Cape Town between 2001 and 2017. Data collected included gender, ethnolinguistic ancestry, age of referral to the genetic clinic, referral system followed, age at molecular diagnosis and method of molecular diagnosis used. Description of the cranio-facial features and CHD if present and notes on behavior were also documented.

Results: Fifteen (79%) patients were of mixed-race ancestry and 4 (21%) of indigenous Black African ancestry. The cohort included 11 male patients and 8 female patients. The majority of children (58%) were referred from cardiology. The average age at molecular diagnosis was 4,8 years, ranging from 1 to 10 years. Two patients were referred with a confirmed diagnosis. 15 patients received diagnostic confirmation after their first visit and in 2 patients the diagnosis was not initially suspected. Most of the patients had some cranio-facial features commonly associated with WBS. Eleven patients (58%) had CHD, the most common type being supravalvular aortic stenosis which was present in 6 of the 19 patients (32%). Ten patients presented with typical behavioural phenotype. Diagnostic confirmation was attained through FISH in 17 cases. The two remaining cases, those in whom the diagnosis was not initially suspected, were diagnosed by MLPA (1) and chromosomal microarray (1).

Conclusion: These results demonstrate that the use of available international diagnostic criteria can be effective in the diagnosis of most South African children affected with WBS. Despite that the diagnosis remains delayed and the diagnosis often not recognized by other health care professionals. We believe that training of more clinicians in Dysmorphology could potentially lead to an earlier diagnosis of WBS and reduce the number of undiagnosed patients in our environment. This emphasises the importance of a multi-disciplinary approach in resource limited settings.

Understanding the genetic causes of Vitiligo

Nonhlanhla Cynthia Mhlongo

University of South Africa

Correspondence e-mail: nonhlanhla72@gmail.com

Is Vitiligo genetic disease? Vitiligo is a disorder that affects the skin. People who suffer from vitiligo experience a loss of pigmentation in the skin when melanin-producing cells either die or experience dysfunction. When Vitiligo causes a lack of melanin in certain areas of the skin, the affected areas lose colour and often appear as white patches. The patches can occur anywhere in the body; although areas exposed to the sun are most commonly affected.
Pigmentation is heritable, and understanding the causes of vitiligo is still an ongoing process, as research continues to investigate the root cause of Vitiligo. Most experts agree that Vitiligo is likely to be the results of a combination of genetic, immune and triggers. The complex genetics of vitiligo involves multiple susceptibility loci, genetic heterogeneity and incomplete penetrance with gene-gene and gene-environment interactions.

Studies indicate that variations in many other genes also affect the risk of vitiligo. Many of these genes are also involved in immune system function or melanocyte biology, and variations in each likely make only a small contribution to vitiligo risk. Some of the gene changes associated with an increased risk of vitiligo have also been associated with an increased risk of other autoimmune conditions.

Many genetic disorders result from gene changes that are present in essentially every cell in the body. As a result, these disorders often affect many body systems, and most cannot be cured. However, approaches may be available to treat or manage some of the associated signs and symptoms.

There are many studies by experts all over the world – working on understanding and locating genes involved in the cause Vitiligo. Even though reading your genes can't tell you for sure whether you'll get vitiligo, understanding which one influence getting the disease tells us a lot about what causes it, and maybe gives us clues into how to better treat it The author would like to stress that, there is no cure for vitiligo, but effective treatment is available. The best way to treat Vitiligo is Phototherapy with UVB light therapy for home use or Phototherapy with UVA plus the drug psoralen. These treatments are more on re-pigmentation and repairing damaged cells rather than working on the gene mutation, which led to vitiligo.

Genome-wide discovery of long noncoding RNAs in HIV-1 non-progressors

Stanford Kwenda, Nikki Gentle*, Maria Paximadis, and Caroline T. Tiemessen

*Cell Biology Lab, Centre for HIV and STI, National Institute for Communicable Diseases, Johannesburg, South Africa; * School of Molecular and Cell Biology, University of the Witwatersrand, Johannesburg, South Africa*

Correspondence e-mail: carolinet@nicd.ac.za

Long noncoding RNAs (lncRNAs) are emerging as key regulatory molecules that play significant roles in gene expression in the mammalian immune system. A small number of HIV-1 infected individuals, termed HIV-1 non-progressors, do not always progress to AIDS but remain asymptomatic in the absence of antiretroviral treatment. The precise functional roles and expression patterns of lncRNAs in HIV-1 non-progressors are yet to be fully characterized. Here we present systematic genome-wide identification of lncRNAs in peripheral blood mononuclear cells (PBMCs) from a cohort of 27 HIV-1 non progressive black South African individuals. We used strand-specific RNA sequencing to identify 15,182 lncRNA genes, including 127 novel multi-exon long intergenic noncoding RNA (lincRNA) transcripts, present in at least two individuals. Through stratification and comparison of low viral load (LVL; HIV RNA below 200 copies/ml) and high viral load non-progressors (HVL; HIV RNA above 200 copies/ml), we discovered 1,075 differentially expressed lncRNA genes (FDR0.05). Among the differentially expressed genes, 638 lncRNAs (including 23 novel lincRNA transcripts) showed enriched expression specific to the LVL group. Our genome-wide catalogue of lncRNAs associated with immune responses in HIV-1 non-progressors provides the basis for future efforts to explore and characterize the potential role of lncRNAs in HIV-1 control as biomarkers and exploration of lncRNA based therapeutic strategies.

Status ofartemisinin resistance in Nigerian malariaparasite

Mary Aigbiremo Oboh [1], Daouda Ndiaye [1], Hiasindh Ashmi Antony [2], Aida Sadikh Badiane [1], Upasana Shyamsunder Singh [2], Nazia Anwar Ali [2], Praveen Kumar Bharti [2], Aparup Das [2]

[1] Parasitology and Mycology Laboratory, Université Cheikh Anta Diop, Dakar, Senegal; [2] Division of Vector Borne Diseases, ICMR-National Institute for Research in Tribal Health, Jabalpur, India

Correspondence e-mail: aigbi4god@gmail.com

Evolution and spread of malaria parasite Plasmodium falciparum capable of evading anti-malarial is the prime concern to malaria control. The currently effective drug, artemisinin (ART), is under threat due to the detection of ART resistant P. falciparum parasites in the southeast Asian countries. It has been shown that amino acid (AA) mutations at the P. falciparum Kelch13 (Pfk13) gene provide resistance to ART. Nigeria, a part of the Sub-Saharan Africa is highly endemic to malaria, contributing quite significantly to malaria and resistance to chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) combination drugs have already been reported. Since artemisinin combined therapy (ACT) is the first-line drug for treatment of uncomplicated malaria in Nigeria, and five amino acid mutations have been validated in the Pfk13 gene alongside with candidate mutations for ART resistance, we performed molecular surveillance for mutations (following PCR and DNA sequence analyses) in this gene from two southern states of Nigeria. Statistical analyses of DNA sequences were also performed following different evolutionary models. None of the different validated and candidate AA mutations of Pfk13 gene conferring resistance to ART in Nigeria could be detected. In addition, DNA sequencing and sequence analyses indicated neither evolutionary selection pressure on the Pfk13 gene nor association of mutations in Pfk13 gene with mutations of other three genes conferring resistance to CQ and SP. Currently, the malaria parasite P. falciparum is free from mutations conferring resistance to ART in southwestern Nigeria. Mutations of Pfk13 gene in the present study seem to be under no association with mutations present in the three other drug-resistant genes, and therefore bear no immediate relevance to malaria public health in Nigeria.

Genetic Architecture of Clinically Relevant Variations

Mboowa G., Retshabile G, Mlotshwa G, Lesedi W, Mwesigwa S, Swaminathan S, Huang Z, Katagirya E, Kateete D, Wampande E, Kyobe S, Wayengera M, Kisitu G, Maplanka K, Matshaba M, Nsangi B, Marape M, Chester B, Kekitiinwa A, Yu F, Gkrania – Klotsas E, Groom H, Illingworth C, Joloba M, Mpoloka S, Mardon G, Anabwani G, Hanchard N, and for the Collaborative African Genomics Network (CAfGEN) of the H3Africa Consortium

Department of Immunology and Molecular Biology, College of Health Sciences, Makerere University, Kampala, Uganda 2Department of Medical Microbiology, College of Health Sciences, Makerere University, Kampala, Uganda ;Department of Biological Sciences, Faculty of Sciences, University of Botswana, Gaborone, Botswana Baylor College of Medicine Children's Foundation-Uganda, Kampala, Uganda; Department of Bio-molecular Resources, College of Veterinary Medicine, Makerere University, Kampala, Uganda; Genetics Division, Department of Pediatrics, University of Tennessee Health Science Center, Memphis, Memphis, TN, USA 7Le Bonheur Children's Hospital, Memphis, Memphis, TN, USA; St. Jude Children's Research Hospital, Memphis, TN, USA; Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA; ARS/USDA/Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA 12Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX, USA; Botswana-Baylor Children's Clinical Centre of Excellence, Gaborone, Botswana; Baylor College of Medicine Children's Foundation-Swaziland, Mbabane, Swaziland; Department of Medical Laboratory Sciences, University of Botswana, Gaborone, Botswana; Pediatric Retrovirology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Correspondence e-mail: gmboowa@gmail.com

Introduction: ClinVar database provides a freely available archive of reports of relationships among medically important variants and phenotypes. However, almost all the variants in this database have been identified from well phenotyped non-African populations. Affordable high-throughput sequencing, genomic sequencing is becoming increasingly prevalent in both research and clinical arenas enabling identification of many clinically actionable genetic variants causing congenital diseases as well as pharmacogenetically relevant variation in Africa; particularly important for identifying groups potentially at risk of poor drug response or adverse drug reactions. A better understanding of the distribution of these genetic variants within African populations before embracing public health genomics medicine as an integral part of mainstream healthcare in Africa.

Objectives: 1. Identify and determine the prevalence of clinically relevant genetic variations from the Collaborative African Genomics Network (CAfGEN) Exomes, 2. Describe the distribution of the above genetic variants in African populations, 3. Compare frequency of clinically relevant genetic variations between African and non-Africa populations, 4. Identify and describe Genetic Variants of Uncertain Significance (VUS).

Methodology: Exome sequencing of 800 exomes from the Collaborative African Genomics Network (CAfGEN) was carried out. Read mapping to a human reference genome (hg19) was done using Burrows-Wheeler Aligner (BWA). Sorted and marked duplicate reads using Picard tools. Genetic variants were called using the Genome Analysis ToolKit (GATK-3.5-0-g36282e4). Extensive quality control was performed to generate a clean joint GenotypeVCF using HaplotypeCaller. Genomic variant annotations and functional effect prediction will be done using ClinEff and ANNOVAR tools.

Next Steps: Using SnpEff to identify clinically relevant genetic variations from the joint GenotypeVCF

Microsatellite Instability:NR21, NR24 in Nigeria and Senegal

Aniefiok J. Udoakang [1], Fatimata Mbaye [1], Adeyinka Ademola [2], Ganiyu O. Arinola [3], Temidayo O. Ogundiran [2]; Mbacke Sembene [1]

[1] Equipe de Génétique pour la Gestion des Populations, Département de Biologie Animale, Faculté des Sciences et Techniques, Université Cheikh Anta Diop de Dakar, BP. Box 5005 Dakar, Sénégal; [2] Department of Surgery, College of Medicine, University of Ibadan, Ibadan, Nigeria; [3] Department of Chemical Pathology and Immunology, College of Medicine, University of Ibadan, Ibadan, Nigeria

Correspondence e-mail: mandith2004@yahoo.com

Microsatellite Instability (MSI) analysis has been proposed as a first step in the identification of cancer patients to be tested for mismatched repair gene mutations so as to ascertain the treatment type for each patient. The evaluation of two quasimonomorphic mononucleotide repeats have also been recommended to be sufficient for the detection of all tumours with mismatched repair protein expression. Therefore, the aim of this study was to assess two of the five mononucleotide repeats (NR-21 and NR-24) proposed for the clinical evaluation of MSI in tumours among breast cancer patients in Nigeria and Senegal. One hundred histologically confirmed breast tumours collected from female breast cancer patients of between 15 to 80 years in Nigeria and Senegal were genotyped by Polymerase chain reaction followed by sequencing of the two markers of interest. The results obtained showed MSI in NR-21 and NR-24 (84% and 69.8% of the tumours respectively). High haplotype diversity was observed for both genes among Nigerian (NR-21: 0.74 ± 0.03; NR-24: 0.91 ± 0.03) and Senegalese (NR-21: 0.71 ± 0.01; NR-24: 0.87 ± 0.03) patients. While the highest number of haplotypes for NR-21 was observed among tumours obtained from Senegal (8 haplotypes), for NR-24 the highest haplotypes (21 haplotypes) was observed in Nigeria. The molecular analysis of the markers showed low frequency of polymorphism indicating clonal expansion and purifying selection in the studied population. The evolution of multiple tumour clones at a higher rate than usual has been linked as a natural outcome of genomic instability phenotype in cancer. These results show a promising outcome in the utilization of these markers for prognosis and treatment of breast cancer in West-Africa. We suggest that more studies be carried out in other parts of Africa as combine effort from all parts of the continent is needed to tackle and reduce the burden of the disease.

Breast Cancer Risk Perceptions and Genetic Counseling

Derrick Bary Abila

Makerere University

Correspondence e-mail: abilabary@yahoo.com

Some people have inherited gene faults that increase their risk of developing particular types of cancer. Some gene faults can increase the risk of more than one type of cancer. There is an increased risk of breast cancer among the first degree relatives. In breast cancer, the genes that increase the risk of breast cancer and can be tested for are BRCA1, BRCA2, TP53 and PTEN. First degree relatives of breast cancer patients can be tested for these genes and screen regularly. The aim of the study was to assess the self-perceived risk of breast cancer and engagement in risk reduction behaviors among the first degree female relatives of breast cancer patients. These results formed a baseline for designing a larger study on risk perception and risk reduction practices in Uganda. We searched through various literature published in PUBMED and Oncology journals in HINARI published in English. The papers were carefully appraised to identify key outcomes of the studies.

Women engaged in risk reduction behaviors like smoking cessation, reduction in alcohol intake, physical activity and screening for breast cancer. Women aged 54 years and below had a higher perceived lifetime risk of breast cancer (39.5%) compared with those aged ≥55 years (30.6%) who perceived themselves at lower risk. Being unrealistically optimistic was significantly associated with high level of educational attainment while women who did not know their risk were less educated. Women who accurately perceived their 5-year risk of breast had a higher annual income. There was a significant association of the stage of breast cancer, time since diagnosis and perceived breast cancer risk among the relatives. High risk perception is associated with increased need to engage in risk reduction behaviors. Fatalism amongst women was the primary reason not to engage in breast cancer screening. Genetic counseling could be explored to find out whether I can reduce the unrealistic optimism and increase engagement of first degree relatives of breast cancer patients in risk reduction behaviors.

Prothrombin mutation prevalence in hereditary thrombophillia

Shareefa Isaacs

Stellenbosch University, Tygerberg Academic Hospital, National Health Laboratory Services

Correspondence e-mail: 18284906@sun.ac.za

Heritable thrombophilia which predisposes individuals towards thrombosis is a multifactorial disorder with high mortality and morbidity. The more prevalent inherited risk factors are the gain-of-function mutations in coagulation factors, Factor V-Leiden (FVL; F5G1691A) and Factor II or prothrombin (FII; F2G20210A). As the prevalence of FVL and FII mutations within our setting is unknown, we aim to conduct an audit on the number of molecular tests requested and investigate the prevalence of Factor II and screen for a novel mutation Arg596Leu; c.1787G>T in exon 14 of Factor II. Molecular reports reviewed over a period of 12 years to determine the number of FII requests and associated epidemiological data. One hundred patients with and without known positivity for the FII and FVL mutations will be screened for Arg596Leu; c.1787G>T mutation using RFLP and Sanger sequencing. For the audit, out of 664 cases requested over the 11 year period, 527 requests were for the FVL mutational screening and 24 requests were for PTB, and 98 of the requests were for both FVL and PTB. Of this only 20% of the request were for FII highlighting that 80% was not screened for Factor II as it was not specifically requested. Of the total test requests, 3% was positive for the F5G1691A mutation while a higher incidence of 7% was positive for the F2G20210A mutation. The epidemiology of the FVL and FII mutations has not been well studied within the South African/African context. The fact that 80% of cases did not request FII while a higher incidence of the FII mutation was observed in our population highlights big gaps and shows that this requires further investigation as these results would aid in the improvement of thrombophilia screening at TBH. Likewise including the screening of a newly identified mutation as well as the Methylenetetrahydrofolate reductase (MTHFR C677T) mutation in our screening panel will aid in strengthening diagnosis.

Interleukin–6 (IL-6) rs1800796 and cyclin dependent kinase inhibitor (CDKN2A/CDKN2B) rs2383207 are associated with ischemic stroke in indigenous West African Men

Onoja M. Akpaa, Rufus Akinyemi a,b, Donna K. Arnett c, Hemant K. Tiwari d, Bruce Ovbiagele e, Fred Sarfof, Vinodh Srinivasasainagendra d, Marguerite Ryan Irvin d, Abiodun Adeoye a, Rodney T. Perry d, Albert Akpalu g,Carolyn Jenkins e, Lukman Owolabi h, Reginald Obiako i, Kolawole Wahab j, Emmanuel Sanya j, Morenikeji Komolafe k, Michael Fawale -, Philip Adebayol, Godwin Osaigbovo m, Taofiki Sunmonu n, Paul Olowoyo o, Innocent Chukwuonye p, Yahaya Obiaboq, Sylvia Melikama, Raelle Saulson e, Raj Kalaria r, Adesola Ogunniyi a, Mayowa Owolabi a,s, for the SIREN Investigators

a University of Ibadan, Ibadan, Nigeria; b Federal Medical Centre Abeokuta, Nigeria; c University of Kentucky, KY, USA; d University of Alabama at Birmingham, Birmingham, USA; e Medical University of South Carolina, SC, USA.; f Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; g University of Ghana Medical School, Accra, Ghana; h Aminu Kano University Teaching Hospital, Kano, Nigeria; i Ahmadu Bello University Teaching Hospital, Zaria, Nigeria; j University of Ilorin Teaching Hospital, Ilorin, Nigeria; k Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria; l Ladoke Akintola University Teaching Hospital, Ogbomosho, Nigeria; m Jos University Teaching Hospital, Jos, Nigeria; n Federal Medical Centre, Owo, Nigeria; o Federal University Teaching Hospital Ido-Ekiti, Nigeria; p Federal Medical Centre, Umuahia, Nigeria; q Delta State University Teaching Hospital, Oghara, Nigeria; r Newcastle University, Newcastle upon Tyne, UK.; s WFNR-Blossom Specialist Medical Center Ibadan, Nigeria

Correspondence e-mail: onojamatthew@yahoo.co.uk

Background: Inherited genetic variations offer a possible explanation for the observed peculiarities of stroke in sub - Saharan African populations. Interleukin–6 polymorphisms have been previously associated with ischemic stroke in some non-African populations. Herein we investigated, for the first time, the association of genetic polymorphisms of IL-6, CDKN2ACDKN2B and other genes with ischemic stroke among indigenous West African participants in the Stroke Investigative Research and Education Network (SIREN) Study.

Methods: Twenty-three previously identified single nucleotide polymorphisms (SNPs) in 14 genes of relevance to the neurobiology of ischemic stroke were investigated. Logistic regression models adjusting for known cardiovascular disease risk factors were constructed to assess the associations of the 23 SNPs in rigorously phenotyped cases (N=429) of ischemic stroke (Men=198; Women=231) and stroke– free (N=483) controls (Men=236; Women = 247).

Results: Interleukin-6 (IL6) rs1800796 (C minor allele; frequency: West Africans=8.6%) was significantly associated with ischemic stroke in men (OR = 2.006, 95% CI = [1.065, 3.777], p = 0.031) with hypertension in the model but not in women. In addition, rs2383207 in CDKN2A/CDKN2B (minor allele A with frequency: West Africans= 1.7%) was

also associated with ischemic stroke in men (OR=2.550, 95% CI=[1.027, 6.331], p=0.044) with primary covariates in the model, but not in women. Polymorphisms in other genes did not show significant association with ischemic stroke.

Conclusion: Polymorphisms rs1800796 in IL6 gene and rs2383207 in CDKN2A/CDKN2B gene have significant associations with ischemic stroke in indigenous West African men. CDKN2A/CDKN2B SNP rs2383207 is independently associated with ischemic stroke in indigenous West African men. Further research should focus on the contributions of inflammatory genes and other genetic polymorphisms, as well as the influence of sex on the neurobiology of stroke in people of African ancestry.

Computational Elucidation of Important Interacting Proteins

Jumoke Soyemi [1,2], Itunuoluwa Isewon [2,3], Marion Adebiyi [2,3], Jelili Oyelade [2,3], Ezekiel Adebiyi [2]

[1] Department of Computer Science, Federal Polytechnic, Ilaro, Ogun State, Nigeria; [2] Department of Computer and Information Sciences, Covenant University, Ogun State, Nigeria; [3] Covenant University Bioinformatics Research (CuBRe), Covenant University, Ogun State, Nigeria

Correspondence e-mail: jumoke.soyemi@federalpolyilaro.edu.ng

The need to develop vaccines that targets the parasite erythrocytic invasion stage becomes imperative because the estimated reduction in malaria has not been commensurate with the much effort put in place by the world health organization. Identification of important interacting proteins between host and parasite at those crucial stages precedes vaccine development. There are several interactions predicted between host and parasite but the mechanism related to this invasion is poorly understood. Again, invasion has been identified as a conceptually attractive vaccine target, most especially because it is one of the few stages when the parasite is directly exposed to the host immune system. Therefore, the need to identify important interacting proteins (IIPs) that targets the invasion stage. This study, therefore, predicted important interacting proteins between human Red Blood Cells and Plasmodium falciparum merozoites based on RNA-Seq gene expression profiles using K-nearest neighbour supervised machine learning algorithm. The predicted results were also shows 63% IIPs that are corroborate with predictions from literature and 37% novel predictions. The IIPs predicted when taken further for experimental validation could be used as drug targets for vaccine development against the parasite invasion of the red blood cells.

African-specific NPHS2 V260E mutation in SR-FSGS cases

Govender M.A.1, Fabian J.2, Gottlich E.3, Levy C.4, Moonsamy G.5, Maher H.6, Winkler C.A.7, Ramsay M.1

[1] Sydney Brenner Institute for Molecular Bioscience and Division of Human Genetics, National Health Laboratory Service and School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [2] Wits Donald Gordon Medical Centre, Division of Nephrology, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; [3] Wits Donald Gordon Medical Centre, Transplant Unit and Department of Paediatrics, University of Pretoria, South Africa; [4] Nelson Mandela Children's Hospital, Division of Nephrology, Department of Paediatrics, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [5] Charlotte Maxeke Johannesburg Academic Hospital, Division of Nephrology, Department of Paediatrics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [6] Wits Donald Gordon Medical Centre, Johannesburg, South Africa; [7] Basic Research Laboratory, Center for Cancer Research, National Cancer Institute, Leidos Biomedical Research, Inc., Frederick National Laboratory, Frederick, MD, USA

Correspondence e-mail: melanieanngovender@gmail.com

Introduction - In children who present clinically with nephrotic syndrome, the most common type of primary glomerular disease-causing end stage renal disease (ESRD) is focal segmental glomerulosclerosis (FSGS). There is evidence of a more rapid progression of FSGS to ESRD in black patients compared to other ethnic groups and few studies have been performed in black South African children. The aim of this study was to determine genetic associations with apolipoprotein L1 (APOL1) risk variants and podocin (NPHS2) variants in black children with FSGS.

Methods - Thirty unrelated black South African children and two siblings with biopsy proven FSGS were recruited from two clinics in Johannesburg. Three APOL1 risk variants were genotyped and the exons of the NPHS2 gene sequenced in the cases and healthy ethnically matched controls. Genetic association analysis with APOL1 risk variants and NPHS2 variants were performed in a case:control analysis. The NPHS2 V260E variant was correlated with kidney function and treatment in all FSGS cases. Two families were examined for allelic segregation with FSGS.

Results - There was no association of APOL1 risk variants and haplotypes with FSGS (p= 0.097). Steroid resistant nephrotic syndrome (SRNS) and steroid sensitive nephrotic syndrome (SSNS) was present in 22 (69%) and 10 (31%) of the cases respectively. The OR of having SRNS increases from 38.6 (95% CI, 3.414 to 396.721; p= 0.002) to 119.6 (95% CI, 12.815 to 1116.22; p=6.653e-9) when carrying one and two copies of NPHS2 V260E, respectively. The presence of the NPHS2 V260E variant is associated with a more rapid decline in kidney function (p= 0.009).

Conclusion - The NPHS2 V260E variant is strongly associated with SRNS in black South African children. Genotyping the V260E variant in black children with FSGS could provide useful information in a clinical setting to guide treatment and prevent serious adverse events from steroid use.

PG and PK of CNS penetration of tenofovir/emtricitabine

Eric Decloedt [1,2], Phumla Sinxadi [2], Gert Van Zyl [3], Lubbe Wiesner [2], Saye Khoo [4], John Joska [5], David Haas [6,7], Gary Maartens [2]

[1] Division of Clinical Pharmacology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa; [2] Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa; [3] Division of Medical Virology, Faculty of Medicine and Health Sciences, Stellenbosch University and National Health Laboratory Service, South Africa; [4] Department of Molecular and Clinical Pharmacology, University of Liverpool, UK; [5] Division of Neuropsychiatry, Department of Psychiatry and Mental Health, University of Cape Town, South Africa; [6] Vanderbilt University School of Medicine, Department of Medicine, Nashville, Tennessee, United States of America; [7] Meharry Medical College, Department of Internal Medicine, Nashville, Tennessee, United States of America

Correspondence e-mail: phumla.sinxadi@uct.ac.za

Background: There is limited data on pharmacogenetics and pharmacokinetics of central nervous system penetration of efavirenz, tenofovir and emtricitabine.

Objectives: We investigated genetic polymorphisms associated with cerebrospinal fluid (CSF) concentrations of efavirenz and its metabolites, tenofovir and emtricitabine and explored the relationships with neurocognitive performance.

Methods: We included 47 HIV-infected South African Black adults with and without HIV-associated neurocognitive disorder on efavirenz-tenofovir-emtricitabine and collected paired plasma-CSF samples. We considered 2049 single-nucleotide polymorphisms (SNPs), including SNPs known to affect plasma efavirenz exposure, from potentially relevant genes (ABCC5, ABCG2, ABCB1, SLCO2B1, SCLO1A2, ABCC4, CYP2B6 and CYP2A6) and 880 met a linkage disequilibrium (LD)-pruning threshold.

Results: We identified 9 efavirenz slow, 21 intermediate and 17 extensive metabolizers. The composite CYP2B6 15582/516/983 genotype in univariate analyses predicted log10-transformed concentrations of plasma efavirenz [β=0.34, P=1.7 x10-05], plasma 7-hydroxy-efavirenz [β=0.45, P=5.9 x10-05], plasma 8-hydroxy-efavirenz-to-efavirenz ratio [β=-0.29, P=3.7 x10-08] and CSF efavirenz [β=0.33, P=1.7 x10-05]. Lower plasma 7-hydroxy-efavirenz concentrations were independently associated with CYP2A6 rs10853742 [β=-0.55, P=3.5 x10-05], ABCB1 rs115780656 [β=-0.65, P=4.1 x10-05] and CYP2A6 -48A→C [β=-0.59, P=1.0 x10-02]. CYP2A6 -48A→C was independently associated with higher CSF 8-hydroxy-efavirenz-to-efavirenz ratio [β=0.54, P=4.8 x10-02]. CYP2B6 rs2279345 polymorphism was associated with lower plasma 7-hydroxy-efavirenz-to-efavirenz ratio in univariate and multivariate analyses (P0.05). No polymorphisms were associated with CSF-to-plasma ratios for each of the 3 drugs, plasma or CSF concentrations of 8-hydroxy-efavirenz, tenofovir or emtricitabine, or neurocognitive performance.

Conclusion: We identified novel genetic associations with plasma concentrations of efavirenz, 7-hydroxy-efavirenz, 7-hydroxy-efavirenz-to-efavirenz ratio, 8-hydroxy-efavirenz-to-efavirenz ratio, CSF concentrations of efavirenz and 8-hydroxy-efavirenz-to-efavirenz ratio.

A Galaxy Instance for Microarray Data Analysis

Taoufik Bensellak et al.

ENSA of Tangier

Correspondence e-mail: taoufik.bensellak@gmail.com

MicroArray data analysis and interpretation has been possible since the creation of packages and tools implemented in all programming languages, mostly in R language. These packages are available on Bioconductor and CRAN. For researchers with low knowledge of R, using such tools could be a significant challenge. Besides, every known technology has been treated separately which could be confusing. Bioinformatics platforms such Galaxy are hosting tools and workflows for all sequencing technologies, although tools for MicroArrays still unavailable.

Assessment of the Diagnostic Performance of TrueHb® Point-of-Care Hemometer Compared with Sysmex i3 Analyzer among Patients at International Hospital Kampala, Uganda

Ivan Mugisha Taremwa [1], Ivan Ndeze [1], Bashir Mwambi [1], Christine Atuhairwe [1], Diana Inda Achieng [2], Bernard Natukunda [3]

[1] Clarke International University, Kampala, Uganda; [2] Lancet Laboratories, Kampala, Uganda; [3] Mbarara University of Science and Technology, Mbarara, Uganda

Correspondence e-mail: imugisha@ymail.com

Background: Accurate determination of hemoglobin (Hb) levels is vital in elucidating the extent of anemia, and is thus a guide to research and clinical care in harnessing a timely diagnosis. This study assessed the diagnostic performance of TrueHb® point-of-care hemometer compared with Sysmex i3 analyzer at International Hospital Kampala, Uganda.

Materials and Methods: We analyzed ethylene-di-amine tetra acetic acid (EDTA) blood samples to estimate Hb levels using parallel testing with TrueHb® hemometer and Sysmex i3 analyzer. Data were analyzed to ascertain diagnostic performance of the test assays using the Bland and Altman method. Sensitivity, specificity, positive and negative predictive values were calculated.

Results: The study enrolled 402 patients; of these, 156 (38.8%) were males. The average Hb levels were 8.7 ± 1.8 and 13.3 ± 2.6 g/dL for the anemic and non-anemic patients, respectively. One hundred and fifty-five participants were anemic, giving anemia prevalence of 38.56% (95% CI: 35.17- 40.38). The mean difference of the two assays was 2.2219 (SD 1.07915), there was no difference in their measurements (t=-2.407, p-value 0.017, 95% CI -.095--.010), a significant level of agreement t=41.281 (95% CI: 2.1161-2.3277) and correlation (ICC=0.793). The sensitivity, specificity, positive and negative predictive values were 100.00%, 51.01%, 55.16% and 100.00%, respectively.

Conclusion: The TrueHb® point-of-care hemometer is an accurate point of care tool for Hb estimation having a good performance agreement with the Sysmex i3 analyzer. This, coupled with its utility aspects, makes it a good diagnostic tool in a high anemia burden and low resource setting.

Distinct Profiles of warfarin Pharmacogenes in Africans

Arinao Ndadza [1], Edson Makambwa [2], Andre P Kengne [3], Mpiko Ntsekhe [2], Collet Dandara [1]

[1] Pharmacogenomics and Drug Metabolism Research Group, Division of Human Genetics, Department of Pathology & Institute of Infectious Disease and Molecular Medicine (IDM), Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; [2] Division of Cardiology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; [3] Non-Communicable Diseases Research Unit, South African Medical Research Council and University of Cape Town, Cape Town, South Africa.

Correspondence e-mail: NDDARI001@myuct.ac.za

Background: Warfarin is the most widely prescribed anticoagulant for the prevention and treatment of thromboembolic diseases. However, warfarin use is complicated by its narrow therapeutic range and inter-individual variability in starting dose required to achieve a stable international normalised ratio (INR). Genetic and non-genetic factors have been shown to be responsible for inter-individual variability. Thus, there has been an increased interest in pharmacogenetics of warfarin culminating in several dosing algorithms incorporating genetic variation. However, few studies have been conducted on the pharmacogenetics of warfarin in African populations. Therefore, we set out to determine genetic predictors of warfarin in the South African population, recruiting Black Africans (BA) and Mixed Ancestry (MA) participants.

Method: Genotyping for polymorphisms in CYP2C cluster and VKORC1 were carried out on 340 South Africans (89 BA and 251 MA) undergoing warfarin treatment, using Taqman SNP genotyping assay and PCR-RFLP. Results were validated using Sanger sequencing.

Results: We report on significant differences in warfarin dose requirements and genetic variants that affect warfarin predisposition between Black South Africans and the Mixed Ancestry group. The CYP2C rs12777823 G>A variant significantly reduced warfarin dose in BA (p=0.0001), whilst VKORC1 9041G>A (rs7294) significantly increased warfarin dose among the MA (p=0.0001).

Conclusion: We conclude that Africans significantly differ in the profile of variants that are important for warfarin response. This can be supported by the genetic diversity and pronounced admixture observed in Africans. We recommend determination of additional variants in Africans and evaluating their significance which would justify inclusion in warfarin pharmacogenetic algorithms for African populations.

Validation of Cepheid Xpert® BCR-ABL Monitor and Ultra test kits used in the molecular monitoring of chronic myeloid leukaemia (CML) patients

C.K. De Long [1], R. Grewal [1,2], F. Bassa [3], L.V. Paul [4,5], C.C. Swanepoel [1,2]

[1] Division of Haematology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, SA; [2] National Health Laboratory Services, Division of Haematology, Tygerberg, Cape Town, SA; [3] Division of Clinical Haematology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, SA; [4] Division of Medical Microbiology, Department of Pathology, Faculty of Health Sciences, University of Cape Town, SA; [5] National Health Laboratory Services, Division of Medical Microbiology, Groote Schuur, Cape Town, SA

Correspondence e-mail: chantaldl@sun.ac.za

Background: Chronic myeloid leukaemia (CML) results from the reciprocal translocation between chromosome 9 and 22. The molecular consequence of this translocation is the generation of the BCR-ABL oncogene which has elevated tyrosine kinase activity. Highly effective therapies have been developed for CML particularly the tyrosine kinase inhibitors (TKI), however it is not curative. Thus, molecular monitoring of the BCR-ABL transcript has become standard of care as it aids in prognosis, help with monitoring treatment response and help predict relapse. Quantitative reverse transcription PCR (qRT-PCR) is the method of choice used to monitor the treatment response by measuring the amount of BCR-ABL messenger RNA (mRNA) in blood cells. It is thus critical that the BCR-ABL test is accurate, adhere to an international scale (IS) and have improved sensitivity.

Aims and Objectives: The present study aims to evaluate and validate the automated Cepheid Xpert BCR-ABL Monitor and Ultra tests kits using the Cepheid GeneXpert instrument. No studies to date had been published in South Africa to compare the performance of the two kits and to verify the claim of greater sensitivity with the improved Ultra kit. It also aims to do a cost and labour analysis of this automated qRT-PCR methodology compared to the manual methods used in other diagnostics settings.

Materials and Methods: A total of 20 samples was collected for this study, which included, 10 newly diagnosed patients and 10 patients already receiving treatment. The patients' blood was analysed with both the Monitor and Ultra assay using the same blood sample and was run in parallel on the Cepheid GeneXpert system. Furthermore, negative controls were also included.

Results: High concordance was found between the two assays. The obtained results also showed higher sensitivity in the Ultra assay when compared to the Monitor assay. Furthermore, the differences between the assay results had clinical significance, as 50% of patients already receiving treatment had a different treatment response between assays.

Conclusion: It was concluded that the Ultra assay was more sensitive than the Monitor assay, thus supporting Cepheid's claim of greater sensitivity with the improved Ultra

assay. Furthermore, the Ultra assay was found to be an accurate test for the detection of the BCR-ABL transcript based on its high sensitivity and specificity percentages. It was also found to be superior to the manual methods used in other diagnostics settings in terms of specificity, sensitivity, turn-around time and labour intensity.

Integrating next-generation sequencing into clinical cancer genetics practice in Sri Lanka: Experiences and challenges

Nirmala D. Sirisena, Nilaksha Neththikumara, Sajeewani Pathirana, Kalum Wetthasinghe, Vajira H. W. Dissanayake

Human Genetics Unit, Faculty of Medicine, University of Colombo, Colombo 08, Sri Lanka

Correspondence e-mail: nirmala@anat.cmb.ac.lk

Background: Over the past few years, despite lack of government funding and none availability of insurance coverage of genomic tests, giant strides have been made in translating genomic medicine from bench to bedside in Sri Lanka. Our centre serves as the national referral centre for genetics and genomics in Sri Lanka. In 2015, using the Illumina MiSeq next-generation sequencing (NGS) platform and an in-house developed validated bioinformatics pipeline, multi-gene cancer panel testing and clinical exome sequencing were successfully implemented at our centre. Herein, our experiences and challenges in integrating NGS-based testing for hereditary cancer predisposition are described.

Methods: The clinical and genetic test data of 106 consecutive patients from families with two or more patients with cancer who underwent NGS-based germline genetic testing between January 2015 and August 2018 was maintained prospectively in a database and analysed retrospectively. Variants were classified after thorough assessment and review of available evidence which included population frequency databases, in-silico functional predictions, evolutionary conservation, clinical databases/published literature and co-segregation data.

Results: 80 (75.5%) were affected with cancer. 26 (24.5%) were pre-symptomatic at risk individuals. The most common phenotypes were hereditary breast and ovarian cancer (HBOC) - 51 (63.8%), and colorectal cancer (CRC) - 18 (22.5%). Germline variants were identified in 49 (61.3%) cancer affected and 10 (38.5%) pre-symptomatic individuals. They consisted of: non-synonymous variants - 42 (71.2%); small deletions - 13 (22.0%); insertions - 2 (3.4%); synonymous variants - 1 (1.7%); and duplications - 1 (1.7%). They were clinically classified as: variants of uncertain significance (VUS) - 25 (42.4%); pathogenic - 21 (35.6%); and likely pathogenic - 13 (22.0%). 9 (15.3%) were novel variants. Pathogenic and likely pathogenic variants in high-/moderate-penetrance cancer susceptibility genes were attributed to 18 (35.3%) HBOC and 7 (38.9%) CRC phenotypes.

Conclusions: The integration of NGS-based testing has facilitated precise genetic diagnosis and appropriate management of patients with inherited cancer predisposition. The main challenges faced were bioinformatics analysis and clinical interpretation of variants in the local context due to non-representation of variants in the Sri Lankan population in public databases. This limitation is gradually being curtailed by continual optimizing of our in-house bioinformatics pipeline and the build-up of a catalogue of genetic variants in the Sri Lankan population. The findings of several VUS and novel

variants highlight the importance of further investigating these variants to validate their functional significance.

A systematic assessment of the Copy Number Variation (CNV) landscape in ADME genes in Sub-Saharan African populations

Laura Cottino, Venesa Sahibdeen, Scott Hazelhurst

University of the Witwatersrand

Correspondence e-mail: lauracottino@gmail.com

The African continent is severely affected by disease and with a high disease burden comes a large proportion of the population receiving medication. However, it has become increasingly apparent that the majority of pharmaceutical drugs and their recommended doses do not have a uniform effect across all patients. An individual's genetic composition plays a major role in this variable response to drugs, in particular, variation in genes that encode proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. Currently, known SNPs only explain a portion of the variation in drug efficacy and toxicity that is observed, and while SNPs have been extensively studied, a systematic assessment of the copy number variation (CNV) landscape in ADME genes is lacking, especially in African populations. A recent study performed by Santos et al. (2017) looked directly at CNVs in ADME genes and involved the analysis of whole genome sequences and exome sequences from various population groups in order to identify CNVs in 208 pharmacogenes. 97% of the ADME genes contained novel CNVs and in total, 2611 deletions and 2978 duplications were detected. In order to assess the CNV landscape in ADME genes in sub-Saharan African populations, CNVs from 274 African, high coverage whole genome sequences obtained from the Heredity and Health in Africa (H3A) Consortium will be identified using several CNV calling tools including GenomeSTRiP. Following the detection of known and novel CNVs, various bioinformatics tools will be utilized for CNV annotation. The frequencies of the CNVs will be determined and compared between the different African populations as well as with populations living outside of Africa. Lastly, a list of the CNVs most relevant in an African context in terms of function and frequency will be compiled. Nextflow will be used in order to develop a scalable and reproducible workflow for CNV detection and annotation.

Genetic Genealogy - Using Y-STRs for: Surname Studies, Population and Forensic Genetics Based on Males (Specifically Indians) In the Durban KwaZulu-Natal Region

Surina Singh, Jenny Lamb

UKZN

Correspondence e-mail: surinsingh@hotmail.co.za

The combination of molecular genetics and surname analysis of STR data has the potential to shed light on population structure and history and falls within the field of forensic DNA analysis. Since the Y-chromosome DNA along with surnames are paternally inherited, non-related males sharing a surname should be more closely related in comparison to the general population. Currently, no surname studies based on the Indian population in South Africa exist. This study aims to explore the genetic genealogy, population and forensic genetics of (1) samples comprising male Indians with a variety of surnames, geographic origins and religions and to compare the genetic structure found to that of other ethnic groups, such as male Zulus with different common surnames, all currently residing in the greater Durban area of KZN. This was achieved by: (1) Collecting samples and generating DNA profiles from 224 non-parentally related North Indians males, using the Yfiler® Plus kit to amplify 27 Y-STR loci and generating DNA profiles from this; (2) Comparing the genetics of the experimental group referred to above to that of other groups with South Indian and Zulu African surnames found in the forensic lab database. Hypotheses were formulated to analyse differences in relationships at ethnic, region, religion, language and surname-based levels (Figure 1). AMOVA, used to search for the presence of genetic structure among surname groups, was significant for all levels tested. Structure and PCoA analysis showed the presence of 2 significant sub-populations, which were ethnic based. Preliminary results suggest that population structure and diversity was not surname based and is at an ethic level. This could be attributed to polyphyletic origin (many surname origin) of the analysed surnames. The Data generated in this study will contribute to the Indian DNA profiling database and could potentially serve as a baseline for further research.

Novel Alleles of Immunoglobulin Variable Domain in Africa and Broadly Neutralizing Effect against HIV Infection

Rahaman Ademolu Ahmed [1], Cathrine Scheepers [2], Khalid Adekoya [1]

[1] Medical Genetics Unit, Cell Biology and Genetics Department, University of Lagos, Nigeria; [2] National Institute for Communicable Diseases, South Africa

Correspondence e-mail ahmedrahman158@gmail.com

Identification of vaccine-compatible antibodies capable of eliciting absolute protection against HIV infection is a global quest. Africa representation in the antibody gene databases is however low among which potent antibodies against infectious and communicable diseases may be found. Following ethical approval from the National Institute of Communicable Diseases, south Africa and informed consent from participants, Immunoglobulin heavy chain variable domain (IGHV) of 28 HIV infected subjects in Zulu ethnic group of South Africa was sequenced using Roche 454 and Illumina Miseq sequencer while rearranged novel antibodies were screened for broadly neutralizing effect against HIV infection. 239 alleles of IGHV were identified among which 48% were not found in the Immunogenetics database. 85 novel alleles were identified and at least 8 expressed broadly neutralizing effect against HIV infection. This suggests that novel functional immunoglobulin gene variants are embedded in Africa population. We therefore want to further explore antibody gene diversity in Nigeria being the largest population in Africa and with diverse heterogeneous ethnic groups. This study will contribute to effective antibody utilization for a quality HIV vaccine development and other infectious diseases. It will also be of great importance to the Antibodyomics project which is aimed to provide holistic and cross-sectional information on human antibodies for future intervention.

GJB2 and GJB6 mutations in non-syndromic childhood hearing impairment in Ghana

Samuel M. Adadey [1], Noluthando Manyisa [2], Khuthala Mnika [2], Victoria Nembaware [2], Osbourne Quaye [1], Geoffrey K. Amedofu [3], Gordon A. Awandare [1], Ambroise Wonkam [2]

[1] West African Centre for Cell Biology of Infectious Pathogens (WACCBIP), University of Ghana; [2] Faculty of Health Sciences - University of Cape Town; [3] Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Correspondence e-mail: ambroise.wonkam@uct.ac.za

Aim: Our study sought to examine the major causes of pre-lingual and post-lingual hearing impairment (HI) in Ghana as well as to investigate the role of connexin 26 and 30 genes (GJB2 and GJB6) mutations in familial and non-familial HI cases. Method: The medical reports of 1104 students were analyzed to enroll HI patients. PCR and Sanger sequencing were used to investigate mutations within the coding region of GJB2 and multiplex PCR and Sanger sequencing were used to analyze the prevalence of GJB6 deletion.

Results: Ninety-seven (97) families segregating HI and 19 isolated/non-familial cases were sampled. The male to female ratio was 1.49 and about 59.6% of the patients had their first comprehensive HI test between 6 to 11 years. Convulsion and cerebrospinal meningitis were major causes of post-lingual HI. Over 754 patients have pre-lingual HI of which 92.8% were congenital. Pedigree analysis of the families suggested that more than 95% might had autosomal recessive fashion of HI inheritance. Molecular analysis of mutations in GJB2 revealed that GJB2-R143W mutation, previously reported as founder a mutation in Ghana accounted for 21.6% (21/97) of familial and 10.52% (2/19) non-familial HI cases. The other 7 previously reported GJB2 mutations in the Ghanaian population were not identified in our study. The analysis showed that, none of the study participants had GJB6 deletion.

Further analysis: Variants from a multiple sequence alignment of HI patients will be compared to participants with normal hearing in order to investigate other GJB2 and GJB6 mutations in the Ghanaian population. Whole Exome Sequencing will be performed for those families that are negative for GJB2 and GJB6 mutations. Conclusion: GJB2-R143W mutation accounts for nearly a quarter familial non-syndromic HI cases in Ghana and should be investigated in clinical practice. Connexin 30 mutations do not account for congenital non-syndromic HI in Ghana.

High-throughput RFLP assay for the identification of glycophorin B deletion variants

Dominic Selorm Yao Amuzu [1,2], Kirk Rockett [2,3], Ellen Leffler [2,3], Felix Ansah [1], Nicholas Amoako [1], Christina Hubbart [2], Kate Rowlands [2], Anna Jeffreys [2], Dominic Kwiatkowski [2,3,4] Lucas Amenga-Etego, Gordon A. Awandare [1]

[1] *West Africa Centre for Cell Biology of Infectious Pathogens, Department of Biochemistry, Cell and Molecular Biology, University of Ghana, Legon, Accra, Ghana*
[2] *Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK*
[3] *Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridgeshire, UK*
[4] *Big Data Institute, University of Oxford, Oxford, UK*

Correspondence e-mail: dsyamuzu@st.ug.edu.gh

Genetic variation in the glycophorin region of human chromosome 4 (containing the GYPA, GYPB and GYPE genes) has been linked with a 40% reduction in the risk for severe malaria (Leffler et al. Science 2017). In particular, a large structural rearrangement and hybrid variant known as Dantu was identified in several East African populations that was linked to this signal. This region is of particular interest because the glycophorin genes have been shown to act as receptors for erythrocyte invasion by Plasmodium falciparum (Chung et al. 2005). Apart from Dantu (which is absent in W. Africa), a number of other large structural variants have also been identified in the glycophorin region on chromosome 4, the most common variants give rise to the deletion of the whole GYPB gene and surrounding region. In Africa, particularly West Africa, these deletions account for between 5 and 15% of individuals. In order to investigate the effect of these glycophorin B deletions on malaria invasion and growth, it was first necessary to identify individuals carrying these different variants. Here we report the development of high-throughput RFLP assays for the two main GYPB deletion variants known as GYPB DEL1 and GYPB DEL2. One is a modification of the DEL1 assay reported in Leffler et al. (2017), while the DEL2 assay is novel. We also report the identification of the crossover/breakpoint for GYPB DEL2. Futhermore, we report the genotyping of 400 samples from Southern Ghana as well as a panel of 600 DNA samples from the HapMap and 1000G projects. This is the first report of assays identifying specific Glycophorin B deletion types that can be used for high-throughput genotyping of populations. This allows for the identification of Glycophorin B deletions for experimental work and the stratification of genetic association studies as well as understanding the role of this region in malarial disease.

Apoliproprotein L1 (APOLL1) Gene is Associated with Small Vessel Ischaemic Stroke among Indigenous West Africans: Findings From The SIREN Study

Fakunle A. [1], Akinyemi R. [1,2], Tiwari H. K. [3], Arnette D. K. [4], Ovbiagele B. [5], Irvin M. R. [3], Wahab K. [6], Sarfo F. [7], Srinvasasainagendra V. [3], Adeoye A. [1], Perry R. T. [3], Akpalu A. [8], Jenkins C. [5], Arulogun O. [1], Gebregziabher M. [5], Owolabi L. [9], Obiako R. [10], Sanya E. [6], Komolafe M. [11], Fawale M. [11], Adebayo P. [12], Osaigbovo G. [13], Sunmonu T. [14], Olowoyo P. [15], Chukwuonye I. [16], Obiabo Y. [17], Onoja A. [18], Akinyemi J. [19], Ogbole G. [19], Melikam S. [1], Saulson R. [5], Owolabi M. [1,20] for all SIREN Investigators

[1] Center for Genomic and Precision Medicine, University of Ibadan, Ibadan, Nigeria
[2] Federal Medical Centre Abeokuta, Ibadan, Nigeria
[3] University of Alabama at Birmingham, Birmingham, AL, USA
[4] University of Kentucky, Lexington, KY, USA
[5] Medical University of South Carolina, South Carolina, SC, USA
[6] University of Ilorin Teaching Hospital, Ilorin, Nigeria
[7] Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
[8] University of Ghana Medical School, Accra, Ghana
[9] Aminu Kano University Teaching Hospital, Kano, Nigeria
[10] Ahmadu Bello University, Zaria, Nigeria
[11] Obafemi Awolowo University, Ile-Ife, Nigeria
[12] Ladoke Akintola University of Technology, Ogbomosho, Nigeria
[13] Jos University Teaching Hospital, Jos, Nigeria
[14] Federal Medical Centre, Owo, Nigeria
[15] Federal University Teaching Hospital, Ido-Ekiti, Nigeria
[16] Federal Medical Centre, Umuahia, Nigeria
[17] Delta State University Teaching Hospital, Oghara, Nigeria
[18] Department of Epidemiology and Medical Statistics, University of Ibadan, Ibadan, Nigeria
[19] Department of Radiology, University of Ibadan, Ibadan, Nigeria
[20] WFNR-Blossom Specialist Medical Center, Ibadan, Nigeria

Correspondence e-mail: fakunz@yahoo.com

Introduction: Globally, the highest frequencies of Apolipoprotein L1 (APOL1)-associated kidney variants are found in indigenous West Africans among whom small vessel disease (SVD) ischemic stroke is the most common stroke phenotype.

Objective: The objective of this study was to investigate the association and effect sizes of 23 selected SNPs in 14 genes of relevance, including the APOL1 G1 variants, with the occurrence of SVD ischemic stroke among indigenous West African participants in the Stroke Investigative Research and Education Network (SIREN) Study.

Materials and Methods: Cases were consecutively recruited consenting adults (aged 18 years or older) with neuroimaging—confirmed first clinical stroke. Stroke-free controls were ascertained using a locally validated version of the Questionnaire for Verifying Stroke-Free Status (QVSFS). Logistic regression models adjusting for known vascular risk

factors were fitted to assess the associations of the 23 SNPs in rigorously phenotyped cases (N = 154) of SVD ischemic stroke and stroke-free (N = 483) controls.

Preliminary Results: Apolipoprotein L1 (APOL1) rs73885319 (OR = 1.52; CI: 1.09-2.13, P-value = .013), rs2383207 in CDKN2A/CDKN2B (OR = 3.08; CI: 1.15-8.26, P–value = .026) and rs2107595 (OR = 1.70; CI: 1.12-2.60, P-value = .014) and rs28688791 (OR = 1.52; CI: 1.03-2.26, P-value = .036) in HDAC9 gene were associated with SVD stroke at 0.05 significance level. Polymorphisms in other genes did not show significant associations.

Conclusion and Next step: This is the first report of a specific association of APOL1 with a stroke subtype. Further research is needed to confirm these initial findings and deepen understanding of the genetics of stroke in people of African ancestry with possible implications for other ancestries as all humans originated from Africa.

Characterization of inter-species protein interactions: Use of SLiM motif to infer the interactions between Plasmodium falciparum and its host

Yasmine Ochi [1,2], Oussema Souiai [2,3], Alia BenKahla [2]

[1] *Faculty of Mathematical, Physical and Natural Sciences Tunis, El Manar*
[2] *Institut Pasteur de Tunis*
[3] *Higher Institute of Medical Technologies of Tunis*

Correspondence e-mail: yasmineo52@gmail.com

Introduction: Malaria remains the most widespread vector-borne disease worldwide and the most deadly. Its inference reaches 50% of the world's population (3.3 billion people in 109 countries). Plasmodium falciparum is the most common species that induces the most severe forms with the occurrence of severe cerebral access responsible for malaria deaths. Although malaria has been eradicated in Tunisia since 1979, this disease still a health issue due to the persistence of mosquitoes and coexistence with a potential parasite reservoir in the form of imported cases. This reemergence led us to conduct this study aiming at better characterizing the proteins interactions between it and its hosts.

Objectives: The objective of this work is to better characterize and analyze the protein interactions (PPI) of Plasmodium falciparum in its sporozoite and trophozoite forms and their target hosts, respectively hepatocytes and mature erythrocytes. Following the identification of the aforementioned PPI, a functional analysis will be carried out in order to highlight the immune disturbances induced by the pathogens in its various forms.

Methods: We propose a protocol to deduce the most likely interspecies interactions network by following this steps sequentially: Integrate, all the interspecies interactions from protein interaction resources like APID, IntAct and MPID. Identify the protein sequences for Plasmodium falciparum and human from various databases such as NCBI, UNIProt, PlasmoDB, Ensemble Protiste...etc. Extract SLiMs (using SliMFinder/IUPred2a), playing a key role in interspecies interactions, from the interactions and the sequences of the 2 species mentioned above. Apply the Bayesian Framework ,which is based on structural affinity, on the identified SLiMs. Select the best common SLiMs couples between P.falciparum and its host, among the structurally verified SLiMs, to predict interactions for the following two interspecies models: sporozoite/hepatocyte cells and trophozoite/ cells. Annotate functionally interacting proteins with both forms of Plasmodium.

Preliminary Results: After gathering the most complete sequences of Plasmodium falciparum's cells and its hosts, next to the majority of the interactions established between the 2 species, we used SLiMFinder and IUPred2a to extract enough SLiMs from the data that we have.

Next steps: Since most of the SLiMs of the 2 species have been identified, we will select the ones with higher confidence. For those couples, we will apply a Bayesian approach in order to predict the protein-protein interactions PPI between the parasite and its hosts, and infer the most complete network of interactions between the 2 species.

Identifying new genes and variants involved in Hearing Impairment in Cameroon, using Next Generation Sequence data

Edmond Wonkam Tingang [1], Jean Jacques Noubiap [2], Carmen de Kock [1], Vicky Nembaware [1], Jean Valentin Fokouo [3], Ambroise Wonkam [1]

[1] *Division of Human Genetics, Faculty of Health Sciences, University of Cape Town, South Africa*
[2] *Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[3] *ENT unit, Bertoua Regional Hospital, Cameroon*

Correspondence e-mail: ambroise.wonkam@uct.ac.za

Introduction: Hearing Impairment is the most common sensory disability in children, and has a variety of causes. Concerning Non-Syndromic Hearing Impairment (NSHI), mutations in GJB2, GJB6 and GJA1 genes have a prevalence close to zero in sub-Saharan Africa, except in Ghana. Genetic testing through targeted genomic enrichment and massively parallel sequencing of 116 genes identified 5 novel variants in ten multiplex Cameroonian families segregating a NSHI. These results suggest that NGS is the best way to identify variants involved in NSHI in sub-Saharan African population.

Objectives: The aim of this study is to identify novel genes and variants associated with NSHI in Cameroon, and to establish their involvement and impact on hearing impairment.

Methodology: We are recruiting families segregating NSHI, and isolated HI cases with strong evidence of non-environmental causes. The aim is to recruit 50 families and 200 isolated cases. Clinical examination and audiometric testing is performed for each patient. Informed consent is obtained and a blood sample is collected from all study participants.

Preliminary results: To date, 24 individuals presenting a hereditary hearing impairment and belonging to 10 families, and 61 isolated cases were recruited. Seven out of ten families (70%) segregate NSHI, one family (10%) presents Usher syndrome, and two (20%) segregate Waardenburg syndrome. Concerning our 24 patients presenting a hereditary hearing impairment, 58.3 % (14/24) are males, and 41.7% (10/24) are females; hearing loss is congenital in 95.8% (23/24) of them. The hearing loss is bilateral in all our patients, sensory-neural in 91.7% (22/24), and profound on at least one ear in 95.8% (23/24) of them. The disease is transmitted on an Autosomal Recessive mode in 83.3% (20/24) of our patients, on an Autosomal Dominant mode in 16.7% (4/24), and a consanguinity is found in 12.5% (3/24) of our patients.

Next steps: Recruitment for this study is ongoing. Investigation will continue with exome sequencing of samples from two affected family members and follow up variants segregation in parents and at least one non-affected sibling, in isolated cases and available controls. Novel identified variants will be followed-up with functional and expression studies.

Using DM Techniques to Predict the Response of HCV Patients

Mohammed Ahmed Farahat [1], Samar Kamal Kassim [2], Ahmed Sharaf Eldin [1]

[1] *Faculty of Computers and Information, Helwan University, Cairo, Egypt*
[2] *Faculty of Medicine, Ain Shams University, Cairo, Egypt*

Correspondence e-mail mohammed_farahat19@yahoo.com

Hepatitis C virus is a major cause of chronic liver disease, and liver cancer. Genotype 4 is the prevalent genotype in Egypt and has recently spread to Southern Europe. Treatment of HCV has evolved from interferon monotherapy to interferon and ribavirin (RBV) combination therapy followed by pegylated interferon (PEG-INF) and ribavirin therapy. However, interferon based therapies were associated with adverse events and limited response rates. Recently, new direct acting antivirals (DAAs) have caused a revolution in HCV therapy with response rates approaching 100%. Still treatment of chronic hepatitis C genotype 4 has not yet been optimized. Aim is to build a framework to predict the response of chronic HCV genotype 4 patients to various DAAs by applying Data Mining Techniques (DMT) on clinical information. Methodology: Data from 420 HCV Egyptian and European patients with genotype 4 were analyzed. Patients were treated with four different regimens of DAAs. Treatment endpoint is sustained virologic response defines as undetectable HCV RNA 24 weeks following termination of therapy. Framework consisted of three phases: data preprocessing, DM, and evaluation phase. Clinical data has been divided into four groups (TR1, TR2, TR3 and TR4) according to the regimen of DAAs treatments. Feature selection algorithm has been applied on each group. A subset of 10% of the data was selected to test the model and, the 90% to build the classifier. The resulting classes were about the effect of the four treatments on the PCR result, i.e. TR1_Yes or TR1_No. Results: The DT of four modalities of treatment were: 83.3%, 80%, 100% and 57.1% sensitivity, 100%, 100%, 71.4% and 100% specificity, and 90.9%, 90%, 81.8% and 75% accuracy. The averages of the four decision trees were 80% of sensitivity, 93% of specificity and 84% of accuracy. Future work: More data sets will be used to train other classifiers and try more experiments to enhance our framework. More than one technique will be combined to reach highest accuracy. Resulting classes will be the effect of the treatments on the Baseline core Antigen test instead of PCR test as its cheaper and easier to be tested.

Sickle Cell Trait and Chronic Kidney Disease

Ernestine Kubi [2,3], Priscilla Akyaw [2,3], Anita Ghansah [2,3], Alexander Nyarko [2], Barbara Mensah [2,3], Nana Yaa A. Karikari [2], Charlotte Osafo [1], Bamidele Tayo [5], Akinlolu Ojo [7], Babatunde Salako [6], Gordon Awandare [3], David Burke [4] , Dwomoa Adu [1]; H3Africa Kidney Disease Research Network

[1] University of Ghana Medical School; [2] Noguchi Memorial institute for Medical Research (NMIMR), University of Ghana, Legon; [3] West African Centre for Cell Biology and Infectious Pathogens (WACCBIP),; [4] University of Michigan, Department of Human Genetics, Ann-Arbor – U.S.A, [5] Loyola University, USA; [6] University of Ibadan, Nigeria, [7] University of Arizona, Department of Medicine

Correspondence e-mail: ernestine.kubi@gmail.com

Chronic Kidney disease (CKD) is a significant global public health threat with a disproportionate burden on African populations who have about a 4 to 5 times higher risk of developing end stage kidney failure as compared with Europeans. Previous studies have reported a strong association between APOL1 risk alleles and chronic kidney disease in African Americans and Africans but these only partially explain the high predisposition of Africans to CKD and ESRD. Thus, the need to investigate other genetic factors involved in increasing the risk of CKD in Africa. One such potential genetic factor is sickle cell trait (Haemoglobin AS). There are conflicting reports on whether sickle cell trait increases the risk of developing CKD. This study aimed to investigate the associations and interactions between Hb AS, and APOL1 variants in individuals with CKD of unknown aetiology. We studied a total of 201 patients with CKD and 210 healthy controls. Isolated genomic DNA was multiplex-PCR amplified and Ligation-Detection Reaction assayed for single-base variants (HbS-rs334, APOL1 G1-rs60910145, rs73885319, G2-rs71785313) identified by polyacrylamide gel electrophoresis. Association between these SNPs and CKD was determined using the chi square test, odds ratio was calculated to determine strength of genetic association in a logistic regression model. There was no significant association between Hb AS genotype and the risk of nephropathy (OR= 1.32, 95% CI=0.83-2.09, P=0.231). APOL1 G1 allele imposed an increased risk (70-100%) of having nephropathy (p-value=0.008,0.01). In individuals with Haemoglobin AS, the presence of an APOL1 G1 variant increased the risk of nephropathy by 130% indicating a possible synergistic interaction between Hb AS genotype and APOL1 G1. This finding is rather intriguing, as it presents us with a possibility that Hb S carriers may be at risk of renal damage as they are likely to be exposed to other genetic variants and such an interaction between haemoglobin AS and APOL1 risk variants may explain some of the increased risk of CKD in Africans.

Genetic Investigation of South Africans with the Noonan Syndrome Phenotype using Targeted Next Generation Sequencing

Cedrik Tekendo-Ngongang, Alina.I Esterhuizen, Gloudi Agenbag and Ambroise Wonkam

Division of Human Genetics, Departments of Medicine and Pathology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Correspondence e-mail: cedrik.ngongang@uct.ac.za

Noonan Syndrome (NS) is a common autosomal dominant developmental disorder, caused by germline mutations in more than ten genes encoding proteins integral to the Ras/MAPK signaling pathway. Clinical features associated with NS include short stature, distinctive craniofacial dysmorphism, cardiovascular abnormalities and developmental delay. Despite significantly advanced knowledge on the phenotypic and mutational spectrum in NS thanks to Next-Generation Sequencing (NGS) technologies, very little is known about phenotypic specificities and variants distribution in affected individuals of African descent. The present study investigates a group of South African individuals with a clinical diagnosis of NS from a clinical and molecular perspective. This cross-sectional study included familial and simplex NS patients recruited in Cape Town over a 2-year period, based on Van der Burgt scoring system. Clinical features were carefully documented in a total of 26 patients, including pediatric and adult cases. Targeted NGS was subsequently performed on 16 unrelated probands, using a panel of 14 genes, comprising PTPN11, SOS1, RIT1, A2ML1, BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, RAF1, SHOC2 and SPRED1.
The median age at diagnosis was 4.5 years (range: 1 month – 51 years). Individuals of mixed-race ancestry were most represented (53.8%), followed by black Africans (30.8%). Our cohort revealed a lower frequency of pulmonary valve stenosis (34.6%) and a less severe developmental phenotype. Out of the 16 DNA samples analyzed, six (n=6; 37.5%) different missense variants were detected in CBL (n=2; 28.6%), PTPN11 (n=2; 28.6%) and MAP2K1 (n=2; 28.6%), four of which were novel. Variant's pathogenicity was assessed by family segregation studies using Sanger sequencing and functional analysis using available pathogenicity prediction tools. The proportion of CBL and MAP2K1 variants was relatively high compared to other series. Genotype-phenotype correlations revealed that clinical features of NS were more characteristic in patients with variants in MAP2K1, and less in those with variants in CBL.
This first application of targeted NGS for the molecular diagnosis of NS in South Africans suggests that, while there is no major phenotypic difference compared to other populations, the distribution of NS variants in South Africans may differ from that reported in other series. Further study of a larger South African cohort ideally using Whole Exome Sequencing is warranted to comfortably infer these preliminary results.

Detailed investigation of genetic variants in Sickle Cell Disease individuals with extreme fetal hemoglobin levels in Dar es Salaam, Tanzania.

Siana Nkya, Liberata Mwita, Leonard Malasa, Happiness Kumburu, Marco Van Zwetselaar , Emile R. Chinusa, Raphael Sangeda, Stephan Menzel, Julie Makani.

[1] *Muhimbili University of Health and Allied Sciences*
[2] *Dar es Salaaam University College of Education*
[3] *Kilimanjaro Clinical Research Institute*
[4] *Department of Pathology, Division of Human Genetics, University of Cape Town*
[5] *King's College of London*

Correspondence e-mail: leonard.myjoy@gmail.com

Background: Up to 11,000 children are born with SCD in Tanzanian every year. HbF is known to reduce disease severity but the levels vary from one individual to another. HbF is genetically influenced by both common and rare variants. However, so far most approaches have been mainly on determination of common variants across populations. In addition, identified loci do not fully account for HbF variation across populations including Tanzania. This work aimed at investigating additional, both, rare and common genetic variants that influence HbF levels in SCD patients in Dar es Salaam Tanzania with extreme HbF levels (>7.8%=high HbF) and (2.6%=low HbF). Objectives : The overall objective of this study was to perform a detailed investigation of genetic pattern in sickle cell disease patients with extreme fetal hemoglobin levels in Dar es Salaam, Tanzania.

Specific objectives were: 1. To Describe the multiple variations identified across targeted regions. These include single nucleotide polymorphisms (SNPs), Insertions-deletions (INDELs) and copy number variations (CNVs), 2. Compare between variations found in those with high HbF versus those with low HbF levels.

Methodology: Study participants: Individuals with SCD with either high or low HbF levels). Sequencing: Targeted next generation sequencing (Illumina_Miseq) which interrogates SNPs, INDELs, CNVs was used.

Results: The sequence regions covered exon and full regions for validated and unvalidated fetal hemoglobin associated loci including B-cell lymphoma/leukemia 11A (BCL11A), proto-oncogene, transcription factor (MYB), Homeobox A9 (HOXA9), hemoglobin subunit gamma 2 (HBG2), chromodomain helicase DNA binding protein 4 (CHD4), Kruppel like factor 1(KLF1), methyl-CpG binding domain protein 3 (MBD3), zinc finger and BTB domain containing 7A (ZBTB7A) in chromosomes 2, 6, 7, 11, 12 and 19, respectively. Analysis: Preliminary data indicate inter-individual variation across the sequenced regions.

Conclusion: This will be the first study in Tanzania to interrogate multiple human genomic variants associated with SCD using next generation sequencing approach.

Knowledge, perception and acceptability of genomics research in Kaberamaido district in Uganda

Harriet. Nankya [1], Fred. Nakwagala [1], Enock. Matovu [2], John. Barugahare [3], Vincent.P. Alibu [4]

[1] *College of Health sciences (CHS)*
[2] *College of Veterinary Medicine, Animal Resources and Biosafety (COVAB)*
[3] *College of Humanities and Social Sciences (CHUSS)*
[4] *College of Natural Resources (CONAS)*

Correspondence e-mail: harrietana@gmail.com

Introduction: There are signs that the health needs of low-income countries are gaining increased attention among scientists and research funders, and one example of this is the growth of genomics research in Africa. The major challenge of the "genomic era" is ensuring that members of the general public have the knowledge and proper decision-making capacity to engage in genomics activities. The current level of knowledge and perceptions on genetics and genomics in Africa is unclear. In Uganda, there are no published reports on either knowledge, perception or acceptability of the general public to participate in genomics studies.

Objective: To assess the public's knowledge and perceptions on genomics and their willingness to participate in genomics research in Kaberamaido district in North Eastern Uganda.

Methods: A cross sectional study will be conducted in Kaberamaido district between July and September 2018. A Systematic sampling technique will be used to select 164 participants for enrollment into the study. Participants will be interviewed using a guided questionnaire. SPSS and Microsoft Excel for Windows software will be used in data analysis.

Next steps: This study will give information on how the public in Kaberamaido understand and perceive genomics and their willingness to participate in genomics research. This knowledge will shed light on what motivates and/or stops the public from participating in genomics research. The results of this should aid inspire wide research as part of efforts to identify and address the barriers or concerns on participating in genomics research and possibly also address misconceptions about its potential benefits.

Genome-wide Association Studies, Imputation and Fine Mapping in African Populations Identify Novel Risk Loci for Orofacial Clefts

Lord J J Gowans [1], Peter A Mossey [2], Mekonen A Eshete [3], Waiu L Adeyemo [4], Tamara D Busch [5], Brad Amendt [5], Charles Rotimi [6], Mary L Marazita [7], Robert Cornell [5], Adebowale A Adeyemo [8], Jeffrey C Murray [5], Azeez Butali [5]

[1] *Kwame Nkrumah University of Science and Technology*
[2] *Universityof Dundee, Orthodontics*
[3] *Addis Ababa University*
[4] *University of Lagos*
[5] *University of Iowa*
[6] *National Institutes of Health, NHGRI*
[7] *University of PIttsburgh*
[8] *National Institutes of Health, National Human Genome Research Institute, Center for Research on Genomics and Global Health*

Correspondence e-mail: ljj.gowans@gmail.com

Orofacial clefts are common congenital developmental abnormalities that pose significant clinical, economic, cultural and psychological problems. We conducted genome-wide association studies, imputation and fine mapping analyses for isolated cleft palate (CPO) and cleft lip with or without palate (CL/P) with ~17 million SNPs in sub-Saharan Africans from Ghana, Ethiopia and Nigeria. After imputation, replication and combined analyses, we identified novel loci for CPO at or near genome-wide significance on chromosomes 2 (near CTNNA2, rs80004662, p= 7.41X10-9), 19 (near SULT2A1, rs62529857, p=7.63X10-8) and 13 (near DACH1, rs2325377, p=3.31 X10-07). In situ hybridization of Sult2a1 in mice showed that SULT2A1 was expressed in mesenchymal cells in palate, palatal rugae and palatal epithelium in the fused palate. The previously-reported 8q24 locus for CL/P was the most significant (rs72728755, p=1.52×10–6) in our study and fine mapping of the shorter African haplotype at this loci has for the first time implicated the regulatory RNAs LINC00824 and LINC00977as the probable candidate genes at this loci, a loci which has been reported in previous studies as intergenic and a gene desert. Moreover, luciferase functional assays to test for enhancer activities at the 8q24 loci could not confirm the long-held hypothesis that the 8q24 loci may harbour enhancer elements. We also replicated several previously reported loci, including IRF6, PAX7, VAX1, PTCH1 and COL8A1. Again, fine mapping of these previously implicated loci in the shorter African haplotypes, either confirmed already reported genes or suggested alternative genes, whereas new genes were implicated in loci that were either classified as intergenic or no gene was implicated in previous studies. Moreover, our genomic analysis either confirmed or deviated from the effect allele or direction of effect in previous studies. Through Sanger DNA sequencing of some newly implicated genes or loci, novel variants were observed in ACVR2A (p.Leu187Pro) and DACH1 (p.Gly739Ser) in Nigerian and Ghanaian cases, respectively. These observations buttress the point that the shorter haplotype blocks of the African genome offers an invaluable tool for the fine mapping of disease loci. It also reinforces the need to replicate GWAS signals in different

populations due to variations in allele frequencies and implicated SNPs. In conclusion, our study has implicated several loci in the aetiology of both CPO and CL/P, with fine mapping of the shorter African haplotype blocks playing crucial role. Our study is relevant for elucidating the genetic architecture of OFCs and offers invaluable support to preventive, predictive and personalized medicine.

Cross-sectional genetic analysis of Plasmodium falciparum Rh5 interacting protein (PfRipr) and cysteine-rich protective antigen (CyRPA) genes in Kilifi, Kenya

Kevin Omondi Ochwedo

University of Nairobi

Correspondence e-mail: kevinochwedo@gmail.com

The discovery of antibodies against the Reticulocyte binding-protein homologue (Rh) 5 interacting protein (Ripr) and Cysteine-rich protective antigen (CyRPA), which are crucial in the invasion process across all parasite strains has brought new hope to the vaccine development field. Determining whether the Ripr and CyRPA genes in P. falciparum isolates from malaria-endemic population in Kilifi-Kenya are polymorphic provide data that is important in vaccine development targeting the two antigens. These results aid in preventing the development of a malaria blood-stage vaccine that would not proceed beyond the clinical trial stages due to the presence of multiple antigen variants. The genomic DNA of P. falciparum extracted from blood samples collected in 2013 and 2014 from 162 children aged below 8 years were used in the study. These children suffered from uncomplicated malaria and were admitted at Kilifi County Hospital. From the extracted genomic DNA, Exon 1 and Exon 2 of CyRPA gene were separately amplified by different primer sets whereas Ripr gene was amplified using two different primer sets. Good quality amplicons were sequenced and analysed using CLC Genomics Workbench 7, MEGA 6.0 and DnaSP 5.10.01 software. Sequence assembly was done using CLC bio and subsequent analysis conducted using DnaSp software and MEGA 6.0. A total of three mutations were detected in sequences of exon 2 of CyRPA gene at positions 193, 1005 and 1086. SNPs at position 193 and 1005 resulted in non-synonymous mutations, whereas position 1086 was a synonymous mutation. The identified SNPs were under purifying selection, suggesting a possible stabilization of the CyRPA gene. The parasites tend to ensure that mutations that may interfere with the CyRPA antigen functionality are eliminated. Such a result reaffirms CyRPA antigen as a possible candidate in developing a blood-stage malaria vaccine in the future. Similar to Exon1 of CyRPA gene, the Ripr gene lacked polymorphisms. The result was obtained from analysis of 39 samples which accounted for 24.1% of the total samples analysed. The lack of polymorphism in Ripr, Exon1 of CyRPA sequences and polymorphisms in Exon 2 of CyRPA show that both these genes appear to be highly conserved with hardly any polymorphisms making them good vaccine candidates since there will be no limitation of allele-specific immunity.

Pharmacogenetics and comparative bioavailability study in Mexican population applied to pharmacokinetic variables assessment

Diaz-Tufinio Carlos Alejandro, Palma-Aguirre [2], José Antonio [2], González-Covarrubias, Vanessa [3]

[1] *Pharmacogenomics Lab, National Institute of Genomic Medicine (INMEGEN), Mexico / National Autonomous University of Mexico, Mexico City*
[2] *Principal Investigator, Axis Clinicals Latina, Mexico*
[3] *Pharmacogenomics Lab, National Institute of Genomic Medicine (INMEGEN), Mexico*

Correspondence e-mail: cdiaztuf@gmail.com

Massive analysis of genetic variants now-a-days is allowing researchers and healthcare professionals to take the promise of personalized pharmacological therapy and genomic medicine from the bench to the bedside. On this same track, the objective of the present work is to quantify the biological variability given by genetic factors to apply them in bioequivalence and comparative bioavailability studies for generic product testing, ultimately to control within-subject and between-subject variabilities. Moreover, the aim of this project is to stablish a proof-of-concept that the genetic variation in healthy volunteers in this type of studies is relevant and possibly to extrapolate this knowledge to the pharmacological practice in real patients in a near future. Through a bioequivalence study performed after Fluoxetine Hydrochloride administration in healthy volunteers, with additional genotyping of the participant volunteers, the fact that the genetic variation in healthy volunteers in this type of studies is relevant was tested and confirmed. Following to the calculation of the pharmacokinetic variables of test and reference products in 24 volunteers, the genetic variants were explored, analyzed and statistically correlated with other clinical and pharmacological information, mainly the calculated primary pharmacokinetics and elimination-phase variables. The exploratory analysis spotlight was on the metabolizing enzymes variants (mainly the group of CYP450 family), especially those known to be related with Fluoxetine metabolism (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 & CYP3A5). More than 60 different genotypes were interesting after this selection, and the volunteers' pharmacokinetic phenotypes were associated and studied. After the statistical tests, subjects could be classified according to its metabolic profile for Fluoxetine and this classification was confirmed with the genetic information obtained, demonstrating the usefulness of the genetic profiling for bioequivalence studies when subjects' genetic idiosyncrasy could be relevant or wanted to be explored. Future perspectives on this work is to continue exploring the phenotype-genotype relationship with the information retrieved in this controlled trial, to be able to relate more variants and polymorphisms blindly with the pharmacokinetic phenotypes of the volunteers participating in this study. Based on this, a more relevant and refined statistical model is expected to be obtained integrating more genetic variables. With this, our aim of establishing the technical and scientific basis to make bioequivalence studies safer and more controlled for Mexican and abroad regulations, as well as to contribute with these experiences in controlled clinical trials to the pharmacological practice in the bedside, can be fulfilled.

Characterization of active TB disease establishment in HIV/ TB co-infected children in sub-Saharan Africa using integrated genomic analyses

Busisiwe Mlotshwa [1], Masego Tsimako-Johnstone [1], Sununguko W. Mpoloka [1], Moses Joloba [2], Adeodata Kekitiinwa [3,4], Chester W. Brown [5,6,7], Graeme Mardon [8,9], Neil Hanchard [8,10], for the Collaborative African Genomics Network

[1] University of Botswana, Department of Biological Sciences, Gaborone, Botswana
[2] Makerere University, College of Health Sciences, Department of Medical Microbiology, Kampala, Uganda
[3] Baylor College of Medicine Children's Foundation, Kampala, Uganda
[4] Baylor College of Medicine, Department of Pediatrics, Pediatric Retrovirology, Houston, TX, USA
[5] University of Tennessee Health Science Center, Department of Pediatrics, Genetics Division, Memphis, TN, USA
[6] Le Bonheur Children's Hospital, Memphis, TN, USA
[7] St. Jude Children's Research Hospital, Memphis, TN, USA
[8] Baylor College of Medicine, Department of Molecular and Human Genetics, Houston, TX, USA
[9] Baylor College of Medicine, Department of Pathology and Immunology, Houston, TX, USA
[10] Baylor College of Medicine, Department of Pediatrics, ARS/USDA/Children's Nutrition Research Center, Houston, TX, USA

Correspondence e-mail b.mlotshwa@hotmail.co.uk

Background and Objectives: Globally, sub-Saharan Africa has the highest rates of HIV and M. tuberculosis (TB) co-infection. Reported estimates suggest that approximately 10 - 60% of childhood TB cases occur in HIV infected children. However, the mechanisms promoting susceptibility of people with HIV to tuberculosis disease are not well understood, due to their complexity resulting from the multifactorial processes associated with the diseases. This study aims to identify functionally important genes and pathways that characterize active TB disease in HIV/ TB co-infected children in sub-Saharan Africa and relate these molecular targets to clinical outcomes.

Methods and Results: Following IRB approvals, we sequenced RNA from 24 matched, case-control pairs from HIV/TB co-infected pediatric cohorts in Uganda and Botswana using the Illumina HiSeq2000 Sequencing System. Determination of differentially expressed genes (DEG) was based on the consensus of three statistical tools: Cufflinks, edgeR and DESeq2. Transcripts were assembled using the Tuxedo suite and DEG identified using identical thresholds in all three tools: FDR 0.05 and log2fold change 1.0. For the edgeR and DESeq2 workflows, mapped reads for each sample were summarized into a gene-level count matrix (Rsubread v1.31.4) that was used as input for gene expression analysis. The matrix of read counts was filtered to retain only coding genes (n

= 21 430) before analysis in CIBERSORT to estimate proportions of different cell types. Correlation was performed between CIBERSORT results and FBC results for a subset of the data. Proportions were compared between cases and controls for 5 cell types identified to be of interest. Cell type proportions which differed significantly between cases and controls were determined to be Neutrophils, CD4+ naïve T cells and CD8+ T cells. These categories were flagged for input into an extended gene expression analysis model. Cufflinks identified 524 significantly up-regulated genes and 65 down-regulated genes. EdgeR and DESeq2 identified 456 and 714 significantly up-regulated genes, and 91 and 168 down-regulated genes respectively. Consensus between the three tools yielded a 1055 gene set including HP, MMP9 and IL1R2 genes, which are well-known to be implicated in TB disease. Top GO terms identified included myeloid leukocyte activation, inflammatory response and cytokine production.

Conclusions: The results of this training dataset reveal a transcriptional TB signature for our African, pediatric cohort. Further work is required to validate our findings and evaluate our TB signature against published gene signatures of active TB.

Exploring the Molecular Basis of Hereditary Spinocerebellar Degeneration in a Large Sudanese Family

Arwa Babai [1], Inaam Mohammed [2], Ahlam Hamed [3], Maha Elseed [2], Elhami Alnaeem [1], Isra Eltazi [1], Mohammad Mubarak [2], Esra Emad [2], Shaimaa Omer M.A. Taha [3], Ashraf Mohammed [4,5,6], Liena Elsayed [4]

[1] *Institute of Endemic Diseases, University of Khartoum, Khartoum, Sudan.*
[2] *Faculty of Medicine, University of Khartoum, Sudan.*
[3] *Department of Radiology, Dar Al Elaj specialized hospital, Khartoum, Sudan.*
[4] *Department of Biochemistry, Faculty of Medicine, University of Khartoum, Sudan.*
[5] *Institut du Cerveau et de la Moelle épinière, INSERM U1127, CNRS UMR7225, Sorbonne Universités, UPMC Universités Paris VI UMR_S1127, 75013 Paris, France.*
[6] *Ecole Pratique des Hautes Etudes, EPHE, PSL Research University, 75013 Paris, France*

Correspondence e-mail: arwababai@gmail.com

Background: Spinocerebellar neurodegenerative disorders (SCD) are known for their complex phenotypic and genetic heterogeneity forming a heterogeneous spectrum of disorders with hereditary spastic paraplegias (HSP) on one end and hereditary ataxias (HA) on the other. In clinical practice, limb spastic weakness and cerebellar ataxia are frequently found together and present the hallmark of SCD. The genetics of SCD has been a target for extensive researches in many parts of the world, yet little is known about the genetics of SCD in Sub-Saharan African population.
Methods: In this study, we recruited a large consanguineous Sudanese family with five affected siblings. Genomic DNA was extracted and screened for genetic variations using Whole exome sequencing. Analysis was done to identify the culprit variations using bioinformatics tools and in-silico prediction of variants pathogenicity.

Results: Clinical results showed a complex phenotype of progressive spastic-ataxia complicated with deafness. Microcephaly was detected in the two eldest patients. Analysis of whole exome sequencing data and variant prioritization suggested two homozygous missense variants in two candidate genes (MYO15A and SEMA5D) that were not reported to be linked to similar disease before. The first variant in MYO15A gene (NM_016239.3: c.1634C>T) was reported to cause autosomal recessive hearing loss but was not reported to similar neurological disease. The second variant (NM_006378.3:c.1588G>A) was in SEMA4D gene which involved in brain development but not reported to be associated with inherited neurological conditions before. Both variants were extremely rare and highly conserved. They were predicted to be highly pathogenic using bioinformatics tools.

Conclusion: The scarcity of genetic data in the highly consanguineous Sudanese population makes whole exome sequencing a powerful and cost effective strategy to identify both known and new pathogenic variations and genes. Sanger sequencing and further functional studies are recommended to prove the association of MYO15A gene and SEMA4D gene with the complex clinical phenotype of deafness, spasticity and ataxia.

Admixture mapping of TB susceptibility in two admixed African populations

Yolandi Swart, Marlo Moller, Caitlin Uren

Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, DST-NRF Centre of Excellence for Biomedical Tuberculosis Research, South African Medical Research Council Centre for Tuberculosis Research, Stellenbosch University, Cape Town, South Africa

Correspondence e-mail: yolandi01@sun.ac.za

Africa is at the epicenter of the dual epidemic of tuberculosis (TB) and HIV. Centuries of exposure to TB in Europe may have resulted in adaptive selection to TB resistance, whereas groups in sub-Saharan Africa were only relatively recently exposed to the virulent European Mycobacterium tuberculosis strains, so they appear to be more susceptible. Previous investigations performed in our lab indicated that excess African ancestry is associated with an increased risk of progression to active pulmonary TB whereas European ancestry exhibits a protective function.

Although the 1000 Genomes Project and the HapMap Project significantly improved our understanding of genetic variation globally, African populations are still severely underrepresented in biomedical and human genetic studies (Gurdasani et al., 2015). The uniquely admixed populations (those that receive ancestry contributions from more than one population) found in Africa makes it the ideal setting for admixture mapping studies, since the admixture between populations originating on different continents can be exploited to detect disease susceptibility loci at which risk alleles are distributed differentially (Hoggart et al., 2003).

This study focused on localizing and investigating ancestry-specific genetic regions associated with TB susceptibility in a two-way admixed Gambian population and a complex five-way admixed South African population. This may provide further evidence of the involvement of genetic ancestry in TB susceptibility and related traits.

A case study of X-linked MICPCH caused by a contiguous gene deletion at Xp11.4p11.3

Rizqa Sulaiman-Baradien, Careni Spencer, Karen Fieggen, Theresa Ruppelt

University of Cape Town, Division of Human Genetics

Correspondence e-mail: rizqa.sulaiman-baradien@uct.ac.za

Introduction: Microcephaly with pontine and cerebellar hypoplasia (MICPCH) is a well described X-linked syndrome caused by a fully penetrant null mutation or deletion of the CASK gene located at Xp11.4. In females, it is characterized by moderate to severe intellectual disability and progressive microcephaly with or without ophthalmological abnormalities and sensorineural hearing loss. Presentation in males range from early lethality to more typically postnatal microcephaly, profound ID and early intractable seizures. A milder phenotype consisting of X-linked ID with or without nystagmus is described in males and females with a hypomorphic mutation of CASK.

Clinical Report: The proband, a 4-year-old female presented with global developmental delay (most markedly in expressive speech), progressive microcephaly, dysmorphic features (arched drawn in eyebrows, broad nasal tip, long philtrum, thin vermillion border and large ears) and axial hypotonia. Her mother reported frequent aggressive outbursts and difficulty interacting with other children. A CT brain revealed ponto-cerebellar hypoplasia. Her ophthalmology and audiology evaluations were normal. Her parents are well and clinically unaffected, but she has a 16-year-old brother with learning difficulties, but no dysmorphic features or structural abnormalities and a normal systemic exam and another maternal half-brother with mild intellectual disability and schizophrenia.

Results: arr (hg19) Xp11.4p11.3 (41,134,163-44,221,231) x 1 Based on her clinical features a chromosomal microarray analysis using the Cytoscan Optima Array was requested. Microarray testing only became available through our National Health Laboratory Services (NHLS) in 2017. It revealed a 3.1MB interstitial deletion of the X chromosome involving p11.4 to p11.3. A smaller deletion in that area of 2.9MB has been reported with a similar phenotype. This area includes 5 OMIM morbid genes: CASK, DDX3X, MAOA, NYX and NDP. DDX3X and MAOA aberrations are associated with intellectual disability, and behavioral problems. NYX and NDP aberrations are associated with visual disturbances and retinal disease respectively.

Discussion: Patients with a CASK related phenotype have been reported to have either null-mutations or deletions of the gene. Several reports also indicate that a contiguous gene deletion, including the CASK gene, cause a similar phenotype. This probands' phenotype is consistent with those previously reported in the literature. The mild phenotype of her brothers is not in keeping and further investigation is warranted to see if this is etiologically related to her condition, but also to tailor their management and more accurately counsel on risks to their offspring.

The development of a precision medicine laboratory

Ravnit Grewal, Junaid Gamaldien, Alan Christoffels

South African National Bioinformatics Institute, University of the Western Cape, Cape Town, South Africa

Correspondence e-mail: ravnitgrewal@gmail.com

Background: The future for the diagnosis and management of patients in oncology, lies is precision medicine. The idea behind precision medicine is in molecularly profiling the tumor. DNA is extracted from the tumor cells directly or from circulating tumor cells or circulating DNA in blood, this is then molecularly profiled using Next generation sequencing and then based on these findings personalized treatment is given. This now allows the clinicians to plan on specific surgical and chemo-therapeutic decisions based on the molecular abnormalities found. The processes involved are firstly to collect the sample, followed by DNA/RNA extraction, applying tumor specific genes, sequencing, data generation through bio informatics analysis and finally generation of a report.

Methods: We aim to offer a cutting-edge research diagnostic laboratory for precision medicine in par with international trends. Setting up a Precision Diagnostics Laboratory using an international laboratory that has succeeded in such an endeavor as a bench mark Institution. Once this is achieved, we then need to involve the medical genetics team and create a “molecular diagnostics unit”. After this we can get involved in clinical trials comparing personalized treatment to current chemotherapy.
Anticipated results: We envisage that we will firstly set up a precision laboratory, which then offers diagnostic tests with the aim to enroll in clinical trials in personalized medicine.
One of our envisaged aims as other institutions have done is to create a tumor board for the treatment of tumors which will consist of pathologists, clinicians, molecular scientists and a bioinformatics scientist. And lastly, the team can work together towards offering a certificate in Molecular Pathology Conclusion: Currently, according to our knowledge, there is no diagnostic facility offering this service in South Africa (SA) or Africa. In order to assess clinical feasibility in our population we need to ensure that we establish and provide the most efficient and effective precision medicine diagnostic laboratory as without the precision in diagnostics whether for research or routine service the treatment cannot be monitored adequately. There is a clear need to create research facilities in our local institutions. Our aim is to create such a facility at SANBI, UWC. Furthermore, we need to educate our pathologists/clinicians /scientists by offering workshops/courses/and eventually offering fellowships/certificates in precision diagnostics.

Characterization of Single Nucleotide Polymorphisms Associated with Response to Antidepressant Drugs in Sudanese Populations

Suaad Balla khalafalla , Mohamed O Elsiddeig, Muntaser Eltyeb Ibrahim

Institute of Endemic Disease – University of Khartoum.

Correspondence e-mail: mibrahim@iend.org

Background: Antidepressant drugs [AD] prescribed for major depressive disorders are associated with therapeutic failures in approximately 40% of patients after initial dosing. Pharmacogenetic (PGx) variances play a significant role in these failures and therefore, using genetic data in decision-making for population-based dosing may both enhance efficacy and reduce adverse effects. Prior knowledge of allele distributions of the (PGx) biomarkers in different countries can help towards patient stratification for most populations during the drug prescribing process. However, Allele frequency distributions for gene polymorphisms associated with [AD] response in the Sudanese population and Africa in general remains largely not characterized.

Objective: To investigate single nucleotide Polymorphisms [SNPs] affecting several pharmacodynamic and pharmacokinetic variables associated with response to [AD] in Sudanese and to compare the data with the global geographical data reported in gnomAD genome database from different ethnic populations.

Design: Out of 764 SNPs in 7 candidate genes affecting response to [AD] in 242 healthy Sudanese individuals genotype data, a total of 46 SNPs chosen according to deleteriousness and clinical annotation reported in PharmGKB database. Minor allele frequency (MAF) of clinically actionable SNPs compared with gnomaAD genome population frequencies using Chi-square test.

Results: Among deleterious SNPs, nine are unreported in gnomAD database, two SNPs were common, MAF>5%, SLC6A4 rs138004662 (8%) and ABCB1 rs2032582 (15%). Of the clinically actionable variants, 3 SNPs (ABCB1 rs1045642, rs2032582, and BDNF rs7103411) show significant differences (p-value 0.05) between Sudanese and all other populations with the lowest frequency in Sudanese. ABCB1 rs1272006 was monomorphic (that is, no variation) across all population tested. 2 SNPs (rs7103411 and rs7124442) associated with better response to citalopram is less common in Sudanese compared with other populations.

Conclusion: Since therapeutic decision relies mainly on the US FDA or European Medical Agency guidelines for dosing instructions, understanding of the inter-ethnic differences in the pharmacogenetic is critical to guide more effective global drug prescriptions. Such data will be useful for future clinical and for drug dosage recommendations in the Sudanese population.

The Sudanese Genetic Variation Portal Enabling personalized medicine in understudied populations

Mohammed OE Abdallah

Institute of endemic diseases, University of Khartoum

Correspondence e-mail: melsiddieg@gmail.com

I am Mohammed Omar Elsiddieg Abdallah. I have graduated from Faculty of Medicine, Khartoum university in 2005, obtained my master's degree in Molecular Medicine in 2012 from the Institute of endemic diseases, Khartoum university, with an overall excellent grade, and since then, and because of my excellent skills in Linux and computational biology software, I have been recruited to work as a bioinformatician and genomics researcher at the same institute, where I Now I serve as the head of the bioinformatics team of the molecular biology department. I am currently preparing to defend my my PhD in Molecular/Computational Biology entitled "Integrative Computational strategies for variant prioritization in the context of rare genetic disorders Computational challenges and opportunities". I am a member of the OpenCB (Open-source software for Computational Biology) project. I finished a three-month period of computational biology research training at Cambridge university in 2016, where I worked with professor Ignacio Medina head of the Computational Biology Lab of the HPC center. There I contributed to multiple computational biology projects under the umbrella of the OpenCB initiative including R and Python clients for CellBase https://github.com/opencb/cellbase and Opencga https://github.com/opencb/opencga. I am the maintainer of cellbaseR (available from Bioconductor http://bioconductor.org/packages/release/bioc/html/cellbaseR.html), which offers a fast and efficient way of fetching rich genomic annotations in R based on the high performance Cellbase Database and web services, and also contributed to OpencgaR, an R interface to Opencga, the genomics analysis framework used by Genomics England (The 100K Genomes Project). I have also developed R clients for the PanelApp web services https://panelapp.genomicsengland.co.uk/, providing well-curated and up-to-date gene panels for rare genetic disorders. My latest project is The Sudanese Genetic Variation Portal, a database - and a user-friendly web interface - comprising more than 3 million SNPs from about 300 Sudanese individuals based on the OpenCGA platform and Shiny web interface for real-time analysis of genetic and pharmacogenomics data of the Sudanese population. My work as a head of the bioinformatics team include running NGS analysis pipelines for (whole exome sequencing) according to GATK best practices, utilizing state of the art GKNO or WDL pipelines. I also run various Bioconductor or GALAXY workflows for genomic and epigenomic analyses (methylome analysis). My current focus is rare genetic disorders, although I also have long experience with cancer genomics data (colorectal and breast cancer).

Eleganpro: A Novel Bioinformatics Tool for C. elegans Transcriptome

Olaitan Awe, Angela Makolo and Segun Fatumo

[1] *University of Ibadan, Nigeria.*
[2] *Wellcome Trust Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, CB10 1SA, UK*

Correspondence e-mail: laitanawe@gmail.com

In this research, we developed a computational model to analyse the gene expression data of humans and we used Caenorhabditis elegans (C. elegans) as a case study because of its simplicity and significance in studying the genetic and molecular mechanisms of human development and disease. Leveraging and processing the data in C. elegans RiboNucleic Acid (RNA) molecules provides a path to understanding this organism of interest and we now have a huge amount of RNA sequence data available from high throughput experiments. Traditional transcriptomic data analysis methods have not been able to obtain the desired level of accuracy for the computational discrimination of protein-coding or non-coding RNA Transcripts. We first trained our computational model with labeled RNA transcripts by using machine learning techniques and we evaluated how successful we have been at scoring each transcript. We used a computational technique, resulting in a perfect confidence level in the predictions and obtained accurate results when predicting previously unseen RNA transcript class. For C. elegans, our computational predictions were compared with results from validated experimental data and the model was right in 100% of the instances. For humans, our tool identified protein-coding and non-coding regions in the human transcriptome with 97% accuracy, 97% F1-score, 97% sensitivity and 97% specificity. We have therefore designed an efficient bioinformatics tool that achieves accurate results in class prediction for C. elegans transcriptomes. In determining the computational and molecular make-up of a C. elegans protein, this work is a step forward. We hope that this work will help investigators in the analysis of transcriptomes and in the annotation of genomes.

Interleukin-6 (−174G>C and −572G>C) gene promoter polymorphisms, C-reactive protein and glycated haemoglobin as predictor of risk of Type-II Diabetes Mellitus in obese and non-obese subject

Oyekale Adesole.O [1], Ayelagbe Olubunmi.G [1], Ojurongbe Olusola [2], Akeem Akindele A [3], Samuel Adedokun. A [3]

[1] Department of Chemical Pathology, [2] Department of Medical microbiology and parasitology, [3] Department of Community Medicine, College of Health Sciences, Ladoke Akintola University of Technology, Osogbo, Osun State, Nigeria

Correspondence e-mail: aooyekale@pgschool.lautech.edu.ng

Background: Type 2 diabetes occur through the development of obesity related insulin resistance; more than forty percent of diabetes burden is attributable to obesity. Environmental risk factors attributed to the global increase in obesity include genetic predisposition, in Nigeria the prevalence of obesity and diabetes ranges from 3% and 22.2%, respectively. Obesity increases the risk of developing not only type 2 diabetes but also cardiovascular disease, stroke, osteoarthritis and some forms of cancers. Type 2 diabetes is associated with low-grade chronic inflammation resulting in part from the activation of the innate immune system. This activation leads to the release of pro-inflammatory cytokines such as interleukin-6, Nigeria is expected to be among worst hit by the epidemic with an anticipated 170% increase by 2020 in its prevalence. The aim of the propose study is to assess the association between Interleukin-6 (−174G>C and −572G>C) gene promoter polymorphisms, Interleukin-6 protein expression, C-Reactive Protein and Glycated Haemoglobin as Predictor of Risk of Type II Diabetes Mellitus in Obese and Non Obese Subject with the view to determine differences in the distribution of genetic and environmental risk factors that may be associated with the disorders.

Methodology: This structural proposed study is expected to span 2 years (2018-2020), cross-sectional sampling survey will be adopted in selection of 300 subjects aged between 20 and 60 years that fulfill inclusion criteria. The study has been approved by the Ethical Committee of state specialist Hospital Asubiaro Osun state, Nigeria. Five mls of fasting blood samples will be collected into a EDTA bottle to obtain sample for IL-6 geneno typing and glycated haemoglobin, and plain bottle, for the determination of lipid profile and inflammatory markers of compliment reactive protein, informed consent will be obtain from all subjects.

Methodology: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) assays will be used to determine IL-6 gene polymorphisms, Amplification will be performed on an automated Thermal Cycler (Techne Flexigene, Cambridge, UK). Statistical analysis will be done using IBM Statistical Package for the Science Solution (SPSS) version 21.0 software package and graph pad prism 5.0 to determine the means, standard deviation, correlations and one-way analysis of variance (ANOVA) will be employ to determine variance among study groups.
Expected contribution: Generate data on IL-6 genetic polymorphism to predict diabetes mellitus risk in obese and non obese Nigerian subjects.

A New Tool for Prioritizing Candidate Genes

Ayyoub Salmi, Romain Philippe, Veronique Blanquet, Ahmed Moussa

Systems and Data Engineering Team, University Abdelmalek Essaadi, Tangier, Morocco

Correspondence e-mail: ayyoub01@gmail.com

The identification of genes implicated in a disease or in a complex trait from high-throughput experimental studies remains a challenge. Gene prioritization methods play an important role in identifying the most prominent genes in a study. They typically produce their output either by filtering genes using a set of criteria, or by scoring and ranking genes from most relevant to least relevant. In this paper we present a new tool for prioritizing candidate genes by applying text mining to gene expression, gene function, homology, knock-out studies and a survey of literature. We tested our tool using genes near a Quantitative Trait Locus (QTL) related to bone weight in cattle, and differentially expressed genes related to Parkinson Disease.

Profound biotinidase deficiency caused by (D444H) resulting in recurrent early childhood death in a Sudanese Family

Reem Salah, Rayan Ali, Montaser E Ibrahim, Imad Fadl-Almula

Institute of endemic diseases, University of Khartoum

Correspondence e-mail: Dean@assafa.edu.sd

Introduction: Biotinidase deficiency (BTD) is an autosomal recessive disease in which biotin recycling from biocytin or biotinylated peptides is impaired. The disorder is caused by absent or markedly deficient activity of biotinidase.

Material and Methods: Two healthy parents presented with history of two daughters who had neurological cutaneous and respiratory manifestations who died at early childhood. They also had two healthy living daughters (8 and 4 years-old). Whole exome sequencing was done for the mother and then specific BTD gene sequencing was done for the father which were analyzed through bioinformatic tools.

Results: whole exome sequencing analysis of the mother genomic DNA showed heterozygous missense mutation in BTD gene with rs 13078881 was found. Identical mutation was latter identified also in the father DNA.

Discussion: This present mutation behaved in unusual way since it caused profound biotinidase deficency in homozygous state. According to our knowledge this the first ever case with profound biotinidase deficency in homozygous state to be reported.

Conclusion: In the absence of neonatal screening programmes whole genome sequencing remain the only effective way of diagnosis metabolic Mendelian disorders in underdeveloped countries.

Insecticide Resistance and Intra-species Indoor and Outdoor-resting Behavior of Malaria Vectors In Northern Ghana

Majidah Hamid-Adiamoh [1,2], Alfred Ngwa [2], Davis Nwakanma [2], Yaw Afrane [3]

[1] West African Centre for Cell Biology of Infectious Pathogens (WACCBIP), University of Ghana, Legon, Ghana
[2] Medical Research Laboratories, Malaria Research Programme, The Gambia
[3] Department of Medical Microbiology, College of Health Sciences, University of Ghana, Ghana

Correspondence e-mail: mojeedamid@gmail.com

Introduction: Selection pressure from continued exposure to insecticides used for malaria control including indoor residual spraying (IRS) and long-lasting insecticide treated nets (LLINs) seem to be driving development of insecticide resistance and changes in resting behaviour in malaria vectors. These have been implicated to contribute significantly to the increasing residual malaria transmission in several malaria endemic settings. The aim of this study was to examine the influence of insecticide resistance in intra-species indoor and outdoor-resting behaviour in mosquito populations in Northern Ghana to understand their contribution to residual malaria transmission.

Methods: Live adult mosquitoes were collected indoors and outdoors from two communities in Ghana. A subset of fed mosquitoes was allowed to lay eggs in the insectary and the larvae were reared to adults. WHO insecticide susceptibility tests were carried out to determine phenotypic resistance. All mosquitoes were examined for sibling species identification, genotypic resistance, host blood meal and Plasmodium sporozoite detection using targeted molecular assays.

Results: The species composition in the study sites include Anopheles arabiensis, An. coluzzii and An. gambiae s.s. Phenotypic resistance to deltamethrin and DDT was higher in the indoor An. gambiae population with 24-hour post-exposure mortality of 63% compared to the outdoor mosquito population with mortality of 99%. Mosquito populations were suspected to be resistant to bendiocarb phenotypically to both indoor and outdoor populations with mortality of 90% and 95% respectively. All mosquito populations were susceptible to malathion (98-100% mortality). Variable allele frequencies for resistance markers including Vgsc-1014F, ACE 1, N1575Y and GSTe2 mutations were found among species, but the Vgsc-1014F mutation was the most common and only in An. coluzzii. Significant association was observed between only knock down resistance (kdr) mutations and resting locations (P=0.03). No association was found in other resistance markers and resting locations.

Data collection is ongoing for blood meal and sporozoite detection. The study will help to understand the contribution of insecticide resistance in residual malaria transmission

Web based genomic medicine training for nurses in rural Cameroon: Report, Experience and Impact.

Kengne Kamga Karen [1,2], Becke Ikala Florence [1], Akong Rose [1], Meya Melanie [1]

[1] District hospital limbe
[2] University of Cape Town

Correspondence e-mail: kkarenke@yahoo.co.uk

Introduction: Genomics is an interdisciplinary field of science focusing on the structure, function, evolution, mapping, and editing of an organism's complete set of DNA including all of its genes. Understanding foundational concepts of genetics and genomics is essential to contemporary nursing practice. The first ever web-based training on genomic medicine for nurses in Africa organised in 2017, was designed to empower African nurses with knowledge on key genetic concepts. Assessing a course is vital to support competency-based continuous education. Hence the following paper aims at presenting a report and give the experience of Cameroonian nurses during this short course.

Methodology: This was across sectional descriptive study which targeted the health personnel in the limbe health area. After obtaining an administrative authorisation, data was collected using a form containing demographic like sex, age profession; their knowledge of the existence of the genomic course for nurses, how they got this information, willingness to take part in future courses, experience before, during and after the course; strength, weaknesses and impact of the course on the day to day activities. Epiinfo 7 was used for data analysis.

Results / Discussion: Seventy-eight (78) health personnel were included with a female predominance (76.6%). Nearly all of them (92.3%) were aware of the short course and they had this information through the site facilitator (61.5%), colleagues (38.5%), internet (21.1%), and flyers (7,7%). The main reason for not participating was the overlapping of the course with their time table (66.7%) and the irregularity of internet. Non-the less, all of them were willing to be part of future genomic courses. Thirteen out of 18 health personnel (72.2%) successfully completed the course. The first week as either difficult or boring for some and exiting for others since it was their first time of taking an online course. Lectures became interesting in due course and by the end of the course 71.4% were satisfied of the course. The strengths were; the site facilitator (83.3%), support from colleagues (66.7%), the WhatsApp group chat (16.7%). The main take home messages were “how to draw a pedigree” and “principles of counselling”. These key topics help participants to improve in their way of receiving patient in their different facilities.

Conclusion: This introductory course has stimulated the interest of rural health personnel to genomic medicine through the experience of the participants and improved patient reception and standard of care in tertiary health facilities of limbe health area.

Quantitative assessment of double-positive JAK2 and CalR mutations in Myeloproliferative Neoplasms (MNPs) at Tygerberg Academic Hospital (TAH)

Megan Cousins, Chantal De Long, Shafieka Isaacs, Zivanai Cuthbert Chapanduka, Carmen Swanepoel, Faghri February

Division of Haematology, Department of Pathology at the University of Stellenbosch

Correspondence e-mail: 16495489@sun.ac.za

Myeloproliferative neoplasms (MPNs) encompass a group of varying clonal stem cell disorders responsible for the excessive proliferation of one or more myeloid cell lineage. The most common causative molecular events in BCR-ABL1 negative MPNs are the result of mutations in genes encoding for the Myeloproliferative leukaemia protein (MPL- MPL exon 10) and Janus associated kinase 2 (JAK2 V617F, Exon 12). These mutations or mutational hotspots currently form part of the diagnostic-screening criteria for MPNs and are thought to be mutually exclusive due to their diverse disease profiles. In the past 5 years, the development and application of next-generation sequencing (NGS) platforms have led to the identification of new novel frameshift mutations within exon 9 of the calreticulin (CALR) gene in MPN patients negative for both JAK2 and MPL mutations.

To date studies of CALR mutations (CALRmut) are predominantly performed on JAK2 mutation-negative, MPN patients. Little information is available regarding the coexistence of the JAK2 V617F and CALR exon 9 mutations worldwide, particularly within developing countries such as South Africa. The most recent studies published on CALRmut frequencies report lower prevalences than those reported in earlier studies, suggesting that the mutational prevalence of CALRmut varies in accordance with ethnicity and geographical ancestry. Studies have indicated that CALRmut -positive patients with Type 1, 52-bp deletion (p. L367fs*46), and Type 2, 5-bp TTGTC insertion (p. K385fs*47), mutations present with dissimilar prognoses. In comparison, patients positive for CALR type 1 mutations present with more favorable prognoses than those positive for JAK2 mutations, however the same cannot be said for patients positive for CALR type 2 mutations, calling attention to the importance of driver mutation identification for improved treatment plans and prognoses.
The aim of this study is to evaluate the prevalence of JAK2mut and CALRmut double-positive, MPN patients within Tygerberg Academic Hospital (TAH) using conventional Polymerase Chain Reaction (PCR), Sanger sequencing and Quantitative real-time PCR (qPCR). Finally, data comparison by means of High-Resolution Melting (HRM) profiles aims to assist in the development of MPN genetic profiles for future diagnostic implementation.

Rural youths' understanding of gene x environmental contributors to heritable health conditions: The case of podoconiosis in Ethiopia

Kibur Engdawork1 [1], Colleen M. McBride [2], Desta Ayode [1], Caitlin G. AllenID [2], Gail Davey [3], Getnet Tadele [1]

[1] *Department of Sociology, College of Social Sciences, Addis Ababa University, Addis Ababa, Ethiopia,*
[2] *Rollins School of Public Health, Emory University, Atlanta, GA, United States of America,*
[3] *Brighton and Sussex Medical School, University of Sussex, Falmer, Brighton, United Kingdom*

Correspondence e-mail kibursosa@yahoo.com

Advances in genomics are increasing scientific understanding that most health conditions worldwide are caused by the joint influence of genetic and environmental (GxE) factors. However, the mechanisms underlying GxE interactions are complex and not well understood by the public. Accordingly, misunderstandings that health conditions with genetic underpinnings cannot be prevented have been well documented in the developing world. Global leaders have called for stepping up efforts to increase genomic literacy in low and middle-income countries. Among the challenges to achieving this imperative is that LMICs have limited health service infrastructure, low levels of general literacy and a majority of the populace lives in isolated rural settings. Podoconiosis is among the disease caused by GxE interactions. Globally, 4 million people are affected by podoconiosis. Ethiopia bears the most burden of the disease with 1.6 million patients and 11 million at risky population. The disease is entirely preventable if genetically susceptible individuals practice footwear and keep foot hygiene regularly. However, studies have shown that accurate understanding of podoconiosis and adoption of preventive actions among rural residents are low. Against this, we assessed the feasibility of engaging rural youth to disseminate accurate information about gene by environmental (GxE) influences on podoconiosis. A cross sectional survey was conducted with 377 youth randomly selected from 2 districts of Southern Ethiopia. Measures included GxE knowledge (4 true/false statements), preventive action knowledge (endorse wearing shoes and foot hygiene), causal misconceptions (11 items related to contagion) and confidence to explain GxE (9 disagree/agree statements). Over half (59%) accurately endorsed joint contributions of gene and environment to podoconiosis and preventive mechanisms (e.g., wearing protective shoes and keeping foot hygiene). In parallel, the youth harbor misconceptions such as contagion and heredity as sole contributors to the disease. Multivariable logistic regression showed that youth with accurate understanding about GxE contributors reported having: some education, friends or kin who were affected by the condition, and prior interactions with community health workers. Surprisingly, higher accurate GxE knowledge was positively associated with endorsing contagion as a causal factor. Accuracy of GxE and preventive action knowledge were positively associated with youth's confidence to explain podoconiosis-

related information. Youth have the potential to be competent disseminators of GxE information about podoconiosis. Interventions to foster confidence among youth in social relationships with affected individuals may be most promising. Efforts to challenge youth's co-existing inaccurate beliefs about contagion could strengthen the link of GxE explanations to preventive actions.

Population parameters, genetic differentiation and socio-economics of Sardinella aurita (Valenciennes 1847) and Pseudotolithus senegalensis (Valenciennes 1833) in South coast, Liberia

Nathaniel D. Leesolee, Dr. Rosaline Macharia, Dr. George Obiero, Dr. Dorcus Sigana

Correspondence e-mail: nathanielleesolee@yahoo.com

I am Nathaniel D. Leesolee, a graduate of the University of Nairobi in MSc. Bioinformatics on September 14, 2018. My research title was "POPULATION PARAMETERS, GENETIC DIFFERENTIATION AND SOCIO-ECONOMICS OF SARDINELLA AURITA (VALENCIENNES 1847) AND PSEUDOTOLITHUS SENEGALENSIS (VALENCIENNES 1833) IN SOUTH COAST, LIBERIA". Regarding my result obtained from objective two of my thesis which had to deal with the genetic differentiation of the two species above, the result showed that Inter-species variability was revealed between Sardinella aurita and Pseudotolithus senegalensis through phylogenetic analysis of the nuclear and mitochondrial DNA markers and their final concatenated alignments included four markers. Comparison was done within 12 taxa including 10 bony fish and two outgroup species.

The combined markers 16s, COI, Cytb and Rag-1 dataset did not support the hypothesis regarding S. aurita and P. senegalensis close phylogenetic relationship. Instead the analysis generated a well-supported monophyly of S. aurita and H. jaguana in trees using 16s rRNA, COI and Rag-1 genes. Despite the lack of a clear morphological apomorphy between S. aurita and H. jaguana, instinctive pre-cladistics approaches initially recognized that S. aurita and H. jaguana are of natural group. None of the phylogenetic tree supported S. aurita and P. senegalensis as sister species.

Currently I serve as Senior Research officer at the National fisheries and Aquaculture Authority, which I draft all major research proposals for the authority and analyze the results obtain from the research. Which help management to make robust decision for compliance purposes.

Associations between genetic variants influencing the IDO pathway and CD4+ T-cell recovery after ART

Sibongiseni Ntuli, Debbie de Assis Rosa, Melinda Suchard

University of the Witwaters, National Institute for Communicable Disease

Correspondence e-mail: 687378@students.wits.ac.za

There are approximately 7,06 million South Africans currently living with HIV. Individuals on Antiretroviral Therapy (ART) can expect to achieve viral suppression and the reconstitution of CD4+ T-cell count. Approximately 21% of patients on ART in South Africa will fail to recover their CD4+ T-cell count despite achieving viral suppression, this is also known as having a discordant immune response (DIR). HIV patients with high levels of immune activation at the initiation of ART are at a higher risk of having a DIR. HIV is characterised by chronic immune activation which is the global activation of innate and adaptive immune system components. One marker of immune activation is high levels of indoleamine 2,3-dioxygenase (IDO) activity. IDO is a key immunoregulatory enzyme that converts tryptophan to kynurenine. IDO expression is induced by pro-inflammatory cytokines and by liposaccharides from bacterial translocation during HIV infection mainly in activated dendritic cells or macrophages. The association between genetic variants, CD4+ count and IDO activity will be tested. IDO is elevated in HIV-positive patients compared to uninfected individuals, highest in those progressing to AIDS. Increased IDO activity are represented as increased plasma K/T levels and is a biomarker for poor CD4+ cell recovery and therefore morbidity and mortality in HIV-positive patients on ART. Theoretically, genetic variations in the IDO pathway and/or genes influencing IDO activity may be biomarkers for poor CD4+ T-cell recovery in HIV-positive patients on ART. The main objective is to identify and genotype SNPs that may potentially affect indoleamine 2,3-dioxygenase activity and compare this to longitudinal CD4+ T-cell data and measured plasma kynurenine/tryptophan levels in the WRHI 001 cohort. The aim of the study is to characterize SNPs in candidate genes related to the IDO/TDO pathway and test whether these SNPs influence plasma K/T levels and CD4+ T-cell counts in a Southern African cohort (WRHI 001 Cohort) on ART. Three genes indoleamine 2,3-dioxygenase 1 & 2 and tryptophan 2,3-dioxygenase will be sequenced for novel variants. This will be included with SNPs found using literature these will be genotyped using Sequenom MassArray. Two main statistical tools will be used to test the association between candidate SNPs, plasma K/T ratio and CD4+ T-cell recovery. The first, PLINK v1.9 is a tool which will be used to analyze genotype and phenotype data in the association study. Secondly, GraphPad Prism v7 can be used to analyze data and graph assembly.

Genetics Study of Hearing Loss in Mali: Preliminary Data

Abdoulaye Yalcouyé [1], Lassana Cissé [1], Seybou H. Diallo [2], Thomas Coulibaly [1], Salimata Diallo [2], Cheick O Guinto [1], Kenneth Fischbeck [3], Mohamed Keita [4], Ambroise Wonkam [5], Guida Landouré [1,3]

[1] Service de Neurologie, CHU du Point "G", Bamako, Mali, [2] Service de Neurologie, CHU Gabriel Touré, Bamako, Mali, [3] Neurogenetics Branch, NINDS, NIH, Bethesda, MD, [4] Service d'ORL, CHU Gabriel Touré, Bamako, Mali, [5] Faculty of Health Sciences, University of Cape Town, South Africa

Correspondence e-mail: abdallahyal@yahoo.fr

Introduction: Hearing loss is the most common sensory deficit, representing about 1 in 1000 births. About 50% of congenital hearing loss has a genetic origin, and 70% of it are non-syndromic (NSHI). However, little is known in the genetics of hearing loss in the African population, and Mali in particular.

Objectives: characterize families with hearing loss and identify their underlying genetic defects.

Methodology: Families with at least two affected were enrolled. All patients were examined by a multidisciplinary team including ENT specialists and neurologists. Laboratory examination including audiometry, tympanometry, auditory evokes potentials were performed. The study was approved by the Ethics Committee of the Faculty of Medicine and Dentistry of Bamako, and informed consent was obtained from all adults and the parents of minors. Candidate gene testing was done, and whole exome sequencing in negative families will be done.

Preliminary results: Six families totaling 12 patients were enrolled. One of them had syndromic hearing loss and four had non-syndromic hearing loss. While three families had an autosomal dominant pattern of their disease, three were autosomal recessive. ENT exploration confirmed congenital profound hearing loss in two patients in the same family. Other evaluation and the genetic testing are ongoing for the remaining patients.

Next steps: For non-syndromic cases, genetic testing of candidate genes (GJB2 and GJB6), representing more than 705 of all NSHI is ongoing. In addition, whole exome sequencing using two patients and two unaffected siblings will be done in negative cases.

A case report of a novel homozygous splice site mutation in PLA2G6 gene causing Infantile Neuroaxonal dystrophy in a Sudanese family

Liena E. O. Elsayed [1], Inaam N. Mohammed [1], Ahlam A. A. Hamed [1], Maha A. Elseed [1], Mustafa A.M. Salih [2], Ashraf Yahia [1,7], Rayan A. Siddig [1], Mutaz Amin [1], Mahmoud Koko [3,8], Mustafa I. Elbashir [1], Muntaser E. Ibrahim [3], Alexis Brice [4,6], Ammar E. Ahmed [1], Giovanni Stevanin [4,5,6]

Correspondence e-mail: melka.el-amin@hotmail.com

Infantile neuroaxonal dystrophy (INAD) is a rare hereditary neurological disorder caused by mutations in PLA2G6. The disease commonly affects children below three years of age and presents with a delay in motor skills, optic atrophy and progressive spastic tetraparesis. Studies of INAD in Africa are extremely rare, and genetic studies from Sub Saharan Africa are almost non-existent. This study reported a novel homozygous splice site mutation (NM_003560.2 c.1427+2T>C) in PLA2G6 gene causing Infantile Neuroaxonal dystrophy in two siblings from Sudan.

Case presentation: Two Sudanese siblings from White Nile area in central Sudan presented clinically with INAD. Brain MRI showed hyperintense signals in periventricular areas and basal ganglia and mild cerebellar atrophy. Whole exome sequencing with confirmatory Sanger sequencing were performed for the two patients and healthy family members.

Conclusion: A novel variant (NM_003560.2 c.1427+2T>C) acting on a splice donor site and predicted to lead to skipping of exon 10 was found in PLA2G6. This is the first study to report mutations in PLA2G6 gene in patients from Sudan.

Ligation Detection Reaction: The new age for genetic disease research

Priscilla Abena Akyaw [2,6], Ernestine Kubi [2,6], Alexander Nyarko [2], Gordon Awandare [6], Anita Ghansah [2,6], Charlotte Osafo [1], Bamidele Tayo [4], Akinlolu Ojo [5,6], Babatunde Salako [5], Dwomoa Adu [1], David Burke [3]; the H3Africa Kidney Disease Research Network

[1] *University of Ghana Medical School.*
[2] *Noguchi Memorial institute for Medical Research (NMIMR), University of Ghana, Legon*
[3] *University of Michigan, Department of Human Genetics, Ann-Arbor – U.S.A*
[4] *Loyola University , USA*
[5] *University of Ibadan, Nigeria*
[6] *West African Centre for Cell Biology of Infectious Pathogens (WACCBIP), University of Ghana, Legon*
[7] *The University of Arizona, Department of Medicine*

Correspondence e-mail: Pakyaw@noguchi.ug.edu.gh

PCR has facilitated several nucleic acid-based detection systems for genetic disorders including bacterial and viral pathogens. Traditional gene-targeting approaches in many experimental procedures employ the use of either an exogenous DNA or allele-specific sequence that allows for genotyping strategies based on the binary readout of PCR product amplification and size selection. Even though there are several post PCR techniques currently used for genotyping of target SNPs, they are either expensive, lack sequence specificity, require costly capital equipment and also necessitate the use of DNA with high integrity. Moreover, several of these techniques fail to distinguish bi allelic combinations for all modes of inheritance; wild-type, heterozygous, compound heterozygous and homozygous mutations. In this study, we show that Ligation Detection Reaction (LDR) can be used to generate genotype data that are sequence-specific and uniquely detected by product size and/or fluorescent tags even when working with DNA of low concentrations. We used this method to genotype variants of the APOL1 and MYH9 genes that are known to be associated with Chronic Kidney Disease patients of varying etiologies using samples collected as part of the H3Africa Kidney Disease Research project.

Assessing concordance among guidelines for genome-guided therapeutic interventions from different research consortia and regulatory bodies

Stefania Koutsilieri [1], Foteini Tzioufa [1], George P. Patrinos [1,2]

[1] University of Patras School of Health Sciences, Department of Pharmacy, Patras, Greece; [2] United Arab Emirates University, College of Medicine and Health Sciences, Department of Pathology, Al-Ain, UAE, # SK is a recipient of an Onassis Foundation scholarship.

Correspondence e-mail stef_k23@hotmail.com

Aim of the study: Pharmacogenomics aims to rationalize drug use by minimizing drug toxicity and/or by increasing drug efficacy. To date, over 150 drugs have been approved by the US Food and Drug Administration and the European Medicines Agency bearing pharmacogenomics information in their labels, accompanied by drug dosing guidelines, which brings precision medicine closer to clinical fruition. However, there are often discrepancies among guidelines from different sources, which often create confusion as to which guideline to follow for genome-guided treatment rationalization.

Methods: In order to reveal such discrepancies, we have extracted and curated information from the published literature and online resources, such as the Clinical Pharmacogenomics Implementation Consortium (CPIC) and the Pharmacogenomics Knowledgebase (PharmGKB). Herein, we selected only those gene-drug pairs having strong evidence for their clinical utility based on the classification of each research network (level A-D for CPIC and 1A-4 for PharmGKB). It is noteworthy that PharmGKB is also in line with the existing information documented in the major regulatory bodies. As such, our repository offers the possibility of easy as well as deep comparison of the concordance between the Pharmacogenomics Working Parties of the US Food and Drug Administration and the European Medicines Agency.

Results: Our literature mining effort resulted in a total of 370 records, involving correlations between 226 drugs and 95 genes, implicated in drug treatment modalities. From these recommendations, the vast majority relates to drug toxicity or lack of efficacy, while a third categorisation corresponds to both aforementioned cases. A small percentage of the gene-drug pairs documented in our study are for information only. Similarities and, most importantly, discrepancies between the regulatory bodies in question were highlighted in an effort to spot the mains causes of these diversities.

Conclusion: Triangulating among drugs, genes and pharmacogenomic biomarkers represents our effort not only to develop a comprehensive and dynamically curated online database catalyzing the application of clinical pharmacogenomics, allowing assessing in real-time the implication of genomic biomarkers in drug response, leading to treatment individualization but also to harmonize guidelines from major regulatory bodies and research consortia.