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*Abstracts*

# 21st Meeting of the Irish Society of Human Genetics

## Friday 21st September 2018 Croke Park, Dublin

### ORAL PRESENTATIONS:

### OP01. GENES INFLUENCED BY MEF2C CONTRIBUTE TO VARIANCE IN COGNITIVE ABILITY IN THE GENERAL POPULATION.

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Myocyte enhancer factor 2 C (MEF2C) is a transcription factor that plays a central role regulating cell differentiation, proliferation, survival and apoptosis. MEF2C has been implicated in each of the most recent GWAS of cognitive ability (CA) and educational attainment (EA). Animal studies have indicated that knockout of Mef2c interferes with healthy development of brain regions associated with cognitive function, e.g. hippocampal dentate gyrus, neocortex. Furthermore, mutation/deletion of MEF2C can cause severe intellectual and developmental disability. We therefore hypothesised that genes regulated by MEF2C would be associated with cognitive function.

We created a set of differentially expressed genes (DEGs) based on an RNA-seq study that captured the transcriptional changes in mouse adult brain that result from early embryonic deletion of Mef2c in cortical and hippocampal excitatory neurons. This mouse DEG list was converted to human orthologues (n=1052) and tested for enrichment of genes associated with 1) CA, and 2) EA, using MAGMA and recent GWAS summary statistics for each phenotype. We also performed hypergeometric tests to investigate if the DEGs were enriched for current primary intellectual disability (ID), autism, and loss-of-function (LoF) intolerant (i.e. highly constrained) genes. We then used Ingenuity Pathway Analysis (IPA) to explore functional pathways implicated by the MEF2C DEGs.

The DEGs were significantly enriched for CA (p=1.08e-07) and EA (p=9.88e-09) genes; along with ID (p=0.008), autism (p=0.001) and LoF intolerant (p=5.55e-21) genes. The top functions IPA predicted to be decreased from these DEGs are 'development of neurons' (p=5.41e-38, z-score=-2.0) and 'formation of cellular protrusions' (p=1.02e-28, z-score=-2.1).

These findings indicate that genes influenced by MEF2C are highly constrained and contribute to cognitive function and neurodevelopmental disorders with severe cognitive deficits.

### OP02. NOVEL DNA METHYLATION LANDSCAPE OF METASTATIC COLORECTAL CANCER REVEALS SIGNIFICANT EPIGENETIC REGULATION OF DISEASE-ASSOCIATED ENHANCER REGIONS

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Nearly 50% of all colorectal cancer patients progress to develop metastatic lesions (mCRC) and despite ongoing efforts the survival rates for these patients remains significantly low (<20%). This to a great extent can be attributed towards a substantial lack of understanding of the genomic and epigenomic architecture of the mCRC tumours, which would ultimately allow us to identify novel diagnostic and/or therapeutic targets. In order to map the DNA methylation alterations in mCRC, we applied targeted sequence capture sequencing approach encompassing variable enhancer loci, p53 binding sites and all known CpG islands to FFPE-derived DNA from 58 mCRC tumours and 10 matched normal. Differential methylation analysis for the first time revealed a 377-loci based tumour specific methylation signature consisting of >90% CRC-specific enhancer regions, which was subsequently integrated with RNAseq derived gene expression in order to identify gene-enhancer pairs. Applying motif and transcription factor identification algorithms to the methylation signature, showed intricate networks of disease-associated transcription factors whose binding sites are significantly impacted as a result of the altered methylation within these enhancer regions. Utilization of deep machine learning approaches to the methylation data, demonstrates specific methylation patterns that allow stratification of patients independent of their clinical features. Finally, we show that two methylation derived patient clusters overlap significantly with expression derived consensus molecular subtype (CMS) -2 (WNT-p53 cluster) and CMS-4 (EMT-like). This study for the first time presents a critical insight into an enhancer driven epigenomic landscapes, which potentially regulates disease-associated phenotype within mCRC.

### OP03. DNA METHYLATION AND INFLAMMATION MARKER PROFILES ASSOCIATED WITH A HISTORY OF DEPRESSION.

Therese M Murphy[1], B Crawford[1], Z Craig[2], G Mansell[1], I White[1], A Smith[1], S Spaull[2], J Imm[1], E Hannon[1], A Wood[1], H Yaghootkar[1], Y Ji[1], Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium[1], N Mullins[3], C M. Lewis[3,4], J Mill[1].

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Depression is a common and disabling disorder, representing a major social and economic health issue. Moreover, depression is associated with the progression of diseases with an inflammatory aetiology including many inflammatory-related disorders. At the molecular level, the mechanisms by which depression might promote the onset of these diseases and associated immune-dysfunction are not well understood. In this study we assessed genome-wide patterns of DNA methylation in whole blood-derived DNA obtained from individuals with a self-reported history of depression (n=100) and individuals without a history of depression (n=100) using the Illumina 450K microarray. Our analysis identified 6 significant (Sidak corrected $P < 0.05$) depression-associated differentially methylated regions (DMRs); the top-ranked DMR was located in exon 1 of the LTB4R2 gene (Sidak corrected $P = 1.27$ x 10-14). Polygenic risk scores (PRS) for depression were generated and known biological markers of inflammation, telomere length (TL) and IL-6, were measured in DNA and serum samples respectively. Next, we employed a systems-level approach to identify networks of co-methylated loci associated with a history of depression, in addition to depression PRS, TL and IL-6 levels. Our analysis identified one depression-associated co-methylation module ($P = 0.04$). Interestingly, the depression-associated module was highly enriched for pathways related to immune function and was also associated with TL and IL-6 cytokine levels. In summary, our genome-wide DNA methylation analysis of individuals with and without a self-reported history of depression identified several candidate DMRs of potential relevance to the pathogenesis of depression and its associated immune-dysfunction phenotype.

## OP04. AAV-MEDIATED GENE REPLACEMENT IN A PATIENT-DERIVED FIBROBLAST MODEL OF RETINITIS PIGMENTOSA

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Mutations in *RP2* are responsible for approximately 15% of X-linked Retinitis Pigmentosa cases. RP2 is ubiquitously expressed and involved in ciliary trafficking of lipid-modified proteins. A patient harbouring the most common nonsense *RP2* mutation, R120X, was identified through the Target 5000 programme. This enabled the generation of a patient-derived primary fibroblast disease model. The aims of this study were (i) to identify a vector capable of effectively transducing primary fibroblasts, (ii) to rescue RP2 expression in the R120X cell model and (iii) to explore potential assays for evaluating rescue of RP2 function in these cells.

Transduction efficiencies were determined by treating normal fibroblasts with a CAG.EGFP construct packaged in AAV2/2, 2/5 and 2/8 capsids. The results were 55.5% ± 2.5, 17.5% ± 15.4 and 2.2% ± 1.0, respectively. The expression level of RP2 mRNA in untreated R120X fibroblasts was 7.5 fold ± 3.2 lower than that of wild type fibroblasts, while RP2 protein was absent in R120X cells. Transduction of mutant cells with AAV2/2.CAG.RP2 resulted in overexpression of RP2 protein by 1.19 fold ± 0.67. The R120X cell line was evaluated for phenotypes associated with absence of RP2, including Golgi fragmentation and mislocalisation of an intraflagellar trafficking protein, IFT20.The areas of both GM130 and IFT20 were significantly larger in mutant fibroblasts compared to control cells. Treatment with AAV2/2.CAG.RP2 was beneficial in reversing Golgi fragmentation, as the Golgi area in transduced R120X fibroblasts was reduced by 1.5 fold ± 0.5 when compared to untreated cells ($p < 0.0001$).

## OP05. GWAS-PATHWAY ANALYSIS AND FUNCTIONAL VALIDATION IDENTIFIES NOVEL GENES INVOLVED IN PANCREATIC CANCER.

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Background: Genome-wide association studies (GWAS) identify associations of individual SNPs with cancer risk but usually only explain a fraction of the inherited variability. Pathway analysis of genetic variants is a powerful tool to identify networks of susceptibility genes.

Methods: we conducted a large agnostic pathway-based meta-analysis of GWAS data using the summary-based adaptive rank truncated product (sARTP) method to identify gene sets and pathways associated with pancreatic ductal adenocarcinoma (PDAC) in 9,040 cases and 12,496 controls. We performed expression quantitative trait loci (eQTL) analysis and functional annotation of the top SNPs in genes contributing to the top associated pathways and gene sets.

Results: We identified 14 pathways and gene sets associated with PDAC at FDR < 0.05. After Bonferroni correction (*P*-value ≤ $1.3x10^{-5}$), the strongest associations were detected in five pathways and gene sets, including maturity onset diabetes of the young (MODY), regulation of beta cell development, role of epidermal growth factor (*EGF*) receptor transactivation by G-protein-coupled receptors in cardiac hypertrophy pathways, and the Nikolsky breast cancer chr17q11-q21 amplicon and Pujana *ATM* Pearson correlation coefficient (PCC) network gene sets. We identified and validated rs876493 and three correlating SNPs (*PGAP3)* and rs3124737 (*CASP7)* from the Pujana *ATM* PCC gene set as eQTLs in two normal derived pancreas tissue datasets.

Conclusion: Our agnostic pathway and gene set analysis integrated with functional annotation, eQTL analysis and experimental validation provides insight into genes and pathways that may be biologically relevant for risk of PDAC, including those not previously identified.

## OP06. DETECTING FINE SCALE POPULATION STRUCTURE, MIGRATION AND RECENT POPULATION EXPANSION IN THE NETHERLANDS.

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We carried out a detailed genetic study of the population structure, local migration rates and population changes across in the Netherlands using cutting edge methods. Our dataset couples genome wide SNP data and geographic information (N=1422), which together allow us to investigate the interplay between genetics and local geography. To interrogate fine scale population structure we applied the haplotype-based method Chromo Painter/ fineSTRUCTURE, which partitions data based on patterns of haplotype sharing. FineSTRUCTURE identified 16 genetic clusters which correlate closely with regional geography. At the finest level, this clustering has the resolution to distinguish subtly different eastern and western genetic groups within the North-Brabant province. At the coarsest level, clustering delineates a clear north/

south split in the Netherlands, reflecting deeper differences. We investigated whether our clustering reflects barriers to gene flow using the "Estimating Effective Migration Surfaces" (EEMS) method, and observed a strong migrational cold spot splitting the country, broadly overlapping the course of the Rhine. We also estimated recent changes in the effective population size (Ne) using the IBDNe method, observing super-exponential population growth across the past 50 generations. This expansion rapidly increases in rate from ~1650 CE onwards, potentially driven by the Dutch Golden age of the 17th Century. Notably our Ne estimates are systematically lower in northern populations than southern suggesting lower diversity in the north, which is consistent with reported ROH and IBD analysis. Combined our results paint a picture of the dynamic population genetics of the Netherlands that are strongly linked to geography.

## OP07. A GENOMIC COMPENDIUM OF AN ISLAND: DOCUMENTING CONTINUITY AND CHANGE ACROSS IRISH HUMAN PREHISTORY.

Lara Cassidy[1], D Bradley[1].

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We present here a demographic scaffold for Irish prehistory based on the palaeogenomic analysis of 93 ancient individuals from all major periods of the island's human occupation, sequenced to a median of 1X coverage. ADMIXTURE and principal component analysis identify three ancestrally distinct Irish populations, whose inhabitation of the island corresponds closely to the Mesolithic, Neolithic and Chalcolithic/Early Bronze Age eras. Large scale migrations into the island are implied during the transitionary periods carrying with them ancestry ultimately derived from Anatolia and later the Russian steppe. Patterns of haplotypic-sharing and Y chromosome analysis demonstrate strong continuity between the Early Bronze Age and modern Irish populations, suggesting no major population replacement has occurred on the island since this point in time. We further dissect the genetic affinities of each Irish population with reference to wider palaeogenomic datasets, using both allele and haplotype-sharing methods, the latter made possible through genotype imputation.

## OP08. TOWARDS ESTIMATING THE INCIDENCE OF RARE DISEASES IN A PAEDIATRIC POPULATION, BORN IN IRELAND IN THE YEAR 2000.

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Background: Rare diseases (RDs) affect at a minimum 5 per 10,000 people. Although individually rare and under-recognised in healthcare systems, collectively RDs are common with up to 8,000 diseases now described. The National Plan for RDs (2014), recommended the need for epidemiological studies, highlighting the requirement for RD coding to identify RD patients and thereby improve both cost efficiencies and care of patients with RDs.

Objectives: To derive an estimate of the number of childhood onset RDs through analysis of records held at TSCUH & OLCHC.

Methods: Reports of patients born in the year 2000 were extracted from: the National Paediatric Mortality Registry office; clinical, cytogenetics and molecular genetics databases, and the Hospital In-Patient Enquiry system (HIPE) TSCUH/OLCHC. RD cases were identified using electronic/manual results and assigned orpha-codes.

Results: 54, 7893 livebirths, census 2000. National Paediatric Mortality Register, 73 deaths of children born in year 2000 of these 60 had a RD (82%). Clinical, cytogenetic and molecular genetics from TSCUH/OLCHC identified 603, 121 and 77 cases of RD respectively. HIPE TSCUH/OLCHC searches to-date have identified 202 and 242 cases of RD respectively.

Conclusions: RD epidemiological data is difficult to acquire in the current structure of the Irish health service, requiring multiple sources and an inordinate amount of time accessing manual records. This study to-date has identified over 1,000 RD patients presenting by age 17 to OLCHC/TSCUH giving a minimum incidence of 2% for paediatric RDs. In the coming year records from TSCUH specialties will be accessed for inclusion in the study.

## OP09. NEWBORN SCREENING FOR CYSTIC FIBROSIS: A 5 YEAR REVIEW

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Background & Aims: Newborn screening for Cystic Fibrosis (CF) commenced in the Republic of Ireland in July 2011. The aim of this study was to do a comprehensive review of the first five years, focusing on those who had CFTR genetic testing following an elevated IRT.

Methods: This study included all neonates screened from July 2011 to June 2016. Data was expanded by cross-referencing patient charts, clinical and lab databases with the Non-NBS database to track down cascade tested relatives.

Results: In this period a total of 342,424 infants were screened. 141 CF and 19 CF-SPID cases were identified in addition to 238 healthy carriers. 2 babies died from unrelated illnesses, before their Sweat Test. A total of 300/400 (75%) couples with a CF/CF-SPID/Carrier child were seen by a Genetic Counsellor. Phe508del was the most common mutation (79.9%) followed by Gly551Asp (8.7%). Consequently, 185/238 Carrier parents (78%) underwent genetic testing, identifying 1 carrier couple. 101/160 (63%) CF/CF-SPID parents were tested. 255 additional relatives came forward for cascade testing - 184 from 68/162 CF affected/CF-SPID/RIP families (42%), resulting in 3 new CF cases, 3 new CF-SPID cases and 64 additional carriers. Two cases were siblings born prior to NBS. One case was missed though NBS. 71 relatives from 33/238 Carrier families (14%) came forward for cascade testing, identifying a further 18 carriers.

Conclusion: Through early detection of CFTR mutations, NBS provides the opportunity of early intervention and complication prevention as well as improvements in prenatal diagnoses and availability of cascade testing.

## OP10. UNCERTAINTY IN INHERITED CARDIAC PATHOLOGIES

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Background: Multi-gene testing is useful in genetically heterogeneous conditions, including inherited cardiac pathologies. Extended panels increased diagnostic yield of variants where pathogenicity is certain (class 5), likely (class 4) and uncertain (class 3). Concerns exist regarding management of class 3 and 4 variants in conditions of oligogenic inheritance or variable expressivity.

Aim:

1. To review diagnostic yield of genetic tests performed in families with inherited cardiac pathologies

2. To assess management of different classes of variants by clinicians internationally.

Methods: A retrospective cohort analysis was undertaken. Patients in whom "cardiac" genetic tests were requested between 2015 and 2017 were identified from a prospectively maintained departmental patient database. Data regarding indication for testing, diagnostic yield, and classification of variants were retrieved by manual chart review. An electronic survey regarding clinical management of variants (www.surveymonkey.com/r/cardiacvariants) was distributed to colleagues internationally via professional bodies and direct email.

Results: 636 tests (630 patients) were performed between 2015 and 2017 in our centre (183 diagnostic; 453 predictive). At least one variant was identified in 71(39%) patients (28(15%) class 5; 9(5%) class 4; 38(21%) class 3. 135 respondents (23 countries) completed the survey. Considering class 4 variants, 110(81%) counselled patients about the possibility of variant reclassification. In the case of a negative predictive test, 17(13%) were fully reassuring that the patient would not develop the familial phenotype.

Conclusion: Considerable variability in management of class 3 and 4 variants exists. Decision-making relies on interpretation of the phenotype, family history and genotype. Close multi-disciplinary working between cardiology and clinical/molecular genetics teams is critical.

## OP11. UPDATE ON GENETIC DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLAEMIA IN THE REPUBLIC OF IRELAND.

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Familial hypercholesterolaemia (FH) is an autosomal dominant disorder due primarily to mutations in *LDLR, APOB* and *PCSK9*, which causes marked increases in LDL cholesterol levels and predisposes to premature CVD. Given a prevalence of 1:250, there are approximately 23,000 FH sufferers in the Republic of Ireland, most of whom are as yet undiagnosed. The most cost-effective strategy for identifying FH is genetic cascade screening in kindreds with an identified proband. We report interim outcomes of a FH genetic diagnostic service configured around an initial screen of 40 known FH variants followed by either a confirmatory analysis or a full variant scan using PCR and direct nucleotide sequencing, in positive and negative screens respectively.

To date our service has genetically diagnosed 69 patients with FH, including 50 index cases and 19 positive cascade screens. In total, 30 disease-associated variants in *LDLR* and *APOB* have been identified including four due to copy number variation using MLPA. Based on phenotypic classification by Dutch Lipid Clinic Network scoring 75% of those designated "Definite/Probable FH" were genetically confirmed compared with <10% of "Possible FH". Regarding the 40 variant screen, 83 subjects with Definite/Probable FH were analysed with 22% reported positive, while all 16 Possible FH patients were screen negative. Mutation positive patients had significantly higher mean serum LDL Chol (7.7 ±1.7mmol/L) relative to patients designated Possible FH (5.6 ± 0.7mmol/L).

Overall, progress has been made in developing an FH genetic diagnostic service. Cost and clinical-effectiveness of this service will depend on the appropriate classification of Definite/Probable FH.

## OP12. VALIDATION OF A BRCA GENE PANEL FOR GERMLINE AND TUMOUR MUTATION ANALYSIS.

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Hereditary Breast & Ovarian Cancer syndrome (HBOC) is caused by mutations in BRCA1/2 genes and is associated with a high life time risk of breast cancer and ovarian cancer. Ovarian tumours with inherited (germline) *or* acquired (somatic) BRCA1/2 mutations respond to drugs that inhibit poly ADP-ribose polymerase (PARPi). Currently, mutation screening for HBOC patients are 'sent away' to the UK, with a predictive (pre-symptomatic) service for known familial mutations offered at DCG. At this time, there is no service for tumour BRCA testing for potential PARPi treatment. Supported by the National Cancer Control Programme, DCG & CMD have collaborated to assess next generation sequencing BRCA gene panels & platforms to establish a pathway for germline & tumour mutation analysis and validate an optimal clinical testing method for diagnostic and therapeutic use.

The ThermoFisher Oncomine panel with the Ion Torrent PGM/S5 was used to target and sequence 64 unique germline samples with a wide range of known BRCA mutations. These were analysed using JSI SeqNext software and others. After optimisation, 99.84% (624/625) variants were detected at some level. However, there were 117 false positive calls, all in homopolymer regions. Distinguishing false positives from some true positives with a low variant fraction was challenging. Subsequently, the Nimagen EasySeq kit (employing single molecule Molecular Inversion Probes, smMIPs) with the Illumina MiSeq was used for 32 samples. There was a 100% variant call rate (376/376) with no false positive calls. Initial tumour results are also very convincing. Now proceeding to a full clinical validation.

## OP13. ANALYSIS OF THE PATHOGENICITY OF A MISSENSE VARIANT C.137G>T P.(SER46ILE) WITHIN A DIAGNOSTIC LABORATORY.

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Establishing the pathogenicity of missense variants detected in Lynch syndrome / Hereditary Non Polyposis Colorectal Cancer (HNPCC) families is a challenge for diagnostic laboratories. Here we consider two families from Northern Ireland who meet Amsterdam II Criteria for HNPCC, in whom the presence of a *PMS2* gene missense variant c.137G>T p.(Ser46Ile) rs121434629 has been shown. This variant occurs within a conserved ADP/ATP binding region of the PMS2 protein. Disruption of this domain is predicted to result in reduced mismatch repair efficiency and has previously been reported in the literature as a recurrent and founder variant in the *PMS2* gene. However, no co-segregation data has been published for this variant.

Adoption of the ACMG Standards and guidelines (Richards *et al* Genetics in Medicine 2015) along with the release of ACGS best practice guidelines for the interpretation of sequence variants has initiated a review of the classification of variants detected within the region against these standards.

Bioinformatic analysis and evidence available in the published press, had led to a classification of likely pathogenic for this variant. However, addition of the co-segregation evidence provided by local families, at the strong level, enables the variant to be re-classified as pathogenic.

In conclusion, we have shown co-segregation of the *PMS2* c.137G>T p.(Ser46Ile) variant with Lynch syndrome associated phenotype to a Path P1 strong level of significance through family studies.

## POSTER PRESENTATIONS

### P01. DNA METHYLATION OF HYPERTENSION-RELATED GENES IS INFLUENCED BY THE *MTHFR* 677TT GENOTYPE AND RIBOFLAVIN SUPPLEMENTATION

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The C677T polymorphism in the folate metabolising enzyme methylenetetrahydrofolate reductase (MTHFR) is associated with hypertension. Riboflavin is a cofactor for MTHFR in one-carbon metabolism, for generating methyl groups important in DNA methylation. Supplementation with riboflavin has been shown to lower blood pressure in *MTHFR* 677TT genotype individuals. The mechanism regulating this gene-nutrient interaction is currently unknown but may involve aberrant DNA methylation also implicated in hypertension. This study examined DNA methylation of hypertension-related genes in adults stratified by *MTHFR* genotype and the effect of riboflavin supplementation on methylation of these genes in the *MTHFR* 677TT genotype group.

We measured DNA methylation using pyrosequencing in a set of candidate genes associated with hypertension including angiotensin II receptor type 1 (*AGTR1*), G nucleotide binding-protein subunit alpha 12 (*GNA12*), insulin-like growth factor 2 (*IGF2*) and nitric oxide synthase 3 (*NOS3*). Stored leukocyte samples from participants with the *MTHFR* C677T genotype who had participated in targeted RCTs (1.6mg/d for 16wks) at Ulster University were accessed for this analysis (n=120). Baseline methylation differed between *MTHFR* C677T genotype groups at *NOS3* (p=0.026) and *AGTR1* (p=0.045). Riboflavin supplementation in the *MTHFR* 677TT genotype group resulted in altered average methylation at *IGF2* (p=0.025) and CpG site specific alterations at the *AGTR1* and *GNA12* loci.

This study demonstrates an interaction between DNA methylation of hypertension-related genes and riboflavin supplementation in adults with the *MTHFR* 677TT genotype. Further work using a genome-wide approach is required to better understand the role of riboflavin in altering DNA methylation in these genetically at-risk individuals.

### P02. THE ASSOCIATION BETWEEN Y CHROMOSOME SNPS AND CHRONIC KIDNEY DISEASE.

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Chronic kidney disease (CKD) is considered a major public health problem, affecting approximately 10% of the global population. While a comprehensive review of known CKD biomarkers yielded many results, it also highlighted a lack of research in chromosome Y. Single nucleotide polymorphisms (SNPs) on chromosome Y have previously been associated with a 50% increase in risk of developing coronary artery disease, a condition with close links to CKD. Therefore, Y chromosome SNPs may also impart increased risk of developing CKD. Individuals from the Genetics of Nephropathy: an International Effort (GENIE) consortium (n=791) and the Northern Ireland Cohort for the Longitudinal Study of Aging (NICOLA; n=1241) were genotyped using the Illumina HumanOmni1-Quad array and the Illumina CoreExome-24 array, respectively, to determine if any association exists between Y chromosome SNPs and CKD, or estimated glomerular filtration rate (eGFR), a measure of kidney function. However, poor coverage of chromosome Y resulted in only 3 SNPs in the GENIE cohort and 421 SNPs in the NICOLA cohort passing quality control. Association analysis of both datasets did not reveal any significant associations. Due to limitations of this study, further analysis is required to determine whether SNPs on chromosome Y are associated with CKD and/or eGFR. An array with greater Y chromosome coverage will be selected and be used to re-genotype these individuals, and individuals from additional cohorts, allowing greater SNP coverage and direct comparison of SNPs between these cohorts. Increased SNP coverage and increased participant numbers will allow meta-analysis to be performed with sufficient power.

### P03. INVESTIGATING THE LINK BETWEEN HYPOXIA AND MIR-21 IN PROSTATE CANCER.

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Background: Tumour hypoxia is a major driver of prostate cancer progression and metastasis. miR-21 is a microRNA which has been previously linked to hypoxia, but this relationship remains poorly characterised in a prostate cancer setting. Therefore, in this study, we investigate the link between hypoxia and miR-21 in prostate cancer cells.

Methods: We have used 2D and 3D cell prostate cell models of hypoxia to investigate the functionality of miR-21. Expression levels of miR-21 have been measured by qPCR and functional bioassays used to examine its effect on prostate cell behaviour. Target genes have been identified and bioinformatic analysis has been employed to investigate a clinical significance for miR-21 in prostate cancer.

Results: miR-21 is induced by hypoxia in prostate cancer cell-lines. Over-expression of miR-21 impacts upon target genes which in turn affects cell behaviour. Data-mining of online repositories of clinical data and bioinformatic analysis of miR-21 cellular networks reveal that miR-21 exerts a wide influence on several important cell processes, the dysregulation of which can lead to development of prostate cancer.

Conclusions: We propose that miR-21 could be an important microRNA in the pathogenesis of prostate cancer and has potential as a biomarker in this disease.

### P04. THE GENETIC HISTORY OF THE MALTESE ARCHIPELAGO DURING THE NEOLITHIC PERIOD.

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The Neolithic period begins in Europe around 8500 years before present (BP) and is characterized by the adoption of farming and domestication of various types of animal. In our project we focus on the structure of the Maltese population during the latter part of the Neolithic period. Nine individuals, from 4900 to 4350 years BP,

collected from the Xaghra Circle site in the island of Gozo, were sampled. DNA was extracted from both teeth and the inner part of petrous bones giving an average endogenous DNA respectively of: 1.7% for 4 teeth and of 21% for 5 petrous bones. We then used a median of 363,579 SNPs from the Human Origin dataset to compare our samples with 37 ancient individuals from Neolithic and Bronze Age period and 604 present-day European individuals already published. PCA analysis shows, for the 5 high coverage samples, places the Maltese individuals with the early European farmers (EEF) from Germany and Hungary. Further analysis with D-statistics depict that the Maltese population do not resemble any hunter-gatherer population from Caucasus or Eastern Europe, while they show a higher affinity with Western European hunter gather individuals (WHG).

## P05. GENE EXPRESSION ANALYSIS FOLLOWING PROSTAGLANDIN TREATMENT *IN VITRO*.

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According to the WHO, glaucoma is the second leading cause of blindness in the world and is the leading cause of irreversible blindness. The total number of suspected cases of glaucoma is estimated to be over 60 million worldwide, increasing to 79.6 million by 2020.

Commonly, glaucoma is treated using eye drops containing prostaglandin analogs, including latanoprost and bimatoprost. However, these treatments come with ocular adverse reactions including ocular surface irritation, acute iritis, conjunctival hyperemia, thickening and elongation of eyelashes, induced iris darkening as well as periocular skin pigmentation. Patient compliance has been shown to be affected by these side-affects including non-compliance for cosmetic reasons with thickening and lengthened eyelashes and the occurrence of pigmentation. This study aimed to identify whether there are differences in gene expression between those prostaglandin treatments containing preservatives and those without preservatives.

Primary human trabecular meshwork cells were stained with phalloidin to determine morphology. The cells were treated with prostaglandins either with or without preservatives, gene expression analysis was performed by PCR to determine differences between preservative containing and preservative free treatments.

Differences in gene expression were shown at different time-points after treatment. Differences were also shown between treatments which were preservative free and those treatments which contained preservative.

With the significant differences in gene expression levels between prostaglandins containing preservatives and those without preservatives, it indicates that prostaglandins without preservatives are likely to produce less side effects in glaucoma patients.

## P06. THE POPULATION GENETICS OF PREHISTORIC PORTUGAL.

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For the majority of its history the field of ancient population genetics was restricted to non-human samples due to the difficulties with modern contamination and the nature of ancient DNA (aDNA) sequences: short, highly degraded, chemically modified and present in low concentrations with high concentrations of microbial contamination. The development of efficient extraction techniques, the discovery that the petrous part of the temporal bone is a rich reservoir for aDNA and the development of high-throughput next-generation sequencing (NGS), have resulted in the rapid expansion of the field, with sequences from over 1000 ancient individuals published to date.

Portugal occupies a unique position in Europe; facing both the Atlantic and the Mediterranean it was connected to two major maritime trade and migration routes, as well as experiencing influx from central mainland Europe throughout its prehistory. Many open questions remain about population changes in the Iberian Peninsula at major transition periods in European prehistory, such as the transition to the Bronze Age involving migrations from the Pontic Steppe, the source for the R1b Y-chromosome haplotype now dominant in European populations.

In this study we present high quality whole genome sequences (0.05-2.9X, 13 samples at ~1X) from 25 ancient Portuguese individuals, covering a period of over 3000 years, to examine the demographic and selection processes acting on prehistoric Portuguese populations. We use principal component analysis (PCA), outgroup $f_3$ statistics, Patterson's *D*-statistic and ADMIXTURE analysis to investigate questions such as hunter-gatherer admixture in the Neolithic and Steppe introgression in the Bronze Age.

## P07. A PHARMACOGENOMIC ASSESSMENT OF ADVERSE DRUG REACTIONS TO THE ANTI-EPILEPTIC DRUG LEVETIRACETAM.

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Background: Epilepsy is a neurological condition affecting an estimated 50 million people worldwide and roughly 40,000 people in Ireland. Levetiracetam (LEV) is an effective anti-epileptic drug, but 10-20% of patients exposed to LEV report behavioural side-effects and up to 1% of those treated experience acute psychosis. We set out to determine contribution of common genetic variation to these adverse drug responses (ADRs).

Methods: Individuals from the EpiPGX study cohort were screened for European ancestry and matched to predefined phenotypic criteria. Controls were exposed to LEV, but without any adverse reactions.

GWAS were carried out on patients who experienced behavioural disorders (n=149), acute psychosis (n=19), or any affective symptoms in response to LEV treatment (n=90).

After identification of a genome-wide significant hit in the affective disorder analysis, a further GWAS was performed in a replication cohort (n=68).

Following this, polygenic risk scores (PRS) for all cases and controls were calculated using the results from the Psychiatric Genomics Consortium's GWASes of Schizophrenia (SCZ) and Bipolar Disorder (BIP).

Results: A genome-wide significant result was found in SNP rs7500119 in the CALB2 gene. Upon replication the SNP lost genome-wide significance but maintained nominal significance. PRS analysis for both SCZ and BIP were predictive of LEV-induced psychosis.

Discussion: The univariate analysis did not identify a genome-wide significant signal for neurological ADRs to LEV that survived replication in an independent cohort. Further work with larger sample sizes may identify such variants.

Increased PRS for SCZ and BIP are associated with LEV-induced psychosis, this analysis will also benefit from a larger sample

## P08. A SIMULATION STUDY ON THE ORIGIN OF NATURAL SELECTION IN AN ADMIXED POPULATION.

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The impact of natural selection on beneficial alleles can be observed in modern human genetic variation; however deciphering the origins of these alleles is complicated by the vast complexity of human history, in which many population splits and admixture events have occurred. Here we describe a new statistical framework of Approximate Bayesian Computation (ABC) that can detect which ancestral group an allele undergoing selection first appeared. We assume a specific model in which a source population splits into two groups that later undergo admixture to form the lineage leading to the contemporary population and simulate the origin of beneficial alleles at different stages of the population's history. Using genetic variation observed at the allele at the present time, as well as the knowledge we have of the timing of demographic changes and admixture events, we test if our approach can accurately predict the time the allele arose, and in which ancestral population it first emerged in. In this presentation, we will show preliminary results from our simulation study and discuss a potential application of the method for whole-genome data from an admixed human population.

## P09. CAN THE RELATIONSHIP BETWEEN SNP-GENETIC PROFILES AND ADVERSE DRUG METABOLITE CONCENTRATIONS HELP US PREDICT DRUG TREATMENTS THAT WOULD WORK BEST FOR PATIENTS WITH RHEUMATOID ARTHRITIS?

Potential personalised treatment modality stratification in Rheumatoid Arthritis by assessment of genetic profiling of SNPs and evaluation of drug metabolites against DMARDs.

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There are over 12000 people in Northern Ireland living with rheumatoid arthritis (RA); a painful, systemic autoimmune disease, causing swelling, stiffness, loss-of-function in joints, disability and significantly lowering ones quality of life.

Various medication options are available; low-dose (10 to 25 mg/wk.) methotrexate (MTX), a small-molecule disease-modifying anti-rheumatic drug (DMARD), is a first-line therapy, due to its affordability, cost-effectiveness and efficacy. Other DMARDs used in RA are sulfasalazine, chloroquine, hydroxychloroquine, azathioprine, and leflunomide. However, there is significant person-to-person variability in treatment responses with nearly 50% of patients indicating poor or no-response to any of these medications.

Serum drug metabolite concentration of 100 RA patients treated with DMARDs were determined using tandem mass-spectrometry. Allelic discrimination analysis using Taqman probes was performed on the following SNPs; rs246240 (ABCC1), rs1476413 (MTHFR), rs2231142 (ABCG2), rs3740065 (ABCC2), rs4149081 (SLCO1B1), rs4846051 (MTHFR), rs10280623 (ABCB1), rs16853826 (ATIC), rs17421511 (MTHFR) and rs717620 (ABCC2). Demographic analysis, clinical parameters and disease scores (e.g. DAS28) were also recorded.

These SNPs are located within the genes involved in the metabolism of DMARDS and anecdotal evidence has been reported in the literature of their participation in modulating normal metabolism and function of DMARDs.

Correlation statistics was used to determine if the genetic profiles associate with the emergence of drug metabolites responsible for poor or non-response to DMARDs.

Our findings suggest that genetic-profiling studies may help predict future treatment responses of patients to certain DMARDs. A stratified medicine strategy can help prioritise treatments to those patients most likely to respond while avoiding ineffective treatments.

Abbreviations: single nucleotide polymorphisms (SNP); rheumatoid arthritis (RA), disease-modifying anti-rheumatic drug (DMARD), methotrexate (MTX)

## P10. SDCCAG8 IS A SCHIZOPHRENIA RISK GENE THAT IS REQUIRED FOR EFFICIENT PRIMARY CILIOGENESIS.

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Rare mutations in genes that encode centrosomal or ciliary proteins cause disorders that present with severe cognitive deficits and variable neuropsychiatric phenotypes. We set out to explore the involvement of centrosomal/ciliary genes in schizophrenia, a neuropsychiatric disorder that affects 1% of adults and is a major global health issue. Our analysis of publicly-available genome-wide association study (GWAS) data revealed that seven schizophrenia risk genes encode proteins with centrosomal functions. Of these, SDCCAG8 is also associated with educational attainment.

To analyse the molecular function of SDCCAG8, we used genome editing to ablate it in SHSY5Y neuronal and hTERT-RPE1 retinal epithelial cells. Loss of SDCCAG8 impairs cells' ability to make primary cilia and the signalling capacity of residual cilia, although centrosome structure appears normal by immunofluorescence microscopy. Recent RNA-Seq analysis on RPE1 SDCCAG8 deficient cells compared to wildtype cells revealed a large number of differentially expressed genes (DEGs; n=2,045) in the absence of SDCCAG8. Pathway analysis of DEGs revealed that there is enrichment in axonal guidance signalling ($p=2.51^{-15}$). There were also significant enrichments for several pathways that are involved in the production and turnover of extracellular matrix (ECM). Previously, many components of the ECM have been shown to be perturbed in patients with schizophrenia.

Using MAGMA gene-set analysis, we found that set of DEGs were enriched for genes associated with schizophrenia (p=0.03) and cognitive ability (p=0.03). This study shows that a combination of gene editing and genomic analyses can help uncover the processes that implicate centrosome/ciliary genes in neurodevelopmental

phenotypes.

## P11. GENETIC ANCESTRY AND POPULATION STRUCTURE OF SCOTLAND AND ITS SURROUNDING ISLES

Edmund Gilbert[1], S O'Reilly[2], M Merrigan[2], D McGettingan[2], V Vitart[3], PK Joshi[4], DW Clark[4], H Campbell[4], C Hayward[3], S Ring[5], J Golding[6], N Timpson[7], P Navarro[3], S M Kerr[3], C Amador[3], A Campbell[8], CS Haley[3,9], DJ Porteous[8], GL Cavalleri[1,10*], JF Wilson[3,4*].

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Scotland and Ireland are separated in places by less than 20 kilometres of sea. They share the Gaelic language and similar frequencies of particular alleles and phenotypes, hinting at shared ancestry. The population structure within England and Ireland have recently been described. However, the extent of structure within the majority of Scotland, its surrounding islands, and their links to Ireland are currently unknown. We present an analysis of the British Isles and Ireland using a combined and comprehensive sample (n=2,556) of all major regions – expanding coverage in mainland Scotland (n=567), the Hebrides (n=57), the Isle of Man (n=40), Orkney (n=111) and Shetland (n=172). By analysing individuals with extended ancestry from specific regions, we demonstrate extensive structure in all regions of the British Isles and Ireland, as well as some of the finest scale structure observed worldwide within Orkney. We resolve the shared genetic history between Ireland and Mainland Scotland, confirm the strongest differentiation of Orkney and Shetland from other populations, show the major differentiation in Mainland Scotland is between the south-west and the north-east, and reveal the distinctiveness of the Hebrides and the Isle of Man. We additionally show decreasing cline of Norwegian ancestries across northern Britain, following the spread of the Norse Vikings. Our work represents a comprehensive description of genetic structure in the British Isles and Ireland and greatly expands the knowledge of genetic stratification within the north of the British Isles, informing on the study of rare genetic variants and genetic trait associations in these populations.

## P12. THE EFFECTS OF GENETIC VARIATION ON THE COGNITIVE PHENOTYPES OF INTELLIGENCE AND WORKING MEMORY AND EPISODIC MEMORY IN SCHIZOPHRENIA.

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The Savage et al. (in press) GWAS meta-analysis of intelligence of healthy controls supports increasing findings on variability in intelligence and evidence of overlap with schizophrenia. Utilising convenience sample of pre-existing Irish dataset of broad psychosis cases (916 cases and 330 controls), wherein the controls participated in the Savage et al. (in press) meta-analysis, the present study functioned as secondary analysis of said meta-analysis findings regarding the broad psychosis cases. With the five most significant single nucleotide polymorphisms (SNPs) as identified by Savage et al. (in press) and patient diagnosis as independent variables, this statistical regression analysis focused on the extent to which these genetic variances were of importance in a clinical population by examining the effects in schizophrenia of previously identified genetic variation associated with intelligence (IQ) in healthy controls. Further objective was to extend the Savage et al. (in press) findings to investigate the effects in schizophrenia of genetic variation on memory (working memory and episodic memory). As hypothesized the present study observed nominal trend association for SNP rs2726491 with decreased errors in performance IQ, and a nominally significant association with decreased errors in working memory for rs2726491 across both healthy and clinical population samples. These nominal associations would be suggestive of stronger effects in psychosis, however, the present study was underpowered to observe an association at the corrected level. Nevertheless, future research building on these suggestive findings could further our understanding of the biological psychopathology of schizophrenia, and crucially bring about improved cognitive function in schizophrenia patients.

## P13. MULTIWAY ADMIXTURE INFERENCE FROM GENOTYPE DATA

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We present a model, algorithm, and results for multiway admixture events. This is where two or more genetically differentiated groups come together. Data from such events can inform us of the demographic history of a species, carry signatures of natural selection, and may increase the power of genome wide association studies. Our model is based on Li and Stephens style haplotype copying and delivers accurate local ancestry estimation along the genome for each admixed individual. Unlike existing methods that return local ancestry, we do not assume knowledge of the relationship between sub-groups of donor reference haplotypes and the unseen mixing ancestral populations. Instead, our approach infers these in terms of conditional copying probabilities. We also infer admixing proportions, timings, and recombination rates. Furthermore, we can estimate drift between modern reference populations and the unseen mixing groups using a version of Fst that is computed on putative partial genomes derived by assignment of chromosome segments to ancestral backgrounds.

We demonstrate compelling results using the Human Genome Diversity Panel, including replication of some known admixture events, and we detail novel findings such as a recent 4-way admixture in San-Khomani individuals.

Keywords: Population Genetics, admixture, demography, local ancestry estimation.

## P14. DONOR-RECIPIENT SHARED GENETIC ANCESTRY DOES NOT PREDICT RENAL TRANSPLANT OUTCOME IN A EUROPEAN POPULATION OF UNRELATED DECEASED DONOR TRANSPLANTS.

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Sibling transplant pairs have better transplant outcomes than unrelated donor-recipient (DR) pairs suggesting shared genetic ancestry between donors and recipients has potential for predicting transplant outcome. We set out to evaluate methods to detect and quantify shared ancestry using GWAS data, to see which could best predict renal-transplant outcome.

We tested three different methods for estimating shared genetic ancestry on deceased donor DR pairs of European ancestry. Method 1 calculated identity by descent (IBD) which was then used to estimate the degree of relationship. Method 2 calculated genetic distance using identity by state which examines the number of shared alleles across the genome. Method 3 created a mosaic of an individual's genome from the haplotypes of the other individuals in the dataset. The similarity of mosaic genomes in a given DR pair was used as a measure of shared ancestry. These measures were then tested against estimated glomerular filtration rate (eGFR) at 1 year (DR pairs, n=1,450) and 5 years (DR pairs, n=1,309) post-kidney transplant, change in eGFR between 1 and 5 years (Δ eGFR; DR pairs, n=982) and time to graft failure (DR pairs, n = 1,806).

We did not find significant correlations between any of the measures of shared ancestry in the European ancestry deceased-donor DR pairs and graft function. The genetic relationship between the vast majority of our donor-recipient pairs was distant, and not detectable via IBD. The effect size of shared ancestry at the genomic level on eGFR is limited, and not detectable in our analysis.

## P15. STRATIFICATION OF TYPE-2 DIABETES COMORBIDITIES USING GENOTYPIC ARRAY AND MACHINE LEARNING

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Background: The treatment of comorbidities remains costly and represents a major priority in Evidence Based Medicine (EBM). Determining genetically the molecular-subclasses of pro-inflammatory comorbid conditions is important to stratify patients that may more effectively respond to specific treatment interventions. The objective of this study is to develop a Machine Learning (ML) based classifier to stratify patients with Type-2-Diabetes and different comorbidities.

Methods: A preliminary dataset of samples from 254 people with Type-2-Diabetes recruited at NICSM were genotyped with an Affymetrix UKBioBank Axiom Array. SNP results for 80 patient samples of class DCM1 (i.e. Type-2 Diabetes associated with comorbidities of circulatory system) and 90 patient samples of class DCM2 (i.e. Type-2-Diabetes associated with comorbidities of digestive system) were filtered through feature selection using ANOVA, Chi-square and Fast Correlation Based Filter. The top-10 SNPs along with information from Electronic Care Records (ECR), were selected for building 5 ML binary classifiers, using Support Vector Machine, Random Forest, Artificial Neural Network, Decision Tree and Naive Bayes algorithms, and their performances were tested with a 10-fold cross validation.

Results: Of the 5 classifiers, the Naive Bayes algorithm outperformed all others with an Area under the Curve score of 0.681, overall Classification Accuracy of 65.68% and Mathews Correlation Coefficient of 0.316.

Conclusion: Further improvement in the performance of our ML classifier is currently in-progress. With the inclusion of further data from ECR, as well as data from public repositories, we hope to build a better classifier.

## P16. INVESTIGATING THE IMPACT OF AGEING AND FOLATE METABOLISM IN DRIVING MITOCHONDRIAL HETEROPLASMY AND NUCLEAR DNA METHYLATION.

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This project aims to investigate the relationship between folate status and the accumulation of mutations within the human mitochondrial genome. Folate is an essential B vitamin that is required for DNA synthesis, methylation reactions and is a major contributor to NADPH production through the folate one-carbon metabolism (FOCM) pathway. As a diet with a suboptimal level of folate can impact on DNA precursor availability, there is a strong biological plausibility that this will cause an increased occurrence of mutations within a cell's genome due to errors in DNA replication. Mitochondrial dysfunction has been linked to many age-related conditions such as cardiac myopathies, neurological disorders and muscular wastage. The accumulation of mutations within the mitochondria over one's lifetime may increase the level of mitochondrial dysfunction thus increasing the likelihood of developing such diseases. This project will look at the potential relationship between folate-status and the frequency of mutations occurring within the mitochondrial genome using a combination of both cell line and animal models plus a human cohort with known folate status and age ranges.

## P17. COMMON VARIANTS ASSOCIATED WITH COGNITION ARE ENRICHED IN HIGHLY CONSTRAINED GENES AND IN GENOMIC REGIONS UNDER BACKGROUND SELECTION.

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Common variants associated with schizophrenia are enriched among highly constrained (HC) genes. As schizophrenia and cognition are genetically correlated, we hypothesized that genes associated with cognitive function are enriched for HC genes. Using MAGMA to perform gene set analysis of the largest available GWAS datasets, we found that HC genes (n=3,230 (loss-of-function intolerant)) are strongly enriched for genes associated with educational attainment(EA; p=1.27E-09) and cognitive ability(CA; p=5.64E-09) in comparison to genes under lesser or weak constraint (p>0.05 for both EA and CA). This signal remained significant following conditional analysis to co-vary for 'brain-expressed' (n=14,243) and 'brain-specific' (n=1,424) gene-sets. In schizophrenia, evidence shows that common variants are likely to persist in the population due to background selection (BGS) mechanisms. BGS refers to the phenomenon by which selection against deleterious variants reduces genetic diversity, impairing the overall efficiency of selection and allowing alleles with small effects to rise in frequency by drift. We ran a stratified linkage disequilibrium score regression (LDSR) analysis to test for heritability enrichment in EA and CA for SNPs within genomic regions that are under various types of selection. The heritability of EA and CA is enriched for SNPs in regions under background selection(p=0.028 for EA and p=0.002 for CA) and depleted for SNPs in regions under positive selection. Recent studies

suggest that natural selection is acting against phenotypes such as EA or CA. This study suggests a mechanism by which variants contributing to these phenotypes are not removed by negative selection and are maintained in the population.

## P18. EXPLORATION OF AN AAV-MEDIATED TULP1 REPLACEMENT GENE THERAPY IN A MURINE MODEL.

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Mutations in the photoreceptor-specific tubby-like protein 1 (TULP1) are associated with recessive retinitis pigmentosa 14 and Leber congenital amaurosis 15; severe, early-onset forms of retinal degeneration. We have explored an adeno-associated virus (AAV)-mediated gene replacement therapy in a murine model carrying a targeted disruption of the *Tulp1* gene (*Tulp1* -/- mice). The human *TULP1* cDNA driven by the chicken beta-actin promoter (CBA) promoter was generated in an AAV serotype 5 (AAV-CBAP-TULP1). 1x10e[11] vg of AAV-CBAP-TULP1 (+1:600 of an AAV-EGFP vector for tracing) was delivered to TULP1$^{-/-}$ mice at postnatal day 2 via sub retinal injection. Immunoblotting and qPCR demonstrated that the replacement TULP1 protein had the correct molecular weight and that the level of expression of protein achieved was ~55 % (n=8; p<0.05) of endogenous Tulp1 in wildtype mice (n=8). Immunohistochemical analysis detected TULP1 in the inner segments and synaptic region in treated Tulp-/- mice similar to endogenous Tulp1 in wildtype mice (n=8). The effect of AAV-CBAP-TULP1 delivery was assessed by histological analysis and TUNEL assay. Preliminary data indicated a modest increase the outer nucler layer thickness compared to AAV-EGFP treated controls; 34.07 µm ± 4.97 SEM and 24.07 µm ± 6.8 SEM respectively (n=8; p<0.05) and TUNEL assays showed a significant reduction in apoptotic cells (n=8; p<0.001). However, no differences were observed using functional assays such as the ERG and OKR. Despite the conserved C-terminal region (~200 bp) of human and mouse Tulp1 proteins, a significant divergence at the N-terminus may possibly contribute to the low efficacy of *TULP1* replacement in Tulp-/- mice and warrants further investigation.

## P19. EVALUATION OF DIFFERENTIALLY EXPRESSED URINARY EXOSOMAL MICRORNAS IN TYPE 2 DIABETIC KIDNEY DISEASE

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Background: Diabetic kidney disease (DKD) is the most frequent cause of end stage renal disease. There is a need for improved biomarkers for the early detection of DKD. MicroRNAs (miRNAs) are short, non-coding regulatory RNA molecules commonly found in urinary exosomes that may be differentially expressed during renal dysfunction. Therefore, we profiled urinary exosomal miRNA expression in type 2 DKD (T2DKD).

Methods: Qiagen Human Urine Exosome Focus miRNA Panel was used to profile 87 miRNAs in a discovery cohort of 14 T2DKD and 15 age and gender matched type 2 diabetic patients with normal renal function (T2NC). Differentially expressed miRNAs were validated in a second cohort of 22 T2DKD, 18 non-diabetic patients with poor renal function (CKD), and 22 T2NC.

Results: Three urinary miRNAs (miR-21-5p, let-7e-5p and miR-23b-3p) were significantly upregulated (P<0.05) and two (miR-30b-5p and miR-125b-5p) were significantly downregulated (P<0.05) in T2DKD compared to T2NC. In a logistic regression analysis adjusted for age, gender and mean arterial blood pressure, only miR-21-5p remained significantly associated with T2DKD (odds ratio=3.28, confidence intervals: 1.14–9.43; P=0.03). Independent validation in the replication cohort confirmed up-regulation of miR-21-5p expression in T2DKD (2.13-fold, p<0.01) and also in CKD (1.73-fold, p<0.05). In contrast, miR-30b-5p was downregulated in T2DKD (1.22-fold, p<0.01) and in CKD patients (1.52-fold, p<0.005).

Conclusion: Our data identified differential expression of miR-21-5p and miR-30b-5p in individuals with poor renal function, although further clarification to determine if these are associated with general mechanisms of renal dysfunction is required.

## P20. WERNER SYNDROME - A UNIFYING HYPOTHESIS FOR NAFLD, INSULIN RESISTANCE AND MULTIPLE ENDOCRINOPATHY.

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Werner syndrome (WS) is a rare genetic disorder due to mutations in the WRN or LMNA genes, with an estimated global incidence of 1 in 1,000,000 - 10,000,000. It is a segmental progeroid disorder characterised by an array of clinical features consistent with accelerated aging. We report the case of a 28 year old female patient, the offspring of a consanguineous union, who was referred to our metabolic clinic for review. She reported a history of vocal cord paralysis aged 19 years and subcapsular cataracts aged 24 years. Moreover, she had been diagnosed with primary hypothyroidism, primary hyperparathyroidism and subfertility despite normal menstruation. Further diagnoses included NAFLD with mild fibrosis. On examination, she had skin atrophy, hyperkeratosis, a loud S2, scalp alopecia, axillary acanthosis nigricans, and marked visceral adiposity with lipodsytrophic upper and lower limbs. Echocardiography confirmed trace regurgitation in aortic, mitral and tricuspid valves and DEXA confirmed osteoporosis. HOMA score was > 11 confirming severe insulin resistance and AMH levels were low. Phenotypically the patient had a diagnosis of definite WS but genetic confirmation was sought. Analysis of *LMNA* did not identify pathogenic variants. An RT-PCR method with direct sequencing was developed in-house to examine the extensive coding region of *WRN*. This revealed a homozygous genotype for the nonsense variant g.129, 248C>T, c.3961C>T, p.Arg132Ter. To our knowledge this is the first reported case of WS in the Republic of Ireland. In cases with multiple early-onset morbidities a genetic basis should be considered, particularly if there is a risk of consanguinity.

## P21. POSSIBLE CANDIDATE INHERITABLE MARKERS BY NEXT GENERATION SEQUENCING INDICATING PREDISPOSING LONGITUDINAL RISK TO LUNG CANCERS WITH ATYPICAL PRESENTATION OF LUNG CAVITATION FROM FUNGAL LUNG DISEASE IN A KENT FAMILY OF IRISH DESCENT.

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Hyperlucent zones within areas of pulmonary consolidations may represent cavitatory lung lesions on CT imaging, from multi-factorial causes such as TB, pulmonary infarction, pyogenic lung abscess, pneumocystis pneumonia, Klebsiella pneumonia and less frequently due to necrotic processes from fungi.

We were presented with this clinical conundrum in a patient against a background of refractory asthma, chronic cough, worsening dyspnoea, poor spirometry results and becoming progressively unwell. Due to a strong history of cancer in the family, EBUS-TBNA was carried out to obtain lung-biopsy samples. Laboratory histological analysis and ROSE revealed hyphae and fungal spores within the tissue samples biopsied, no malignant cells were recovered from the lymph node biopsy samples in all stations. We initiated anti-fungal treatment; itraconazole, 200mg once daily for 2 days after which the patient began to show signs of improvement.

Seven family members with prior history of fungal-lung disease had developed lung-cancer later in life, and anecdotal prior research had shown that a premature stop-codon mutation at the tyrosine-238 residue of the dectin-1 gene in a Dutch family had predisposed patients to risks of contracting fungal-lung disease and subsequently developing lung-cancers in the long-term.

We carried out Sanger-sequencing of all the exons of the dectin-1 gene as well as whole-exome sequencing on the HiSeq (Illumina) platform to identify candidate markers that may explain the heritability in this Kent family of Irish descent. We highlight the results of this study in this presentation.

Abbreviations: endo-bronchial ultra-sound transbroncial-needle-aspiration; EBUS-TBNA, Rapid-OnSite-Examination; ROSE, tuberculosis; TB

## P22. BREAST CANCER IN IRISH PATIENTS WITH LYNCH SYNDROME

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Lynch syndrome (LS) (previously Hereditary Non-Polyposis Colorectal Cancer syndrome) is a cancer predisposition syndrome conferring variable risks of endometrial, colorectal, upper gastro-intestinal, urinary and biliary tract cancers. Lynch syndrome is a dominantly inherited trait, caused by pathogenic germline variants in one of the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, or *PMS2;* and more rarely by deletions in *EPCAM* causing hypermethylation of the *MSH2*promoter.

A recent report suggested that germline variants in MSH6 or PMS2 are associated with an increased incidence of breast cancer. Other data with respect to this association is conflicting, and prospective studies have not shown evidence for this association.

Here, we report a case of a 37-year old female patient with multi-focal breast cancer demonstrating defective MMR, associated with a germline variant in *MSH2*.

This prompted us to undertake a respective cohort study to assess the prevalence of breast cancer in patients with Lynch syndrome managed in our centre. We report on 60 consecutive patients (including the case described here above) tested and found to carry germline pathogenic/likely pathogenic variants in MMR genes were identified from a prospectively maintained departmental database. Pedigrees from these patients were analysed, and number of breast cancers in probands and first and second degree relatives were recorded. Age at diagnosis, phenotypic data and genotype were noted.

## P23. CAG INTERMEDIATE-REPEATS EXPANSION IN *ATXN2* ASSOCIATED WITH INCREASE OF RISK IN ALS

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Amyotrophic lateral sclerosis (ALS), usually23 known as a motor neuron disease, is a fatal neurodegenerative disorder which causes death of neurons controlling voluntary muscles. ALS has no cure, and its underlying cause is mostly unknown, although a strong genetic component is known to play a role. The gene *ATXN2* normally has a repeat structure of around 22-23 triplets encoding for glutamine (CAG) within the reading frame of the gene encoding the ataxin two protein. Studies have shown that harbouring more than 40 repeats causes spinocerebellar ataxia type 2 (SCA2). Recently, it was discovered that intermediate-length repeat expansions (27-33 repeats) in *ATXN2* are significantly associated with the risk of ALS. The aim of this study is to genotype the *ATXN2* gene in a cohort of controls and patients from the Irish ALS bank in order to assess the association between this genotype and ALS. The most common alleles in this cohort were 22, 23, and 27 repeats, at frequencies (cases and control combined) of 87.0%, 8.3% and 1.9%. Trinucleotide repeat counts ≥27, ≥29 and ≥30 for the larger allele were significantly associated with ALS ($p < 3.6\times10^{-3}$, corresponding to $\alpha = 0.05$) and the odds ratio for ALS in the established ALS risk range was 1.90 (95% CI 1.03-3.51). This study further exemplifies the correlation between this gene and ALS in the Irish population, contributing to the research of causative genes for this devastating disease. Currently, our research is assessing the length of repeat expansions in other ataxia-associated genes, including *ATXN1*.

## P24. HOW MANY AT-RISK RELATIVES AVAIL OF HUNTINGTON'S DISEASE TESTING?

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Introduction: Huntington's disease (HD) is a progressive, incurable, autosomal dominant, neurodegenerative disease. Genetic testing for HD has been available in the Department of Clinical Genetics since 1995. This clinic employs the gold-standard multistep approach to genetic testing, involving pre-test counselling, two blood draws and psychiatric review, allowing patients time to consider the consequences of testing and to withdraw at any time.

Aims: To establish the uptake of predictive testing among first-degree relatives of patients diagnosed with HD.

Methods: Families with at least one relative referred for genetic counselling between 2014 and 2016 were identified from a prospectively maintained departmental database. Familial pedigrees were analysed to identify at-risk relatives. Data was collected by retrospective chart review regarding number of first-degree relatives of the family proband attending clinical genetics for predictive testing, number who completed testing, diagnostic yield and patient demographics.

Results: 241 asymptomatic adult first-degree relatives of the proband in 35 families were identified. 125 of these were children of the proband and 106 were siblings. 41 (17.4%) self-referred for predictive testing and 26 (10.8%) completed testing (9 positive; 17 negative). The median age for those seeking genetic testing was 36y (23-69). Patients completing testing were younger than those

withdrawing from process (median 35 (23-55)-vs-40 (33-69y)).

Conclusion: Uptake of genetic testing among relatives of patients affected by HD is currently low, in-keeping with rates reported in international literature. However, this may change in time with increasing advent of therapy. Decision-making in an incurable disorder is complex and may explain this low figure.

## P25. DOWN'S SYNDROME, OBSERVING THE SHIFT IN ACADEMIC FOCUS.

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Introduction: Over recent decades the life expectancy of those with Down Syndrome (DS) has increased dramatically. Much of this improvement can been attributed to early intervention, and the research which supports these interventions. Despite medical advancements, individuals with DS still have a greater mortality and morbidity compared with individuals from the general population and those with other forms of intellectual disability. Demonstrably there is a need for ongoing research to improve the quality and duration of life for those with DS. In modern academia there have been significant developments in the prenatal diagnosis of DS (e.g. Non-Invasive Prenatal Testing). Some of these developments have been met with controversy from members the DS community.

Methods: A structured PubMed search was performed utilising comprehensive terms to identify publications focusing on DS, childhood and the prenatal period. This was compared to the total number of publications available on PubMed per year (1990-2017).

Results: Since 1990, there are has been a general increase in the number of publications focusing on DS. However, the proportion of publications focusing on DS, compared to total PubMed publications, has decreased. Among those publications focusing on DS there has been a decline in the proportion of studies focusing on childhood and a proportionate increase in those focusing on the prenatal period.

Conclusion: The results of this preliminary review of the literature suggest a general decline in the proportion of academic publications focusing on DS and a shift in focus away from childhood and towards prenatal studies

## P26. PHENOTYPIC DELINEATION OF A 12Q21 DELETION SYNDROME

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Introduction: Interstitial deletions of 12q are rare with around 6 cases including 12q21 deletions described in the literature. We identified a male infant with 12q21.1-q21.33 deletion with phenotypic features including wide sandal gap and longitudinal plantar creases, short upturned nose, low set ears, feeding difficulties and delayed development.

Methods: Array-CGH using the Agilent (ISCA*v2) 8x60K oligo array (genome assembly Build GRCh37 )was undertaken on a chorionic villus sample at 13 weeks gestation due to raised nuchal translucency, and confirmed on venous blood after birth. A comparison of a-CGH microarray profiles was undertaken on the existing described cases.

Results: Array-CGH confirmed a ~16Mb deletion containing nine OMIMMorbid genes ALX1 (OMIM *601527), BBS10 (OMIM *610148), CEP290 (OMIM *610142), DUSP6 (OMIM *602748), KITLG (OMIM *184745), MYF6 (OMIM *159991), OTOGL (OMIM *614925), PTPRQ (OMIM *603317) and TMTC3 (OMIM *617218). Using overlapping features of different 12q21 cases allowed microarray profiles to confirm a common deletion region including a non-morbid gene LIN7A. Its role encodes a scaffold protein within the CASK pathway which is important in synaptic function and is a possible responsible gene for the intellectual disability and cortical development present in all described cases. Parental a-CGH was normal confirming our case is de-novo.

Conclusion: We delineate a 12q21 deletion syndrome with characteristic phenotypic features. LIN7A is a consistent deleted gene in this region and may be responsible for the intellectual disability due to cortical maldevelopment in this syndrome.

## P27. DO NOT MISS TRISOMY 18 IN BILATERAL RADIAL RAY ANOMALIES

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Trisomy 18 (T18) is a relatively common chromosomal disorder with a prenatal prevalence of ~1/2,500. Features associated with T18 include congenital heart defects (CHD), microcephaly, over-riding fingers and rocker bottom feet. Radial ray anomalies (RRA) occur in ~ 1/10,000 pregnancies. RRA are associated with prenatal teratogen exposure, abnormal glycaemic control in pregnant women and syndromic disorders. To date there are few reported cases of T18 and bilateral RRA in the literature.

We describe two cases of T18 with bilateral RRA:

Case A: Male infant who passed shortly after delivery at 31 weeks gestation to 37 year old mother with a history of Crohn's disease. PM identified CHD, significant growth restriction, overlapping fingers, bilateral talipes equinovarus and bi-lateral absent radii and thumbs.

Case B: Male infant born at 16+4 weeks gestation to a 44 year old mother. PM examination identified significant growth restriction, an omphalocele, absent left radius, dysplastic right radius and absent thumbs, among other anomalies.

For Case A and B karyotype and FISH analysis performed at post mortem confirmed T18. In both cases the diagnosis of T18 was not made antenatally.

Here we discuss the importance of antenatal assessment which combines the use of ultrasound, clinical, genetic, cytogenetic and molecular testing in order to obtain the correct diagnosis from a wide spectrum of differentials. Foetal karyotype analysis should be considered in cases of RRA, especially if other malformations are detected. Cases with bilateral lesions have a significantly higher association with aneuploidy, in particular T18.

## P28. TRIAGE IN A CLINICAL GENETICS SETTING - INVESTIGATING CONSISTENCY WITHIN AND BETWEEN UNITS.

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Background: Clinical Genetics services provide a diagnostic, counselling and genetic testing service for children and adults

affected by, or at risk of, a genetic condition, most of which are rare, or genetically heterogeneous. Appropriate triage of referrals is crucial to ensure the most urgent referrals are seen as quickly as possible, without negatively impacting the waiting times of less urgent cases.

Aim: To examine triage practice in 6 Clinical Genetic centres across the UK and Ireland.

Method: Thirteen simulated referrals were drafted based on common referrals to Clinical Genetics. Copies of each referral were forwarded to each centre, where 10 nominated clinicians were asked to triage each referral. Triaged referrals were returned to the coordinating author for analysis. An electronic questionnaire was contemporaneously completed by clinical leads in each unit to gather local demographic details and local operating procedures relevant to triage.

Results: Widespread inconsistencies were noted both within and between units, with respect to acceptance of referrals to services, prioritisation, and designated clinic type. Referral rates, staffing levels, and waiting lists varied widely between units.

Conclusion: Inconsistencies observed between units are likely influenced by a number of factors including; staffing levels, referral rates, and average family size. Inconsistency within units likely reflects the complex nature of many Clinical Genetic referrals and triage guidelines should help improve decision making in this setting.

## P29. LOSS-OF-FUNCTION AND MISSENSE VARIANTS IDENTIFIED IN A WEST OF IRELAND BREAST CANCER POPULATION

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Ireland's breast cancer(BC) incidence is 122.6/100,000. 3% of BCs are attributed to variants in *BRCA1*/*BRCA2*. Knowledge of pathogenic variants drastically changes the risk management of patients. Variants in other genes(*CHEK2*, *ATM*) confer moderate-risk; up to 50% of inherited BC risk is unexplained. Analysing multiple genes in a cost-effective manner is possible through next-generation sequencing(NGS).

We aimed to identify variants contributing to Irish BC susceptibility using NGS.

A custom gene-panel was designed; genes were primarily selected from clinical panels (BC, BC and ovarian cancer, broad cancer) and candidate genes identified through GWAS. Captured libraries from 90 BCs and 77 controls were sequenced using Illumina's NextSeq. Variant calling was performed following GATK best practices. Following variant annotation (VEP, ANNOVAR, SnpEff), loss-of-function(LOF) and missense variants were analysed. Missense deleteriousness prediction scores were obtained from five sources. Clinvar reports were considered. Frequencies were obtained from ExAC/gnomAD.

LOF variants were identified in BCs/controls in known BC risk genes *BRCA1, ATM, CHEK2,* and M*SH6*(candidate risk gene). A splice-region LOF variant in *PBRM1* was identified (4 BCs:1 control). 22 novel LOF variants were identified.

Deleteriousness prediction tools unanimously scored 40 missense variants "damaging"; three in *BRCA1, BRCA2, ATM* had opposing Clinvar reports. Rare missense variants were identified in *FANCD2, SFN, ARID1B*. Novel missense variants were identified in genes appearing on clinical panels(*XPC, FANCA)* and reported in GWAS(*PTGS2, NOTH2, CYP1B1)*.

These results demonstrate the challenges of accurately predicting variant pathogenicity, and highlights the need for caution when considering the use of broad panel testing on an unselected population.

## P30. A SEARCH FOR RARE VARIANTS IN A FAMILY-BASED STUDY OF ASD

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Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with a population frequency of ~1 in 88, frequently co-occurring with other psychiatric disorders. While it is accepted that ASD is a highly heritable disorder ($h^2$>0.8), much of the effect of genetic variation on autism remains unclear. A major search is currently underway to seek out the variation underpinning this disorder.

Methods and Results: A family was enrolled comprised of unaffected parents and 4 ASD-affected offspring. DNA was extracted from saliva samples using Perkin Elmer Prepito D cyto kit. All six samples were sequenced using SOPHiA GENETICS Whole Exome Panel covering 26,000 genes, run on HiSeq 4000 (2x250). QC was performed as standard. Data analysis was carried out using SOPHiA DDM. The identification and annotation of variants implicated in ASD will be reported.

Discussion: This study will contribute to the autism genomics field with the most up to date technology in a clinically relevant family based study. The genes identified will add to those already associated with ASD, giving a deeper understanding of the genomics of the disorder. In turn, this genomic understanding will bring a clearer picture of the mechanism of disease, both on an individual level and on a global level. This gives the opportunity to develop personalised therapies and management strategies, improving patient outcomes. Genomics is certain to play a crucial role in the diagnosis and intervention of ASD in the future.

## P31. MITOCHONDRIAL DISEASE IN IRELAND – CHARACTERISATION OF PATIENTS ATTENDING THE NATIONAL CENTRE FOR METABOLIC DISEASE/ADULT METABOLIC SERVICE

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Background: Little is known of the true epidemiological burden or character of mitochondrial disease in Ireland. Yet such information is important for provision/planning of evidence-based health policies/ future services.

Aim of study: 1) to characterise the cohort of patients with mitochondrial disease attending the National Centre for Inherited Metabolic Disease(NCIMD)/Adult Metabolic Service in reference to phenotype (clinical and biochemical), genotype, treatments/ management and outcomes.

Methods: A retrospective study was conducted on all patients attending the NCIMD/Adult Metabolic Service with a diagnosis of mitochondrial disease.

Results: Fifty five patients (33/55 (60%) male and 22/55 (40%) female) have a mitochondrial disease diagnosis. Pathogenic variants were identified in 39/55 (71%), testing pending in 5/55 (9%) and no pathogenic variants were identified in 11/55 (20%).

31/55 (57%) patients have MELAS; 2/55 (4%) have Kearns-Sayre syndrome and 1/55 (2%) have leber hereditary optic neuropathy or pyruvate dehydrogenase deficiency (PDD) deficiency or neuropathy, ataxia and retinitis pigmentosa. 19/55 patients (34%) have another mitochondrial disorder with only 9/19 (47%) having a confirmed genetic diagnosis.

Conclusions: MELAS, due to m.3243A>G, is the most common mitochondrial disorder which is in keeping with international studies.

30% of patients have a mitochondrial diagnosis due an abnormal biochemistry. Mitochondrial disease criteria (Wolf NI *et al*., 2002) will be applied to identify those for further genetic testing.

Low numbers of patients suggest there is a large cohort of mitochondrial patients not yet captured by this clinic.

The study will be expanded to calculate the prevalence of adult mitochondrial disease in the Irish population.

## P32. ATYPICAL CASES OF SILVER RUSSELL SYNDROME AND ITS MOLECULAR CHANGES.

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Abnormal methylation affecting allele-specific expression of the H19, IGF2, KCNQ1 and CDKN1C genes at the 11p15.5 locus are variably associated with congenital disorders of growth including Beckwith Weidemann syndrome (BWS), Silver Russell syndrome (SRS), and isolated lateralizing overgrowth. Methylation defects causing isolated hemi-hypertrophy commonly overlap with those causing BWS.

At the 11p15.5 locus, hypomethylation of the H19 DMR (differentially methylated region) (IC1) on the paternal allele, or hypermethylation of the KCNQ1OT1: TSS – DMR (IC2) on the maternal allele are mechanisms underlying SRS.

We present atypical cases related to SRS methylation abnormalities at the 11p15.5 locus.

Patient 1 is a 2y-old girl with leg-length discrepancy, and asymmetric facies. Relatively small at birth (5lb 4oz), post-natal growth velocity was normal. Patient 2 is a 16y-old boy measuring over 6ft with isolated hemi-hypertrophy. In both cases, hypomethylation at H19 was reported. Patient 3 is a 2y-old boy with history of IUGR, speech delay and short stature. Investigations identified a maternally inherited duplication of KCNQ1OT1: TSS – DMR. His mother inherited the same duplication from her mother, and was mildly affected, with final adult height of 4' 11", without growth hormone treatment, and no issues with development or feeding.

The Netchine-Harbison Clinical Scoring system outlines diagnostic criteria for SRS, including pre- and post-natal growth restriction, feeding issues, and characteristic facies. None of these cases would fulfil these criteria and yet have molecular defects consistent with SRS. A low threshold for investigation of methylation abnormalities should be adopted in cases of short stature or isolated hemi-hypertrophy.

## P33. AN UNUSUAL CASE OF SHOX

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SHOX deficiency is characterised by a clinical spectrum from idiopathic short stature to Leri Weill dyschondroestosis with triad of disproportionate short stature, Madelung deformity and mesomelia. Heterozygous mutations or deletions of the SHOX gene located in terminal Pseudo-Autosomal pairing region (PAR1) of either Yp11.2 or Xp22.33, cause this condition in both sexes. This disorder behaves as an autosomal dominant disorder, (rather than X linked) due to its location within the pseudo-autosomal region.

Case: The proband was seen by clinical geneticist due to a co-incidental paternally inherited chromosome deletion in her son. The proband was noted to be short (143cm, 7cm below 3rd centile) and has shortened and bowed forearms. Analysis by aCGH showed an atypical Xp chromosome deletion of 881kb that included the SHOX gene. (Typical deletion involving SHOX is about 1.5Mb). In addition, she had gain of Yq11.221-q12 chromosomal material, which was inserted onto the distal region of Xp.

She and her elder sister attended paediatric endocrinologist 25 years ago for their short stature. Her sister responded to growth hormone therapy, pre-treatment height (10cm below the 3rd centile) improved to above 3rd centile, height 10cm > than the proband who was not treated. Their parents heights were both <3rd centile. Her father is short (152cm <<3rd centile) and has bowed forearms.

Both sisters are fertile, proband has one child and her sister 5 children despite the presence of significant amount of Yq chromosomal material.

This case illustrates that fertility can be preserved despite the presence of a large amount of Yq chromosomal material.

## P34. MALAN SYNDROME: SHOULD THE PHENOTYPE OF THIS OVERGROWTH SYNDROME INCLUDE AORTIC ROOT DILATATION?

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Malan syndrome, also known as Sotos 2 syndrome as it clinically resembles Sotos syndrome, is a recently described overgrowth syndrome.

It is associated with deletions or mutations affecting the N terminal DNA binding site and dimerization domain (exons 2 and 3) in the Nuclear Factor I type X encoding gene (NFIX) on chromosome 19p13. Other mutations within the donor splice site of exon 6 of NFIX are known to cause the distinct clinical entity Marshall Smith syndrome.

Typical clinical features are tall stature, macrocephaly, craniofacial features such as narrow and long face with high forehead, developmental delay, intellectual disability and behavioural abnormalities such as autistic traits and anxiety. Musculoskeletal abnormalities such as advanced bone age and scoliosis are also well described.

Here we report a case of Malan syndrome with typical and atypical features, thus expanding the known phenotype, who was originally treated and referred as clinically suspected Marfan's syndrome. She presented to the Department of Clinical Genetics at 13 years of age having been referred by her General Paediatrician. She was tall and slim, macrocephaly, with mild intellectual disability who showed a mildly dilated aortic root for which she was prescribed a beta-blocker. Subsequent to genetic and biochemical investigation, a pathogenic mutation was identified in the NFIX gene.

This case emphasises the need to consider NFIX gene analysis in FBN1 negative Marfanoid appearing patients presenting with an atypical history and features such as intellectual disability, joints contractures, and dilated aortic root. Moreover, screening

Malan syndrome patients for aortic root dilatation may help further understanding of the possible involvement in vasculature development of the NFIX gene function.

## P35. RETROSPECTIVE ANALYSIS OF BRCA 1 AND 2 SCREEN OUTCOMES FOR HIGH GRADE SEROUS OVARIAN CARCINOMAS THROUGH THE NORTHERN IRELAND REGIONAL GENETIC SERVICE APRIL 2016 – APRIL 2018.

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Guidelines published by the Institute of cancer research (2013) and NICE (2017) recommend testing all women diagnosed with high grade serous ovarian carcinoma (HGSOC) for germline pathogenic variants in the BRCA1 and BRCA2 genes. It is predicted that using these guidelines that 10% of cases in this cohort harbour a pathogenic variant. We have carried out a retrospective study on 2years of data (April 2016-March 2018) from genetic screening of BRCA1 and BRCA2 genes on HGSOC patients. The aim of this audit was to establish the number and incidence of germline BRCA1 and BRCA2 pathogenic variants identified within this cohort in Northern Ireland and to explore the contributing factors to these results.

During this period, 155 women with ovarian cancer were screened for germline mutations in the BRCA1 and BRCA2 genes by fluorescent sequence analysis of the coding sequence and associated splice sites and screening for whole exon deletion/duplication variants. The clinical details and family history of these patients were reviewed in light of existing screening guidelines and amendments to local testing protocols considered.

## P36. IRISH ASSOCIATION OF GENETIC COUNSELLORS (IAGC) – SETTING UP A PROFESSIONAL BODY AND WORKING TOWARDS REGULATION.

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The rapidly emerging field of Genomics promises improved diagnosis and personalised medicine at the front line of patient care. Genetic counsellors (GCs) bring essential skills and knowledge for delivering genomic information to patients and in education of healthcare professionals. In the Republic of Ireland there are 13 Genetic Counsellors (GC) working across different hospital sites with a variety of clinical roles. The majority have attained professional registration through the UK Genetic Counselling Registration Board (GCRB) or the European Board of Medical Genetics (EBMG) and/or an MSc in Genetic Counselling. The number of GCs falls significantly below recommendations for the Irish population as compared to other European countries.

We are in the process of setting up a professional body called the Irish Association of Genetic Counsellors (IAGC) to represent the profession in Ireland. To achieve this two working groups have been established:

Professional body: this working group has developed a constitution detailing membership, council roles and setting out the aims for the organisation - advocating for the profession, development of CPD opportunities and education of allied health professionals.

Regulation: Given the significant implications associated with mishandling of genomic information this working group will aim to achieve consideration for the statutory regulation of the Genetic Counselling profession. Initial steps include direct approach to CORU - Ireland's health and social care professional regulator. Our goal is to promote high standards of professional conduct, education, training and competency in the Genetic Counselling profession.

## P37. MANAGING THE EXPECTATIONS: RETROSPECTIVE ANALYSIS OF GERMLINE MLH1 MUTATION DETECTION RATE FOR ISOLATED LOSS OF MLH1 PROTEIN EXPRESSION ON TUMOUR TISSUE

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Immunohistochemistry (IHC) performed on tumour tissue to detect loss of mis-match repair (MMR) protein expression is used to screen individuals at risk of Lynch Syndrome (HNPCC). Germline mutation analysis for HNPCC is guided by loss of expression of MMR proteins on IHC and it has been local practice to arrange MLH1 mutation analysis for isolated loss of MLH1/PMS2 protein expression for all cases without testing the tumour tissue for BRAF or promoter hypermethylation as recommended by NICE guidelines due to lack of access to BRAF/promoter hypermethylation testing locally. Presence of BRAF and/or presence of methylation of MLH1 promoter region suggest sporadic cancer and therefore molecular testing for HNPCC is not indicated in these cases. It is likely that sporadic bowel cancer is being tested for HNPCC based on IHC results alone as per existing practice. This audit would help us to quantify the issue and will help us in creating a testing pathway incorporating BRAF/ promoter hypermethylation testing for better diagnostic yield. This would avoid unnecessary genetic testing and would be a cost saving measure for the service helping us to utilize our resources efficiently

## P38. NAIL-PATELLA SYNDROME PRESENTING WITH PURE RENAL PHENOTYPE: CASE REPORT OF A FAMILY WITH AUTOSOMAL DOMINANT *LMX1B*-ASSOCIATED NEPHROPATHY.

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Mutations in the *LMX1B* gene cause nail-patella syndrome, a rare autosomal dominant disorder which is characterized by abnormalities of the nails, knees, elbows, and pelvis. The features of nail-patella syndrome vary in severity between affected individuals, even among members of the same family. Other areas of the body that can be affected in this condition are eyes (glaucoma) and kidneys where progressive disease can cause renal failure.

The *LMX1B* gene provides instructions for producing a protein that binds to specific regions of DNA and regulates the activity of other genes. On the basis of this role, the *LMX1B* protein is called a transcription factor. The *LMX1B* protein appears to be particularly important during early embryonic development of the limbs, kidneys, and eyes. Mutations in the *LMX1B* gene lead to the production of an abnormally short, nonfunctional protein or affect the protein's ability to bind to DNA. It is unclear how mutations in the *LMX1B* gene lead to the signs and symptoms of nail-patella syndrome.

We describe a family with significant history of kidney failure and no systemic manifestations of nail-patella syndrome

Molecular studies identified a pathogenic variant in one allele of *LMX1B* c.737G>A missense p.Arg246Gln predicted to result in an arginine to glutamine substitution at amino acid position 246. This variant has been described previously in multiple unrelated families who presented with autosomal dominant nephropathy without nail

and patellar abnormalities, which suggest this variant mutation is phenotype specific.

This case reports adds to a growing evidence of *LMX1B*-associated nephropathy without nail and skeletal manifestations seen in classical nail-patella syndrome.

## P39. RETROSPECTIVE ANALYSIS OF BRCA 1 AND 2 SCREEN OUTCOMES FOR TRIPLE NEGATIVE BREAST CANCERS THROUGH THE NORTHERN IRELAND REGIONAL GENETIC SERVICE APRIL 2016 – APRIL 2018.

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ICR guidelines recommended testing all women diagnosed with triple negative breast cancer (i.e. negative for the oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)) under 50 years old should be offered genetic testing for BRCA 1 and 2 pathogenic mutations. It was predicted that testing in this population should identify pathogenic mutations in around 10% of this cohort. This retrospective study will analyse 2 years (April 2016 – March 2018) of BRCA 1 and 2 testing in women diagnosed with triple negative breast cancer under 50 years of age. The main aim would be to find out if BRCA 1 and 2 mutations are accurately represented for our population and to explore the contributing factors to these results. For example, establish true pathology of the triple negative referrals tested and the strength of the family history of cancer in these cases. The hope is to identify whether tighter departmental guidelines for testing and developing a testing criteria proforma for mainstreaming could be beneficial for better mutation pick up rate.

## P40. NEXT GENERATION SEQUENCING TO CHARACTERIZE THE GENETICS OF POLYCYSTIC KIDNEY DISEASE

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Background: Polycystic kidney disease, the most common inherited renal disease, is characterized by renal cysts and progressive reduction in kidney function. Although it is well established that autosomal dominant (ADPKD) is primarily caused by mutations in *PKD1* and *PKD2*, sequencing of *PKD1* is difficult due to multiple pseudogenes. Further, there is considerable unexplained variance in the age-of-onset of PKD even within families.

Aims: Firstly, to apply NGS technologies for the molecular diagnosis of ADPKD. Secondly, to identify, using genomic and clinical data, large PKD 'super-families' to facilitate investigation of genetic modifiers of age-of-onset.

Methods**:** NGS sequencing was performed using a custom Roche NimbleGen SeqCap targeted panel on the Illumina platform. Bioinformatics was performed using a custom, in-house pipeline based on GATK best practices. Copy number variants were identified from NGS data. Whole exome sequencing was performed on selected families using Roche NimbleGen library preparation. Pathogenicity was assigned to variants using ACMG pathogenicity guidelines.

Results**:** 73 ADPKD patients were sequenced and a molecular diagnosis was obtained in 63% (41/73) indicating that NGS technologies were successful for variant identification in difficult to sequence *PKD1* regions. We identified five pairs of individuals recorded as unrelated who shared rare *PKD1* variants and have inflated genomic relatedness (IBD) scores.

Conclusions: NGS with specific capture methods is suitable for the sequencing of renal disease genes including *PKD1*. We identified one large ADPKD pedigree chart using genomic data for the generation of Irish ADPKD 'super-families'. Sequencing of additional ADPKD patients (underway) will facilitate expansion of 'super-families' concept.

## P41. FUNCTIONAL GENOMIC SCREENING IDENTIFIES USP11 AS A NOVEL REGULATOR OF ERA TRANSCRIPTION IN BREAST CANCER

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Approximately 80% of breast cancers overexpress the estrogen receptor α (ERα) and depend on this key transcriptional regulator for growth. The discovery of novel mechanisms controlling ERα function represents major advances in our understanding of breast cancer progression and potentially offers new therapeutic opportunities. Here, we investigated the role of deubiquitinating enzymes (DUBs), which remove ubiquitin moieties from proteins, in regulating ERα in breast cancer.

We performed an RNAi loss-of-function screen using a library of shRNA vectors targeting all 108 known or putative human DUB genes. Suppression of a number of DUBs repressed or enhanced the activity of an estrogen-response-element (ERE) luciferase reporter. Interestingly, suppression of the BRCA2-associated DUB, USP11, was found to downregulate ERα transcriptional activity.

Subsequent validation using two individual siRNAs targeted to USP11 revealed a reduction in expression of endogenous ERα target genes in ZR-75-1 cells, as quantified using qRT-PCR. Estradiol (E2) stimulation enhanced USP11 expression in the cell nucleus, while proteomic analysis by mass spectrometry revealed a significant change to the proteome in USP11 knockdown cells in the presence of E2 only. Furthermore, USP11 expression was found to be upregulated in LCC1 breast cancer cells when compared to other cell lines. RNA-seq in LCC1 USP11 knockdown revealed a downregulation of several putative ERα target genes and many cell cycle-associated genes.

To support the prognostic relevance of USP11, immunohistochemical staining of a breast cancer tissue microarray (103 ERα+ patients) was performed. Kaplan-Meier analysis of this cohort revealed a significant association between high USP11 expression and poor overall (p=0.030) and breast cancer-specific survival (p=0.041).

These results suggest a role for USP11 in ERα transcriptional activity and identify USP11 as a potential therapeutic target in ERα+ breast cancer.