Rare Disease Research and the Malta BioBank

University of Malta

Vella J[1,2], Borg J[3], Grech L[2], Galdies R[4], Scerri J[4], Cassar W[4], Scerri CA[1,2,4], Grech G[5], Soler D[6], Said E[4,7], Borg I[4,5], Vella NR[8], Camilleri Podesta MT[7], Ellul B[5], Felice T[9], Grima D[4], Zammit E[1,2], Said Conti V[10,11], Pace NP[7], Felice AE[1,2,4]

[1] The Malta BioBank, Centre of Molecular Medicine & BioBanking, University of Malta
[2] Department of Physiology & Biochemistry, Faculty of Medicine & Surgery, University of Malta
[3] Department of Applied Biomedical Science, Faculty of Health Sciences, University of Malta
[4] Department of Pathology, Mater Dei Hospital, Malta
[5] Department of Pathology, Faculty of Medicine & Surgery, University of Malta
[6] Department of Paediatrics, Mater Dei Hospital, Malta
[7] Department of Anatomy, Faculty of Medicine & Surgery, University of Malta
[8] Department of Neuroscience, Mater Dei Hospital, Malta
[9] Department of Cardiology, Mater Dei Hospital, Malta
[10] Department of Child and Adolescent Health, Mater Dei Hospital, Malta
[11] Department of Paediatrics, Faculty of Medicine & Surgery, University of Malta

The Malta BioBank

The Malta BioBank forms part of the new inter-faculty Centre of Molecular Medicine and BioBanking at the University of Malta and is the national node of the Bio-Banking and Bio-Molecular Resources Research Infrastructure (BBMRI.mt).

The clinical catalogue holds a number of rare disease collections including haemoglobinopathies, neuromuscular and neurodegenerative diseases, renal disorders and various cancers.

The Department of Physiology & Biochemistry and the Department of Pathology within the Faculty of Medicine & Surgery at the University of Malta caries out various lines of research amongst which are KLF mutation analysis, familial breast cancer, mitochondrial disorders, sudden cardiac death and rare kidney disorders.

Figure 1: -80C freezers and cryoboxes in the Malta BioBank

Familial Breast Cancer

High penetrance genes associated with an increased risk to cancer development are exemplified by the BRCA1 or 2 mutations in breast cancer. In western Countries, familial cases account for 10% of breast cancer. BRCA1 or 2 mutant genes, are associated with a higher incidence of the disease in close relatives, increasing significantly the risk within a family. Inherited mutations in p53 (Li-Fraumeni Syndrome) and Phosphate and Tensin homolog (PTEN) (Cowden Syndrome) have a high incidence of breast cancer development, but the syndromes are very rare.

121 samples were collected from the Malta BioBank between 2012-2014 of which 72 were cancer patients. 29% of cases had the BRCA1 or 2 mutations.

Further samples shall be collected and banked and exome sequencing will help to identify other variants.

Mitochondrial Disorders

A total of 17 patients identified with mitochondrial disorders including mitochondrial myopathies, Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-Like Episodes (MELAS) and Kaerns Sayre Syndrome were identified from a patient register at Mater Dei Hospital. Genetic analysis will be carried out on patients and their families to increase the scientific understanding of these rare syndromes.

Sudden Cardiac Death

Another project focuses on research into Sudden Cardiac Death (SCD) in subjects under 40 years old. 55 SCD cases over a 10 year period were identified from Mater Dei Hospital Mortuary records. Mitochondrial genome sequencing will help to identify mutations that might be associated with SCD and determine if certain mutations are specific to certain mitochondrial DNA haplogroups. Family pedigrees will be investigated.

Globin Bank Research

An important feature of β-thalassaemia trait is increased haemoglobin A2 (Hb A2). Several mutations within the haemoglobin beta (HBB) gene give rise to increased or borderline Hb A2 but when the HBB is normal, the reason remains elusive.

A prospective and retrospective search in the biobank for samples with borderline or increased Hb A2 was carried out. 248 samples with Hb A2 between 3.1% and 4.5% were collected.

The Kruppel Like Factor 1 (KLF1) gene was sequenced and the common SNP (-158C→T) of the HBG2 promoter was detected by PCR-RFLP with XMN I restriction enzyme. Genotyping of individual SNPs in the HBS1L-MYB and BCL11A loci (Figure 2) was performed using a TaqMan genotyping assay.

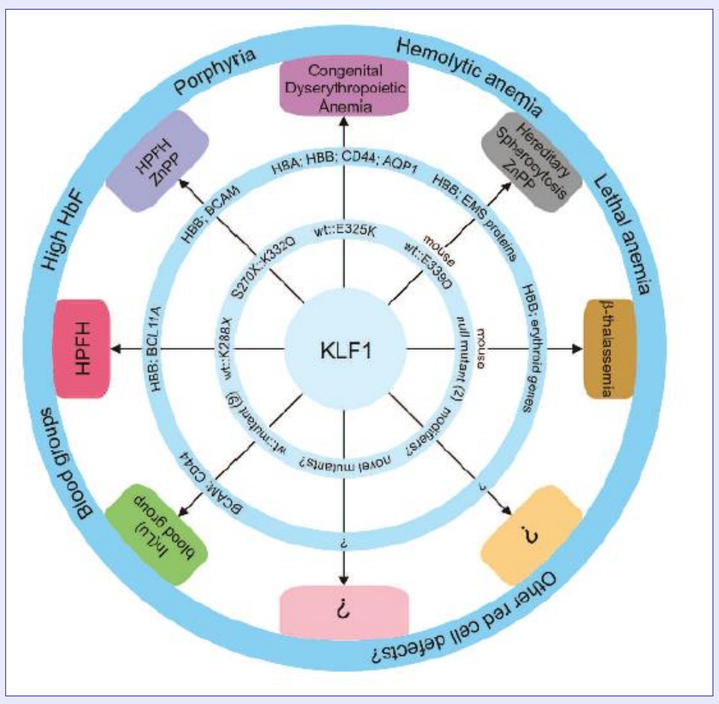

Figure 2: Phenotypes that occur due to KLF1 mutations. KLF is responsible for various mutations and potential modifiers (inner ring) that target a variety of genes (middle ring) and affects their expression. Once these genes are affected by the KLF1 mutation, they produce abnormal phenotypes (outer ring) which may or may not pose serious haemotological conditions[1].

Renal Disorders

Knowledge of the genetic background of rare renal disorders will allow the development of new diagnostic tools that will support early clinical diagnosis and enable the development of new targeted therapeutic methods for patients.

The Clinical Bank of the Malta BioBank is being developed to include a rare renal disorder collection. Patients and families with Nephrotic Syndrome, Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) and Bartter Syndrome are being collected.

Mutation profiling of Maltese patients with Finnish-type Congenital Nephrotic Syndrome will determine if any modifier genes are responsible for a milder clinical phenotype seen locally. A homozygous nt3478(C→T) R1160X NPHS1 nonsense mutation in exon 27 has already been identified in Maltese cases[2]. Genetic analysis on CAKUT samples will contribute to a deeper understanding of the disease[3].

Rare gene variants in Diabetes Mellitus

Rare gene variants are increasingly being implicated in common complex diseases like Type 2 Diabetes Mellitus (T2DM) (Figure 3). T2DM often clusters in families and is characterized by wide ranging clinical and genetic heterogeneity. Rare gene variants that cluster in families and exert large effects on disease risk have been identified in Maturity-Onset Diabetes of the Young (MODY).

Ongoing research on T2DM aims to investigate the association of rare variants in the MODY genes: glucokinase(hexokinase4) (GCK) and Hepatic Nuclear Factors (HNF1, HNF4A) with the risk of T2DM and gestational DM.

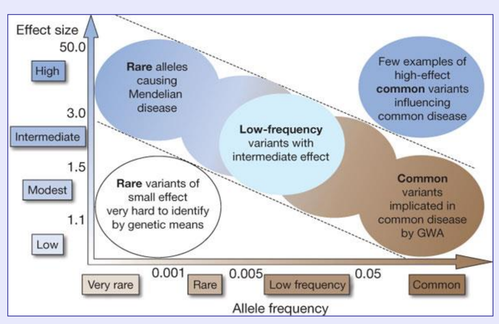

Figure 3: Most disease-associated variants identified from GWAS have modest effect sizes and are not useful for clinical risk prediction studies.

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