Spoken Presentations:

OP01

Deletion of a prodegenerative gene preserves visual function in a mouse model of retinal degeneration

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Sex differences are seen in several neurodegenerative conditions, including Leber hereditary optic neuropathy, multiple sclerosis and primary angle closure glaucoma. The heterogeneity of these conditions presents a hurdle for the development of gene-specific therapies. However, mechanistic commonalities between conditions indicate key pathways that may, in principle, be targeted using gene-independent strategies. One such pathway features the degeneration of axons in response to injury. Here, we evaluate the modulation of this pathway as a means to preserve the injured optic nerve, RGCs and associated visual function across sexes. We injected rotenone, a complex I inhibitor, intravitreally to mimic the mitochondrial dysfunction and subsequent retinal degeneration seen in Leber hereditary optic neuropathy. We examined optokinetic response measurements in wild type and knockout mice lacking a key gene in this prodegenerative pathway. While both genotypes experienced a reduction in spatial vision following treatment with rotenone, knockout mice treated with rotenone exhibited significantly higher responses than their wild type counterparts. Given the influence of gender on some neurodegenerative conditions, it was of note that this protection was present in both males and females and preserved over time. There was no sex difference within genotypes. Corroborating this preservation of visual function, histological analyses revealed protection of RGC bodies in wholemount retinas. Furthermore, significant preservation of axon density in optic nerves of rotenone-treated knockout mice relative to wild types was obtained.

OP02

Using cellular deconvolution to investigate cell subtype proportions in cortical gene expression data in schizophrenia

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Schizophrenia is a psychiatric disorder that affects 1% of adults and is a major global health problem. Altered gene expression in the brain has been associated with neuropsychiatric disorders. Further analysis of gene expression data to isolate and study predicted cell types could uncover further insights into altered gene expression that contributes to schizophrenia etiology. Cellular deconvolution is used to estimate the proportion of cell subtypes present in bulk expression data. Here, we reanalyzed gene expression data from the PsychENCODE consortium (n=558 schizophrenia cases and 1039 controls; cortical samples) by using new single-cell sequencing data that allowed for an improved cellular deconvolution analysis.

New single cell data for ~30,000 cells was added to the original dataset to give an increased sample of ~62,000 cells. In comparison to the original analysis, we observed alterations in astrocyte proportions between cases and controls, particularly for two distinct astrocyte populations, only one of which had significantly different proportions between cases and controls ($p=<2.2e-16$) with a lower proportion of cells inferred in cases. Oligodendrocytes did not have significantly different proportions between cases and controls ($p=0.588$) as an overall subtype but four distinct subtypes of oligodendrocytes did appear to exhibit differences in proportions ($p<0.05$). Overall, this analysis leveraged new single-cell data to perform a more detailed cellular deconvolution analysis of data from PsychENCODE and identified a number of distinct cell subtypes that differ in proportion between cases and controls. These can be followed up to uncover new insights into the biological functions that influence schizophrenia.

OP03

Rare variant burden influences the rate of disease progression in Polycystic Kidney Disease

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is caused primarily by variants in *PKD1*, and *PKD2.* Disease severity ranges from *in-utero* onset to preserved kidney function into old age. It is well established that the type of diagnostic ADPKD variant can influence disease severity and variants have been identified which modify disease severity or can cause autosomal recessive disease. Here we demonstrate, using robust statistical analyses, that rare variant burden in the gene *PKD1* contributes to ADPKD phenotypic variability.

Methods:Patients (n=449) with an established genetic diagnosis of ADPKD due to a pathogenic variant in *PKD1* or *PKD2* were recruited from five international centres (Dublin Ireland, Genomics England/ Royal Free Hospital London UK, Leipzig Germany, Bologna Spain, Sydney Australia). The association between the presence of rare, additional *PKD1* variants and age at end-stage renal disease (ESRD) was tested using a Cox mixed-effect regression model.

Results:The presence of non-diagnostic, rare, predicted damaging *PKD1* variants was associated with a lower age at ESRD, in patients with an established genetic diagnosis (hazard ratio: 1.62 (1.15-2.29), p=5.2x10^{-3}).

Conclusions:Rare, additional predicted damaging *PKD1* variants impact disease severity in ADPKD. Patients with an additional, rare, predicted damaging *PKD1* variant reached ESRD a median of 3-7 years earlier than those lacking such qualifying variants. These findings have important implications for patient counselling and the assessment of variant pathogenicity in clinical genetics services.

Acknowledgement: This research was made possible through access to the data and findings generated by the 100,000 Genomes Project; http://www.genomicsengland.co.uk.

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OP04

Controlling for background genetic effects using polygenic scores improves the power of genome-wide association studies

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Ongoing increases in the size of human genotype and phenotype collections offer the promise of improved understanding of the genetics of complex diseases. In addition to the biological insights that can be gained from the nature of the variants that contribute to the genetic component of complex trait variability, these data bring forward the prospect of predicting complex traits and the risk of complex genetic diseases from genotype data. Here we show that advances in phenotype prediction can be applied to improve the power of genome-wide association studies. We demonstrate a simple and efficient method to model genetic background effects using polygenic scores derived from SNPs that are not on the same chromosome as the target SNP. Using simulated and real data we found that this can result in a substantial increase in the number of variants passing genome-wide significance thresholds. This increase in power to detect trait-associated variants also translates into an increase in the accuracy with which the resulting polygenic score predicts the phenotype from genotype data. Our results suggest that advances in methods for phenotype prediction can be exploited to improve the control of background genetic effects, leading to more accurate GWAS results and further improvements in phenotype prediction.

OP05

Revealing the recent demographic history of Europe via haplotype sharing in the UK Biobank.

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Haplotype-based analyses have recently been leveraged to interrogate fine-scale structure in specific geographic regions, notably in Europe. An equivalent understanding across the whole of Europe with these tools however is lacking and would provide an updated map of the European genetic landscape. Similarly, a study of Identity-by-Descent (IBD) sharing in a large sample of pan-Europe genotypes would allow both direct comparison between different demographic histories and in parallel identify communities conducive to genetic mapping.

In this context, we sought to investigate the extent of European ancestry captured in the UK Biobank (UKBB), a large genetic dataset with world-wide ancestry. We sampled 4,920 UKBB individuals with a European birthplace and investigated population structure and demographic history in Europe. With one of the largest samples of genotypes from across the geographical extent of Europe we show in parallel the variety of footprints of demographic history in different genetic regions around Europe and expand knowledge of the genetic landscape of the east and south-east of Europe. We highlight novel analysis of island populations such as Malta and the Channel Islands, demonstrating with IBD-segment sharing the extent of population isolation and size. Our work builds and expands upon previous work in Europe and specific populations, highlighting UK Biobank as a source of diverse ancestries beyond Britain. We find novel results in multiple communities in Europe that are of interest to genetic mapping.

OP06

The National Alpha-1 Antitrypsin Deficiency Targeted Detection Programme

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Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder that can cause lung, liver, and rarely skin disease. The most common pathological mutation is Z (Glu366Lys, rs28929474), which is carried by 1 in 25 Irish people (Carroll et al, 2011). Guidelines advocate testing for AATD in COPD, poorly-controlled asthma, cryptogenic liver disease and panniculitis patients, as well as first degree relatives.

Over 21,500 individuals have been screened to date following World Health Organisation and joint American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines in a national targeted detection programme. AAT phenotyping is by isoelectric focusing and AAT quantification is by turbidimetry. Rare and novel mutations are identified by SERPINA1 gene sequencing.

We have identified 404 ZZ, 411 SZ, 122 SS, 4,021 MZ, and over 200 individuals with rare AATD phenotypes (e.g. IZ, FZ, and IS). A number of ultra rare and novel SERPINA1 mutations have also been identified. These include I, F, M_{malton}, $M_{wurzburg}$, and 5 different Null (Q0) mutations, of which 2 were novel (Ferrarotti et al, 2014).

Our results illustrate the high prevalence of AATD in Ireland and the efficacy of targeted detection. Advantages of a diagnosis include increased smoking cessation and family screening. Systematic testing for AATD could help alleviate the burden of COPD which remains the primary cause of hospital admissions during the winter flu season. We strongly advocate that all COPD patients should be tested for AATD, regardless of age or smoking status, as per guidelines.

OP07

Lessons learned about whole genome sequencing from Northern Ireland's participation in the *100,000 Genomes Project.*

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Until recently, clinical molecular diagnostics within the National Health Service for rare and inherited diseases, have utilised targeted gene panels or exome sequencing approaches. These approaches do not necessarily yield a diagnosis for all genetic conditions. Whole Genome Sequencing (WGS) shows potential to increase diagnostic yield and, if integrated into care pathways, could potentially decrease the diagnostic odyssey timeline.

Northern Ireland (NI) recruited 448 rare disease probands to the *100,000 Genomes Project* (100KGP, https://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project/) and to date 1 in 4/1 in 5 participants have received a diagnosis. As part of the 100KGP in NI, we also carried out a translational research workstream. This was a collaborative approach including healthcare professionals, researchers and patients. Outputs will be used to inform how WGS may be integrated into NI healthcare. Areas under consideration included:

1. Comparison of NI diagnostic yield to the wider United Kingdom (UK)
2. How we can improve diagnostic yield
3. Clinical utility of WGS
4. Cost-effectiveness of WGS
5. How we can better integrate WGS into multi-disciplinary healthcare

Key findings included that diagnostic yields and operational process challenges were comparable between NI and the wider UK, yet significant developments are required for WGS implementation (e.g. information technology infrastructure). There is considerable scope to extend research collaborations given adequate resources. Additional investigation of variants of unknown significance, improved phenotyping depth, and extended multiomics may improve diagnostic yield. WGS holds significant promise for the future of NI healthcare although discussions surrounding clinical utility and cost-effectiveness of WGS are ongoing.

OP08

Atypical findings from Non-Invasive Prenatal Testing: a case report.

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Background: Atypical findings from non-invasive prenatal testing (NIPT) can increase anxiety for prospective parents. Obstetricians are often dealing with these time-sensitive results without Clinical Genetics input.

Case report: A 42yr old primiparous woman with an IVF pregnancy underwent NIPT at 11 weeks gestation. Panorama™ test reported low fetal fraction of 2.7%. There were no first trimester ultrasound findings suggestive of aneuploidy. Redraw NIPT was performed and an atypical finding outside the scope of cell free fetal DNA testing was reported. Invasive testing was offered and after considering her options, the patient underwent amniocentesis at 19weeks gestation despite the absence of fetal anatomical concerns.

Partial trisomy 21 was identified on amniocentesis PCR however fetal karyotyping revealed a normal male fetal karyotype, 46 XY. Array CGH revealed a 4.64Mb copy number gain of uncertain clinical significance within the 21q21.1q21.2 region of the long arm of Chromosome 21 (arr[GRCh37] 21q21.1q21.2(19886439_24526668)x3). The patient considered termination of pregnancy, however she was strongly counselled to await parental genotyping.

Paternal genotyping revealed the father to be a phenotypically normal heterozygous carrier of the same copy number gain. A normal male 3.4kg infant was born at 38 weeks gestation.

Discussion: Abnormal NIPT results should always be confirmed by invasive testing. This case highlights the importance of obtaining a full genetic profile of a fetus before acting on results. Obstetricians are often interpreting complex prenatal genomic results in the absence of Clinical Genetics expertise. Ireland's shortfall in Clinical Genetics services impacts pregnant women acutely.

OP09

The utility of an inherited kidney disease clinic employing a broad range of genomic testing platforms: Experience of the Irish Kidney Gene Project

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Introduction: Inherited kidney diseases (IKD) are increasingly identified in adult patients. Here we attempted to identify disease-causing variants and to assess the impact of the IKD clinic (IKDC) from diagnostic and clinical perspectives utilising various technologies (exome sequencing, comprehensive gene-panel, and *MUC-1* sequencing) and immunostaining. **Methods:** We undertook a prospective cohort study of adult patients referred to an academic medical centre with suspected IKD as part of the Irish Kidney Gene Project (IKGP). Patients with chronic kidney disease (CKD) with suspected IKD, family history of CKD, extrarenal features, or CKD of ''unknown cause'' (uCKD) were recruited from various Irish centres.**Results:** Over seven years, genetic testing was performed for 677 adults. We achieved a molecular diagnostic rate of 56.7 %. Among the identified disease-causing variants, PKD was the largest cohort (n= 183, 47.8% for *PKD1* and *PKD2*), while mutations in three other causative genes were most prevalent among the remaining identified 42 genes; *MUC-1* (8.1%); *COL4A5* (7.8%); *UMOD* (3.3%). In 167 disease-causing variants, excluding PKD, the clinical diagnosis was confirmed in 60.5% and 18% of cases were reclassified. A molecular diagnosis was established in 27 (36.5%) patients with uCKD. Based on the genomic testing, a diagnostic kidney biopsy was unnecessary in 13 (7.7%) patients, 80 (47.3%) had their treatment plan altered and a further 76 (45%) patients had appropriate cascade testing.**Conclusions:** The IKDC is a valuable resource and the implementation of a broad range of diagnostic platforms has a direct clinical and therapeutic impact on treatment of CKD patients.

OP10

Reflections on developments from our Northern Ireland Rare Disease Implementation Plan 2015-2020: helping patients get a final diagnosis and optimised care faster

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Rare diseases are a major public health concern, cumulatively affecting ~6% of the population. In 2015 the Northern Ireland rare disease implementation plan (NIRDIP)[1] was published, describing 51 commitments. Key developments for molecular services included:

- The NI Genomic Medicine Centre was funded to facilitate people from NI participating in the 100,000 genomes project (https://tinyurl.com/UK100KGP), gaining whole genome sequencing and improved diagnostic yield.
- Local bioinformatics architecture was developed - GenOCEANIC (Genomics Open Core Engine for Accelerating Northern Ireland Care), with patient experience measures and views from participating healthcare professionals supporting the development of genomic medicine for NI.
- Access to highly specialised treatments has been facilitated for multiple patients with specific molecular diagnoses.
- The development of ENCOMPASS introducing a digital integrated care record for Northern Ireland has significant potential to improve rare disease patient care, with customised training for data coding and input of phenotypic information critical to maximise diagnoses.
- An evolving programme of local workforce development, including CPD accredited events, helps health and social care professionals use genomics and bioinformatics.

- Harmonised rare disease molecular teaching in Queen's University Belfast and Ulster University includes patient voice sessions.

The legacy from our NIRDIP includes the foundation of an All-Ireland Rare Disease Research Network. A knowledge exchange workshop was held in 2020 with multidisciplinary stakeholders to help prioritise recommendations for rare disease progress across NI.

[1] Department of Health, Social Services and Public Safety. Providing high quality care for people affected by rare diseases – the Northern Ireland implementation plan for rare diseases. https://www.health-ni.gov.uk/sites/default/files/publications/dhssps/ni-rare-diseases-implementation-plan-oct-2015.pdf.

Poster Presentations:

P01

Title: Comparison of feature selection methodologies and learning algorithms in the development of a DNA methylation-based telomere length estimator.

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Telomeres are TTAGGG repeats located at the end of chromosomes that maintain DNA stability. Telomere length (TL) has been widely implicated as a marker of biological age, and is associated with several human diseases, including depression, cardiovascular disease and cancer. Previously, scientists identified 7 genetic determinants of TL, providing novel biological insights into TL and its relationship with disease. However, identifying genetic determinants of TL was only the first step, and a second layer of information (the epigenome) provides an additional source of information for estimating TL. The primary aim of this study is to use machine learning methods to train a DNA methylation predictor of TL using large-scale epigenomic profiling data. As feature selection is a critical aspect of handling high-dimensionality DNA methylation data, a range of promising techniques were identified by review of the literature on DNA methylation-based studies such as biological age estimation and cancer classification.

Elastic net is heavily utilised for development of epigenetic aging signatures, with approaches based on F-tests with false discovery rate, Pearson's correlation, variance, and embedded methods being used to reduce dimensions and select the most predictive CpG sites. Using a large cohort (n=1615), we compared models via nested cross-validation, finding the F-test and Pearson thresholded filter methods to have significantly lower MAE than the variance-based methods. A Pearson correlation filter with support vector regression returned the lowest MAE, although the difference was not shown to be significantly different when compared with the best elastic net and random forest models.

P02

A Mendelian randomisation study of the causal association between chronotype and neuropsychiatric disorders.

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Disruption of circadian rhythm is a common feature in many neuropsychiatric disorders including autism and schizophrenia. Chronotype, an individual's synchronisation to the 24 hour day, is commonly used as a proxy for circadian rhythm disruption. Being a morning person, someone who prefers waking and going to bed earlier, is genetically correlated with increased well-being and decreased risk of neuropsychiatric disorders. We performed a two-sample Mendelian randomisation (MR) study to determine the effect of chronotype on risk of six neuropsychiatric disorders. We used 351 independent genome-wide significance loci ($p < 5e-18$) from a genome-wide association study (GWAS) of chronotype in 697,828 European individuals as genetic instruments. Summary-level GWAS data was obtained for the six neuropsychiatric disorders from the largest available studies to date. Results from inverse-variance weighted MR indicated a causal relationship between the morning chronotype and lower risk of autism spectrum disorder (OR = 0.88, 95% CI 0.81, 0.94, IVW p = 0.0004), major depressive disorder (OR = 0.95, 95% CI 0.9, 0.99, IVW p = 0.03) and schizophrenia (OR = 0.9, 95% CI 0.83, 0.96, IVW p = 0.002). Sensitivity tests found no evidence for the presence of horizontal pleiotropy. Further research will be performed to correct for bias due to weak instruments and sample overlap. This study gives further evidence for the role of circadian rhythm disruption in neuropsychiatric disorders. Establishing its causal role can demonstrate the potential for circadian misalignment as a new modifiable risk factor that could be targeted for treatment of neuropsychiatric disorders.

P03

snpQT, an easy-to-use automatic software tool for comprehensive genomic quality control, imputation and association analysis: application to Amyotrophic Lateral Sclerosis

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The rapidly increasing availability of genomic data for association studies (GWAS) highlights the need for standardized, transparent, and comprehensive genomic quality control pipelines to obtain reproducible and reliable results. We present snpQT; a scalable, automatic pipeline using Nextflow and BioContainers, which offers reproducible and interactive quality control and imputation pipelines for genomic data. The implemented workflows can be flexibly combined and tailored to the user's preferences including a large variety of user-modifiable automatic thresholds for sample and variant QC, population stratification, pre-imputation and post-imputation QC, local imputation and finally GWAS analyses. Results are organized into comprehensive .html and .txt reports for easy inspection and better data

exploration. snpQT is a user-friendly software tool demanding only minimal coding experience, automatically installing dependent software as well as setting up a local database for reference and auxiliary files. We apply snpQT to a genomic cohort of 1,000 Amyotrophic Lateral Sclerosis (ALS) patients and 1,000 healthy controls, to highlight the features and the performance of the software. ALS is a progressively fatal disease and the most common late-onset motor neuron disorder, in which the molecular basis of motor neuron death is unclear. In the future, we plan to use snpQT as the main QC and GWAS software in a large ALS/Control cohort of 23,246 samples aimed at exploring the mechanisms of ALS pathology towards effective prognosis and treatment. Code and installation and usage guides for snpQT can be found at:

https://github.com/nebfield/snpQT and https://snpqt.readthedocs.io/en/latest/.

P04

Feasibility study into reliable copy-number variant detection from targeted panel-based sequence data in a clinical laboratory.

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Background: Copy number variants (CNVs) are a type of structural variant (SV) in which large sections of genomic DNA (>1kb) are duplicated/deleted. CNVs are important to population diversity, and have been associated with many genetic disorders. Their clinical relevance underlines the importance of accurate CNV identification in a diagnostic setting. Although next generation sequencing (NGS) technology has revolutionised genetic testing, reliable CNV detection from NGS data remains a challenge. Most CNV detection algorithms infer copy number alteration from changes in target read depth, which for panel-based sequencing is known to be highly variable and influenced by several factors (e.g. batch effect, local GC content, sequence repetition). Consequently, clinical labs have been slow to incorporate an NGS-based approach, favouring more traditional technologies such as array comparative genomic hybridisation (array CGH).

Objectives: The aim of the project is to investigate the feasibility of reliably identifying CNVs within individual samples sequenced at the MMUH NGS Laboratory. The panel-based assay offered by the MMUH targets ~17.5Mb of the genome, covering ~6100 genes with known clinical relevance. The assay was designed for the detection of SNVs and small indels. Samples are typically unmatched, with no corresponding “normal” sample. Consequently, the set of other samples processed on the same sequencing run will be utilised instead as background. The project will assess several computational tools developed for this purpose, to determine their potential suitability as part of a diagnostic workflow. These tools will be benchmarked against publicly available reference datasets, and applied to in-house clinical datasets.

P05

Investigating the role of miR-182 in epithelial-mesenchymal transition in prostate cancer

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Introduction: miR-182 had been suggested to contribute to prostate cancer (PCa) progression in previous studies. It correlates with Gleason grades and prostate-specific antigen levels for PCa grading and diagnosis. In PCa, epithelial-mesenchymal transition (EMT) is a key process for disease progression. A previous *in vitro* study demonstrated dual roles of miR-182 in EMT. However, the exact genes and pathways involved remain unclear. Therefore, this project aims to investigate this *in vitro* and *in silico*.

Methods: miR-182 expression was compared between PCa cells (PC3, 22RV1 and DU145) and normal prostate cells (RWPE-1) by RT-qPCR. miR-182 expression was also profiled in clinical datasets using miR-TV and its functional network was visualised in miRNet. EMT-related target genes were identified from miRTarBase, dbEMT and Regulome Explorer. Correlation with miR-182, expression and clinical significance of the selected genes were investigated.

Results: In vitro tests showed elevated miR-182 expressions in PCa cells compared to normal cells. This was backed up by online clinical dataset analysis (tumour vs normal, $p<0.001$). Visualisation of KEGG network showed significant functional association of miR-182 with PCa ($p<0.001$). Bioinformatics analysis identified SNAI2, MITF and FOXO1 as EMT-related putative target genes (negative correlations, $p<0.001$) that were downregulated in tumour. Low FOXO1 expression was significantly associated with poor prognosis (log-rank $p=0.022$).

Conclusion: Results suggested that miR-182 is a worthy candidate for further investigation in PCa. To improve our understanding of PCa pathology and explore clinical utility, further research is required to elucidate its roles in EMT by validating the interactions with identified target genes.

P06

Social isolation induces transcriptomic changes in female mouse hippocampus

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Early life stress is among the known environmental risk factors for neurodevelopmental disorders such as schizophrenia. Social isolation (SI) is used to model early life stress in animal models by depriving animals of crucial social interactions at vulnerable periods of neurodevelopment. Using RNA-seq, we investigated brain gene expression changes in the SI model. Paired-end sequencing was performed on RNA extracted from the hippocampus of group-housed (n=4) and post-weaning socially-isolated (n=5)

adult female C57BL/6J mice. Differential expression analysis was performed on reads and gene ontology (GO) analysis was performed on sets of differentially-expressed genes (DEGs) with absolute fold change > 1.2 meeting thresholds of FDR < 0.1 and FDR < 0.01. Differential expression analysis revealed 104 DEGs between SI and group-housed animals. Nine DEGs had an adjusted p-value < 0.01: Inppl1, Tbc1d24, Gm20517, Dusp11, Vps33b, Cmtr1, Kntc1, Vmn1r90 and Ccdc120. The full DEG set showed enrichments in cellular compartments including nucleoplasm, cytoskeleton, plasma membrane and cell projections. DEGs meeting FDR < 0.01 showed enrichments in axonal compartments as well as enriched molecular functions incorporating phosphatase activity and catalytic activity acting on RNA. Using RNA-seq, we have gained insight into some of the underlying molecular changes in the brain as a result of SI. GO analysis highlights altered axonal compartments in the most significantly dysregulated DEGs through exposure to SI. Among the most significant DEGs, Tbc1d24 plays a role in axon outgrowth and vesicle transport in neurons. Results suggests that changes in connectivity and signalling in neurons may be induced by SI.

P07 Withdrawn

P08

A co-segregation analysis of ultra-rare variants in families multiply affected by schizophrenia using whole genome sequencing

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Schizophrenia is a highly heritable mental disorder which results in significant co-morbidities and has a lifetime prevalence of ~1% in the general population. Previous genomic work has focused on common DNA variants and rare copy number variants, but the availability of next-generation sequencing has led to a renewed interest in examining rare single nucleotide variants. Recently, the Schizophrenia Exome Sequencing Meta-analysis (SCHEMA) consortium showed a significant enrichment of ultra-rare protein-truncating variants and deleterious missense variants in schizophrenia cases. Family-based studies offer a unique opportunity to evaluate rare variants, since multiplex pedigrees are more likely to be influenced by the same collection of variants than an unrelated cohort.

Here we examine whole genome sequencing data from 41 individuals across seven pedigrees multiply affected by schizophrenia. We applied a rigorous filtering approach to search for ultra-rare, protein-coding variants present in affected individuals in these pedigrees. While no fully co-segregating variants were found, we identified three deleterious missense SNVs in three genes (*ATP2B2*, *SLC25A28*, and *GSK3A*) with a reduced co-segregation pattern. The most compelling evidence was for *ATP2B2*, which is involved in intracellular calcium homeostasis. In the SCHEMA analysis, this gene shows highly suggestive evidence for deleterious missense variants in schizophrenia cases (p=0.000072). *ATP2B2* is expressed in multiple brain tissue types and is predicted to be intolerant to loss-of-function and missense variants. While this work represents an exploratory analysis, we have identified variants likely increasing risk for schizophrenia in three of the seven pedigrees.

P09

Characterization of lncRNA *PSG8-AS1* in brain and cancer

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The lncRNA Pregnancy Specific Glycoprotein 8 Antisense 1 (PSG8-AS1) maps to the human PSG segmental duplication at 19q13 and is predominantly expressed in the brain. Downregulation of lncRNA PSG8-AS1 has been observed in low-grade gliomas (LGG) and glioblastomas (GBM). However, its role in the brain and cancer has not been evaluated. We examined RNA-seq and clinical data from TCGA and the Chinese Glioma Genome Atlas (CGGA) to elucidate the potential genes regulated by PSG8-AS1. High expression of cell adhesion and oligodendrocyte marker genes was associated with high PSG8-AS1 expression in LGG tumors and correlated with better survival in IDH-mutated, 1p/19q co-deleted gliomas (oligodendrogliomas). PSG8-AS1 showed simultaneous expression with myelin synthesis genes in the human brain development dataset from the Allen Brain Atlas. Significant reductions in cell migration, and increased cell adhesion gene expression, have been observed in glioma cell lines in the lab (U87, A172, Hs683) upon PSG8-AS1 overexpression. These results suggest that the previously uncharacterized lncRNA PSG8-AS1 has a role in brain development or function and that its aberrant expression could affect oligodendrocyte function and oligodendroglioma development.

P10

The Role of Common Genetic Variation in Presumed Monogenic Epilepsies

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Background: The developmental and epileptic encephalopathies (DEEs) are a group of severe epilepsies which co-present with intellectual disability, and occur in people without a family history of epilepsy. DEEs are thought to be monogenic, caused by highly damaging rare mutations. Currently, around 40% of DEEs will screen-positive for an identifiable causative mutation following genetic analysis. Little is known about the genetic architecture of the remaining screen-negative DEEs. We used a method known as polygenic risk scoring(PRS) to test whether common risk factors are relevant to the DEEs.

Methods: Genetic data of 2,759 people with DEE across six studies and 477,760 controls were assembled for analysis. All cases were stratified for the presence of an identifiable deleterious genetic variant. Regression analysis was used to compare PRS for 'all epilepsy', 'focal epilepsy', and 'genetic generalised epilepsy' (GGE) between all cases, stratified cases, and controls. Results were meta-analysed across cohorts.

Results: DEE cases had increased PRS for 'all epilepsy'($p<0.0001$), 'focal epilepsy'($p<0.0001$), and 'GGE'($p<0.0002$) relative to controls. While the PRS of DEEs with and without an identified rare deleterious variant were not significantly different, both groups had increased PRS compared to controls.

Discussion: We provide the first evidence that common risk factors contribute to the development of DEEs. Our results suggest common genetic variation contributes to DEE status irrespective of a highly damaging rare genetic variant. These results are potentially impactful in the field of genetic diagnostics and motivate further research into DEEs as complex, rather than strictly monogenic, disorders.

P11

Identity-by-descent analysis of a large Tourette's syndrome pedigree from Costa Rica implicates genes involved in neuronal development and signal transduction

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Tourette Syndrome (TS) is a poorly understood, substantially heritable neuropsychiatric disorder that typically begins in early childhood. Identifying rare variants that make a significant contribution to risk in affected families may provide important insights into the molecular aetiology of this disabling condition. We report data from a large pedigree (>500 individuals), densely affected by TS and co-morbid psychiatric disorders from a genetically isolated Costa Rican population. The pedigree spans 11 generations and shares ancestry from six founder couples. We have generated whole genome sequencing (WGS) data for 19 individuals from this pedigree and performed an identity-by-descent (IBD) analysis. Using this approach, we identified 11 haplotypes that were: >1Mb in length; shared by at least three affected individuals sharing ancestry from the same founder couple(s); and absent in Costa Rican control samples. Fine-mapping of these haplotypes using the WGS data identified rare (MAF< 0.01) and ultra-rare (MAF< 0.001) coding and non-coding variants in candidate genes. In particular we

have identified a rare deleterious missense variation in *RAPGEF1* and two ultra-rare putatively deleterious intronic variants in *ERBB4* and *IKZF2*. *RAPGEF1* has recently been implicated in a family study of neuropsychiatric symptoms, supported by a zebrafish model of this gene. *ERBB4* participates in many critical functions, such as neurodevelopment and synaptic plasticity, while *IKZF2* is a transcription factor shown to play a role in neuronal development. Together, these variants represent biologically relevant targets for investigation in other pedigree and population-based TS data.

P12

Novel adeno-associated virus serotype delivers robust retinal ganglion cell transduction independent of route of administration.

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Purpose: Loss or dysfunction of retinal ganglion cells (RGCs) is a feature of several ocular disorders, including glaucoma and Leber hereditary optic neuropathy. Efficient targeting of RGCs therefore represents a key step in designing gene therapies for these diseases. However, many AAV serotypes do not efficiently transduce RGCs. In the current study, we explored a novel AAV serotype, which has been demonstrated to transduce various neuronal cell types efficiently, to determine the extent of retinal transduction following intravitreal and systemic delivery.

Methods: The ubiquitous cytomegalvirus (CMV) promoter was used to drive the enhanced green flourescent protein (EGFP) reporter gene, packaged within a recombinant AAV expressing the novel capsid (AAV-X.CMV.EGFP). Four weeks post intravitreal or tail-vein injection in adult wild type 129 mice, tissues were harvested, fixed with 4% paraformaldehye and native EGFP expression evaluated using fluorescence microscopy.

Results: Intravitreal injection resulted in strong RGC transduction with some inner nuclear layer cells also transduced, a similar pattern to that found using intravitreal delivery of AAV2/2. Of note, tail-vein administration resulted in retinal transduction akin to utilising intravitreal delivery. However, this was more evenly distributed, providing pan-retinal expression. Tail-vein administration of the novel capsid did not transduce photoreceptors, yet subretinal delivery demonstrated potent photoreceptor transduction.

Conclusion: This serotype provides a useful addition to the RGC transduction toolbox, demonstrating robust RGC transduction for the first time. Notably, completely even expression and pan retinal delivery was achieved via systemic delivery. Some retinal gene therapies should significantly benefit from these features.

P13

Optimisation of gene delivery by AAV vectors in retinal pigment epithelial (RPE) cell models

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Purpose: In Stargardt Disease reduced ABCA4 activity leads to retinal pigment epithelium (RPE) degeneration, causing irreversible and progressive vision loss. In this study we evaluated efficacies of ubiquitous and RPE-specific promoters to drive AAV-delivered transgene expression and determined the optimal AAV serotype for transduction in RPE cell models, including primary RPE cells.

Methods: Constructs with *EGFP* and ubiquitous CMV or CAG promoters (AAV-CMV.EGFP, AAV-CAG.EGFP) were generated as recombinant AAV-vectors of serotypes 2/2, 2/5 and 2/8 and used to examine transduction efficiencies in RPE cell lines ARPE19 and hTERT-RPE1, and in primary porcine RPE cells. Additionally, a construct encompassing the putative RPE-specific VMD2 promoter (AAV-VMD2.EGFP) was packaged into AAV2/8 for evaluation in primary RPE cells, compared to AAV2/8-CMV.EGFP. Cells were transduced with AAV and fixed with paraformaldehyde. EGFP expression was analysed natively and by immunocytochemistry.

Results: Assays evaluating EGFP expression demonstrated that serotype AAV2/2 transduces ARPE19 and hTERT-RPE1 cells most efficiently. The order of efficacy was AAV2/2>AAV2/8>AAV2/5. This was mirrored in primary porcine RPE cells, where AAV2/5 was ~35x less efficient than AAV2/8, which itself was ~30x lower than AAV2/2. Furthermore, the VMD2-promoter mediated strong EGFP expression, but significantly less than CMV.

Conclusion: Our data demonstrate the most efficient AAV serotypes for transducing various RPE cell models. We also evaluated different promoters for transgene expression and showed robust VMD2-mediated expression, albeit lower than CMV-mediated expression. These results will be used to design and evaluate potential therapeutics in disease models.

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P14

Polygenic Risk Scores for Determining Number at Risk

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What can the distribution of Polygenic Risk Scores (PRS) of a sample of individuals tell us about the risk of common disease across a population?

Common diseases are often polygenic in nature and the accuracy of PRS continues to increase as ever larger Genome Wide Association Studies identify more disease associated SNPs and use increasingly

sophisticated statistical modelling to create the PRS. However, it remains the case that individual's scores are often not accurate enough to be clinically useful.

We compare the ability of existing PRS strategies to accurately stratify individuals into risk categories and then explore scenarios in which individual level PRS are not clinically relevant, but where aggregate PRS statistics are potentially useful. Using cardiovascular disease as a case study, we examine UK Biobank data to estimate the number of individuals at risk of disease using PRS of a sub-sample of the population.

We assess what factors this depends upon, including how representative the samples are of the population, the disease prevalence, heritability, accuracy of the polygenic scores, and population structure. We conduct survival analysis with and without PRS after including traditional risk factors in the model, with the aim of identifying the conditions under which cohort level information is of use in identifying effective early interventions strategies. We validate our findings using out-of-sample performance and cross-validation.

P15

The pleiotropy of ALS: A repeat expansion study

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The most common neurodegenerative repeat expansions (NDREs) diseases are Huntington's Disease (HD), Spinocerebellar Ataxias (SCA), Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS). ALS is a fatal neurodegenerative disorder which causes the 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. Repeat expansions (REs) underlie more than 40 diseases, most of them affecting the nervous system. Several REs are pleiotropic; for example, GGGCC RE in *C9orf72* is associated with FTD/ALS and CAG RE in *ATXN2* causes SCA2/ALS. Previous studies on *ATXN2* showed that harbouring intermediate-length repeat expansions are significantly associated with the risk of ALS. Therefore, pleiotropy might be common in ALS. This study aims to genotype 34 neurodegenerative genes that harbour REs, in a cohort of 1000 controls and 1000 patients from the Irish ALS bank to assess the association between expanded genotypes and ALS. The length measurement of each NDRE gene and its possible repeat expansion was done by PCR, Repeat Primed-PCR (RP-PCR), agarose gel electrophoresis and fragment length capillary electrophoresis (FLA). In an Irish population, ALS might be driven by multiple intermediate-length repeat expansion in likely 8 NDREs genes: *ATXN1*, *ATXN2*, *DIP2B*, *FRA11AC1*, *HTT*, *NUTM2B-AS1*, *PABN1* and *ZNF713*. This study will give a better understanding of ALS mechanisms. ALS is a very complex disease that might be caused by pleiotropy of multiple REs and multiple factors.

P16

Maternal genetic effects in autism spectrum disorder

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Around 2% of children in the world are diagnosed with autism spectrum disorder (ASD) that has a complex biology consisting of both genetic and environmental components. There are findings suggesting that maternal genetic composition affects the development of ASD in offspring. The subject matter is underresearched and the replication of findings is problematic. The aim of this study is to identify potential candidate loci in mothers that might increase the risk of development of ASD in offspring. A case-control genome-wide association study was performed on the SPARK dataset (n = 27,290) that consists of quad, trio and duo families where one or multiple individuals can be affected. Affected children's mothers and fathers were used as cases and controls, respectively. Maternal genetic effects were also modelled with log-linear models proposed by Weinberg (1999). In addition, permutation tests were used to assess the significance of the Bayes factor that was used to rank SNPs according to their degree of association. The results indicate involvement of maternal genetic effects in the offspring's development. The finding of variants associated with increased risk of developing ASD is important for understanding the aetiology of ASD, which could lead to better personalized medicine in the future.

P17

Extending the Irish genetic landscape and recent demographic history with over 3400 samples of Irish origin

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Previous studies utilising individuals annotated by geographic origin have demonstrated subtle but discrete genetic structure within the Irish population and have detected admixture signals indicative of gene flow consistent with historical migrations into Ireland. However, these studies were individually limited by sample size, which in turn limited the resolution of their haplotype-based population structure analyses. We therefore set out to assemble a large sample of Irish ancestry references with geographic-origin annotations to expand our understanding of genetic structure across the island of Ireland. We refined the existing fine-scale genetic population structure and offer preliminary insights into the demographic history of Ireland.

Datasets from four studies were combined (n=3461 individuals total) to ensure a more comprehensive representation of the Irish population - the Irish DNA Atlas (n=194), the Trinity Irish population-based ALS case-control cohort (n=991), the Trinity Student Study (n=2232) and the Northern Irish subset of the People of the British Isles dataset (n=44). To our knowledge, the combined data consists of the largest collection of Irish genotype array data with geographical provenance. Leveraging patterns of haplotype similarity, we identified genetic clusters in the Irish population using fineSTRUCTURE; consistent with previous reports, we observed the population substructures separate along geographic boundaries. Additionally, we inferred Irish demographic history for the first time using identity-by-descent (IBD) analysis.

We intend use the results from these analyses to help disentangle the relative effects population structure and demographic history on the genetic architecture of complex diseases, such as epilepsy or amyotrophic lateral sclerosis (ALS).

P18

Polygenic burden for intracranial aneurysm and hypertension in deceased kidney donors who died of intracranial haemorrhage

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Background: Intracranial haemorrhage is a common cause of death among kidney donors, but limited research has been done to investigate polygenic burden for intracranial aneurysm (IA) and hypertension in deceased transplant donors.

Methods: Our data consisted of 2,122 genotyped donor-recipient pairs from the United Kingdom and Ireland Renal Transplant Consortium (UKIRTC) and 5,519 controls from the 1958 British Birth Cohort and UK Blood Service. We created polygenic risk scores for IA and hypertension using published GWAS summary statistics for these traits. We investigated the difference in PRS between the UKIRTC donors who died of intracranial haemorrhage (1,303 individuals) and the controls while adjusting for relevant covariates.

Results: We found that the IA PRS explained 4.1% of the variance between case and control status (p-value: 9.6×10^{-39}). The odds ratio on the phenotype for those in the lowest demi-decile of the IA PRS was 0.52 (95% CI: 0.34-0.82) compared to 2.8 (1.9-4.0) for those in the highest demi-decile. Similarly, the PRS for hypertension explained 1% of the variance (p-value: 7.5×10^{-10}) and the corresponding odds ratios were 0.68 (CI: 0.46-1.0) and 1.5 (1.1-2.3) for those in the lowest and highest demi-deciles respectively.

Conclusions: These observations could have utility in testing relatives of donors who died of intracerebral haemorrhage to determine if they share the same risk for intracerebral haemorrhage and if so to may be useful in advising regarding screening or other precautions to minimise their risk of intracerebral haemorrhage. These observations need to be confirmed in other cohorts.

P19

Identification of pathogenic mutations from whole genome sequencing of two Medieval Irish individuals with Multiple Osteochondromas

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Multiple Osteochondromas is a rare, autosomal dominant condition resulting in the formation of bony tumours in affected individuals. As it is a skeletal condition, it is possible to identify it in ancient individuals, and it has been identified in the paleopathological record from the Middle Bronze Age to the post-medieval period. Two individuals from the Irish Medieval cemetery of Ballyhanna, Co. Donegal (dated to 690-885 AD and 1030-1220 AD) showed evidence of bone tumours consistent with this condition. Whole genome sequencing revealed a missense mutation in the second exon of *EXT1,* a mutation which has been identified in modern patients. The second individual did not carry this mutation, but a different, frameshift mutation in the first exon of the same gene was identified, leading to a premature stop and loss of function. The difference between these individuals is surprising: just 10% of modern cases are suspected to be caused by *de novo* mutation, and clusters of this disease have been identified in modern isolated populations, suggesting founder effects, which would have been expected in the same cemetery in northwestern Medieval Ireland.

P20

Predictive genetic testing in inherited cardiac conditions: findings from a large Irish cohort

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Introduction: Inherited cardiac conditions (ICC), (cardiomyopathies and cardiac ion channelopathies) predispose to sudden death. Predictive genetic testing of at-risk relatives informs patient management and is cost-effective as those who test negative can be discharged.

Aim: Through predictive testing uptake, investigate the demographics and genetic contribution of ICCs from 2003 to 2020.

Methods: Genetic testing data was collated through interrogation of departmental databases and molecular genetics reports at the Department of Clinical Genetics and two tertiary cardiac referral centres.

Results: 1,535 predictive tests for pathogenic/likely pathogenic variants were undertaken in 1,508 individuals from 241 families, including 27 individuals tested for two familial variants. The mean age at

testing was 35 years (range 0.07 - 90 years). From 1,152 adults, more females (58%) were tested than males (42%). On average, six individuals per family were tested (range 1 - 84). Overall, predictive testing was performed for 26 different genes. Testing for long QT syndrome and hypertrophic cardiomyopathy genes represented 48% and 29% of the cohort, respectively. The most frequently tested gene was *KCNQ1* (24% of tests), followed by *MYBPC3* (20%) and *KCNH2* (17%). There was a notable absence of testing for several sarcomeric and arrhythmogenic cardiomyopathy genes.

Conclusion: Predictive testing has allowed up to 789 genotype-negative individuals (and their offspring) to be reassured and discharged from long-term cardiac follow-up. Our data suggests it can be challenging to encourage males to come forward for testing. The absence of testing for several cardiomyopathy genes suggests low frequency of such disease-causing variants in the Irish population.

P21

Everolimus for drug-resistant seizures in tuberous sclerosis complex: an Irish experience

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Background: Tuberous sclerosis complex (TSC) is a genetic disorder characterised by multisystem benign tumours and drug-resistant epilepsy. Aberrant mechanistic target of rapamycin (mTOR) signalling results in the hamartomas and epilepsy associated with TSC. Everolimus, a synthetic mTOR inhibitor is an approved treatment for subependymal giant-cell astrocytoma, renal angiomyolipoma and most recently, drug-resistant seizures in TSC.

Methods: An observational study of the safety and efficacy of everolimus for TSC-related drug-resistant seizures in three Irish epilepsy centres.

Results: Eleven patients have started treatment with everolimus. The mean age was 34.5 years (range 17-54 years). They all had highly active epilepsy (73 seizures per month, mean) and had been trialled on a mean of 8 anti-seizure medications previously. Six patients have *TSC2* mutations, 3 have *TSC1* mutations and genetic testing has not been performed on two patients. The mean duration of treatment is 17 months (range 1-76 months). Eight patients experienced a significant reduction in seizure frequency (>50% reduction). Four patients developed stomatitis and one patient discontinued treatment to become pregnant. No other adverse events were recorded.

Discussion: Epilepsy is a major cause of morbidity and mortality in TSC. Everolimus improves seizures by targeting the specific molecular defect in TSC. Our data supports the use of everolimus for seizures in TSC. Specialised care is required to manage treatment-related complications and to monitor everolimus serum levels.

P22

The Experiences of Families Receiving a Diagnosis of 22q11.2 Deletion Syndrome in Ireland

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Background: 22q11.2 deletion syndrome (22q11DS) diagnoses may not be communicated to families in Ireland in a family-centred manner. Families often wait over one year to see a genetic counsellor. This study aimed to explore the experiences of 22q11DS families regarding the need for timely access to genetic counselling.

Methods: Parents of children with 22q11DS were recruited through 22q Ireland. Semi-structured interviews explored experiences of diagnoses, medical care, genetic counselling and mental health (MH). Interviews were transcribed verbatim and analysed using thematic analysis.

Results: The experiences of 20 participants were classified into five main themes; Receiving Diagnosis, Interactions with Healthcare Professionals (HCPs), Medical Care, Information and Impact of Condition. Participants reported receiving diagnoses for their children in a sub-optimal manner due to inappropriate settings and insufficient information, support and pre-test counselling. Parents reported feeling responsible for managing their child's fragmented medical care. Participants reported insufficient empathy and little awareness of 22q11DS amongst HCPs. Participants perceived genetic counselling to be associated with family planning and reported delayed, if any, access to services. MH was a particular worry amongst participants. 22q Ireland conferences are the main source of information for parents. Participants reported a range of emotions after diagnoses and described the family impact.

Conclusions: Findings suggest associations between HCPs poor understanding of 22q11DS and the perceived lack of empathy and fragmented care. Increased awareness of 22q11DS amongst HCPs and development of a coordinated care pathway for 22q11DS with timely access to genetic counselling may improve care and lead to better outcomes.

P23

Everolimus as a precision therapy for drug-resistant seizures in GATOR1 complex mTORopathies

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Purpose: GAP activity towards RAGs 1 complex (GATOR1) is a negative regulator of mechanistic target of rapamycin (mTOR) signalling. Pathogenic variants in genes encoding GATOR1 (*DEPDC5*; *NPRL2*; *NPRL3*) are associated with drug-resistant epilepsy. Similar to tuberous sclerosis complex (TSC), epileptogenesis in the 'GATORopathies' appears to be mediated by excessive mTOR activation. Everolimus, an mTOR

inhibitor is an approved treatment for TSC-related seizures. Here, we study everolimus as a treatment for drug-resistant seizures in GATOR1 epilepsies.

Method: An observational open-label study of everolimus for drug-resistant seizures in GATOR1 epilepsies. People with epilepsy (PWE) caused by mutations in *DEPDC5*, *NPRL2* or *NPLR3* genes were identified by research whole exome sequencing (WES) and confirmed at an accredited genetics laboratory.

Result: Four individuals with drug-resistant epilepsy and GATOR1 mutations (3 *DEPDC5*; 1 *NPLR3*) have started treatment with everolimus. Three have nocturnal frontal lobe epilepsy, and one has multifocal epilepsy with peri-ictal psychiatric symptoms. Two have intellectual disability. All have normal brain imaging. Prior to commencing everolimus, two had daily seizures and two had 2-3 seizures per week. The mean duration of treatment is 12.5 months (range 6-19 months). Two have experienced a greater than 50% reduction in seizure frequency. No adverse events have led to treatment discontinuation.

Conclusions: Non-TSC mTORopathies are emerging as an important cause of drug-resistant epilepsy. Diagnostic WES should be considered for refractory non-lesional epilepsy or epilepsy due to cortical dysplasia. Preliminary data suggests that everolimus may be an effective targeted therapy for drug-resistant epilepsy caused by mutations in GATOR1 genes.

P24

Postgraduate Training in Cancer Genetics – a cross-specialty survey exploring experience of clinicians in Ireland

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Background: There is an acute need for all medical specialists involved in cancer care to up-skill in cancer genetics as genomic profiling of constitutional and tumour-derived DNA becomes increasingly critical in cancer risk estimation, prognostication and treatment planning. In Ireland, this is particularly crucial given the lower number of vocationally trained Clinical Geneticists in the country compared to European peers. We carried out a cross-sectional survey of medical and surgical trainees, developing a new questionnaire to assess the clinical experience of postgraduate medical and surgical trainees in the Republic of Ireland in cancer genetics.

Aims: We aimed to assess the confidence of postgraduate trainees in handling the results of genetic testing and to evaluate the need for formal cancer genetics training education among postgraduate clinicians to help increase knowledge and comfort with this rapidly expanding and evolving field. The study cohort included 62 senior postgraduate doctors training in Ireland in four specialties all of whom care for patients with cancer: Medical Oncology, Radiation Oncology, Obstetrics and Gynaecology and Surgery.

Methods: Participants completed the online questionnaire anonymously and voluntarily.

Results: Our results revealed a paucity of cancer genetics training in the Republic of Ireland currently. 47 of 62 respondents (75.8%) having “hardly any” or “none at all” during undergraduate training, and 56.5% reporting “none at all” during their specialist training. The majority of those surveyed would value more training in cancer genetics.

Conclusions: Our results emphasise the importance of needs-based education in cancer genetics for postgraduate clinicians working in cancer care.

P25

Diagnostic yield of exome sequencing in patients with ultra-refractory epilepsy without intellectual disability

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Background: The diagnostic yield of whole exome sequencing can be as high as 40% in people with intellectual disability (ID) and seizures. However, the utility of exome sequencing is currently unclear for people with epilepsy without ID. The aim of this study was to evaluate the yield (percentage) of genomic testing, following American College of Medical Genetics (ACMG) guidelines, for pathogenicity in people with epilepsy without learning disability, stratified by response to anti-epileptic drug treatment.

Methods: Cases, identified via the Beaumont Hospital Electronic Patient Record (EPR) system, were clinically phenotyped and sub-divided into 4 groups: super-refractory focal epilepsy (who have failed five or more medications), super-refractory generalized epilepsy (who have failed three or more medications), ILAE-defined refractory epilepsy (despite trials of two medications) and responders (who have achieved seizure freedom with medication). Exome data was analyzed using a genomic analysis toolkit (GATK/in house pipeline and Congenica) and were discussed at an epilepsy-genetics multidisciplinary team meeting.

Results: A total of 327 individuals were included in the study, of whom 3.06% had an identifiable genetic cause for their epilepsy. Of 140 patients with super-refractory epilepsy (combined focal and generalized), the diagnostic yield was 5.71%, elevated beyond the level observed in responsive patients (1%) although the difference was not significant ($p = 0.08$).

Discussion: We have suggestive evidence that super-refractory epilepsy may be enriched for cases with an identifiable ACMG-satisfying mutation. We are currently extending the study to a larger patient group and analysis is ongoing.

P26

Accurately capturing Rare Diseases in developing Irish Electronic Healthcare Records

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Provision of population healthcare requires accurate national data. The HSE has identified Electronic Health Records (EHR) as key for future health delivery and Integrated care. Secondary output from EHR data will populate National Patient Summaries, registries and health service analysis by proposed use of SNOMED-CT medical terminology in EHRs and national datasets.

Accurate capture of diagnosed Rare Diseases (RDs), as-yet-undiagnosed patients, and those with syndromes without a name (SWAN) is necessary. We tested the proposed EHR medical coding using the SNOMED-CT to Orphacode map on hypothetical datasets. We created a list of Irish high-prevalence RDs based on the literature and Irish expert opinion.

We estimate that SNOMED-CT coding in EHRs with mapping to Orphacodes for secondary use would capture 82.0%-94.5% of diagnosed RDs (lowest: rare genetic diseases in Irish Travellers; highest: Irish high-prevalence RDs). This approach is suboptimal for undiagnosed RDs and SWAN, leading to a substantial loss of data affecting ~25% of patients in RD expert centres; ~50% of clinical genetics patients; and 97% of patients in the European Reference Network for Congenital Anomalies Registry. With 52% of paediatric inpatient bed-days being used by children with RDs (E Gunne, personal communication), exclusive SNOMED-CT coding would lead to incomplete coding for ~>9% of bed-use data at Children's Health Ireland.

Inclusion of Orphacodes directly into Irish EHRs would facilitate accurate capture of named RDs, undiagnosed RDs and SWAN; facilitating outcome monitoring of RD treatment and care, economic analysis of RD activity and interoperability with ERNs integrating into national healthcare systems.

P27

Duplicate Referrals - Counting the cost to the Health Service

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The waiting list in Clinical Genetics is prolonged. Anecdotally, we noted our service receiving duplicate referrals (referrals for patients already on the waiting list who hadn't yet been seen). Each of these waste both consultant and administrative time, it diverts attention away from ongoing cases and therefore is a clinical risk. We audited duplicate referrals over a 3 month period (01/11/2020-31/01/2021) to estimate costs to the Irish health service; 82/986 (9%) referrals that were received were duplicate referral, 26/82 were a triplicate or more referral for same patient. The average length of time between first and second referral was 378 days indicating they arise at annual review with original referrer; 52 (63%) were from the same initial referring consultant. Duplicate referrals changed the triage outcome in 7/82 (8.54%) cases.

We performed time analyses managing duplicate referrals from both the referring and receiving consultant and administrative teams. Each individual re-referral costs €47.6. For the study period, the total cost of re-referrals to the health care system was €3,908.6. The National treatment purchase fund (www.ntpf.ie) cited >200,000 patient waiting >12 months for an appointment in the Irish Republic on 01/01/2021. Assuming duplicate referrals are occurring at a similar rate in other specialties (9%), then ~18,000 duplicate referrals are sent annually within the HSE. Extrapolating from this, we estimate the overall cost to the HSE being €856800 per annum. Our study was carried out during covid 19, referrals were down 10% indicating that the true cost is likely higher .

P28

Clinical re-validation of copy number variant referrals on a clinical genetics waiting list

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Increased demands for under-resourced genetic services is managed by consultant triage including restricting referral indications. We conducted a clinical validation of referrals relating to chromosome microarray findings to reduce the waiting list/time (approximately three years for routine referrals in the Irish Republic).New International System for Human Cytogenomic Nomenclature (ISCN) reporting guidelines on copy number variation (CNV) reporting mean that some historic array copy number variants (CNVs) would now be considered benign and not reported. Our study aim was to identify these and provide advice by letter.

Methods: Updates in the Decipher database allowed standarisation of CNV review. 191 referrals matched the validation criteria. Clinical records with test reports were included. The cytogenetic staff reviewed ~40 overlapping cases concurrently. Patients with a significant CNV or clinical phenotype would remain on the waiting list; those with a likely benign CNV and mild phenotype would receive standarised information letters instead of an appointment with notification to referrer.

Results: 191 referrals with a request to review a CNV were included. 58 (30.4%) patients referred had likely benign CNVs with a mild phenotype and were removed from the waiting list. 41 (21.5%) had benign CNVs but appointments are required as the clinical indication was strong; 76 (39.8%) were deemed to have a significant CNV event and require an appointment.

Conclusion: 30% of referrals for interpretation of array showed likely benign normal human variation. It is important to introduce systems to avoid flooding waiting lists with normal human variation identified by new genomic technologies.

P29

Variation in variant assessment, an inter-laboratory comparison.

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The Next Generation Sequencing (NGS) Laboratory has established germline genetic testing for Cardiology patients attending the Inherited Cardiac Conditions clinic at the Mater Misericordiae University Hospital. Inter-laboratory comparison of testing is an essential part of the ISO15159 for medical laboratories. The NGS Laboratory participated in an inter-laboratory comparison with Health in Code (HIC) in Spain.

Sixty-nine samples were included in the comparative assessment. Negative reports, whereby no variants of interest were established, were reported in 42 cases from the NGS Laboratory compared with 33 cases from HIC. The difference in number of negative reports was explored and the discrepancy arose mostly due to variants reported by HIC that were not covered by the test method employed in the NGS Laboratory. Positive reports (variant of interest established) were released for the remaining 27 patients from the NGS Laboratory; positive reports were also released by HIC for these patients. However, a comparison of the reported variants across the two sites identified differences in the classification applied in 9/27 samples (33%). The cause of the deviations was explored and included the classification method applied by the two sites. The comparison of this cross laboratory classification of variants is discussed in the context of internationally reported data.

The aim of participation in inter-laboratory studies is to standardise results across institutions. However, as shown here, certain aspects of variant classification differed across the two sites, highlighting the need for common classification structures as recommended by the American College of Medical Genetics and Genomics.

P30

Cerebellum structural development in individuals with NRXN1 deletions, a rare copy number variant associated with neurodevelopmental disorders

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Rare genetic variants, known as copy number variants (CNVs), such as *NRXN1* deletions, have been associated with neurodevelopmental disorders (NDDs), such as autism spectrum disorder (ASD), intellectual disability, and speech and language delay. NDDs are characterised by cognitive impairments, behavioural difficulties, and atypical brain development. *NRXN1* encodes the presynaptic cell-adhesion protein neurexin which plays an important role in synaptic function. *NRXN1* is widely expressed in the brain, with high levels in the cerebellum. Differences in cerebellar structure and function have been identified in the pathophysiology of some NDDs. This study compares cerebellum structure in individuals with *NRXN1* deletions versus typically developing (TD) controls. It is hypothesised that *NRXN1* deletions

alter gene expression in the cerebellum, which may impact structural and or functional development, with potential cognitive and clinical implications. High resolution T1-weighted anatomical MRI scans were collected in 17 individuals with *NRXN1* deletions (with or without an NDD) and 17 age- and gender-matched TD controls (age = 9-53 years). SUIT software was used to isolate the cerebellum and voxel-based morphometry (VBM) was performed. Total cerebellum grey matter (GM) volume and local grey matter concentrations were compared between *NRXN1* deletion and control groups. Preliminary results show no group differences in total cerebellum volume, with estimated total intracranial volume, age and gender included as covariates. VBM statistics will be performed to assess cerebellar GM differences further. Characterisation of CNVs, such as *NRXN1* deletions, represents a novel method through which an increased understanding of brain development, cognitive function and NDD pathophysiology may be attained.

P31

Neuropsychiatric outcomes in carriers of *NRXN1* deletions compared to idiopathic autism (iASD) and typically developing (TD) controls.

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Background: Neurodevelopmental and neuropsychiatric disorders (NDDs) are clinically heterogeneous and often present with co-morbidities.

Neurogenetics has highlighted the prevalence of genomic changes in NDDs, particularly in rare neurodevelopmental copy number variants (ND-CNV). NRXN1 deletions are one rare ND-CNV linked to a range of NDDs, including ASD, intellectual disability and schizophrenia. By examining clinical, cognitive and behavioural characteristics in individuals with NRXN1 deletions we can gain better understanding of the molecular mechanisms that underly NDDs. This study aims to investigate the prevalence of psychiatric conditions in NRXN1 deletion carriers compared to iASD and TD groups using the Developmental and Wellbeing Assessment (DAWBA).

Methods: The DAWBA and the strengths and difficulties questionnaire (SDQ) were collected from 12 NRXN1 deletion carriers (9M; 4F) aged <18 years at TCD. Age- and gender-matched iASD and TD groups will be identified from the AIMS-2-TRIALS LEAP study to assess differences in the prevalence of DAWBA predicted psychiatric diagnoses.

Analysis: DAWBA data demonstrated that autism, ADHD and oppositional defiant disorder were the most commonly identified disorders in the NRXN1 deletion cohort. 41.7% had a high probability of having one or more psychiatric condition. Additionally, NRXN1 del carriers were more likely than the

other three groups to have a slightly raised hyperactivity level. We will further compare NRXN1 del carriers, iASD and TD groups.

Conclusion: This study will maximise our understanding of NDDs by focusing on ND-CNVs links to clinical and behavioural phenotypes. This may enable integrating genomic research and clinical care and benefit the families impacted by NRXN1 deletions.

P32

Identification of a rare chromosomal insert as the cause of X-Linked Hypophosphatemic Rickets.

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X Linked hypophosphatemic rickets is a common cause of inherited rickets and is most often caused by defects in the phosphate regulating gene *PHEX* located on Xp22.11. Here we consider the underlying genetic abnormality in a local family presenting with hypophosphatemic rickets across two successive generations.

Initial testing in the family proband by targeted NGS panel analysis identified a potential translocation involving 6q21 and Xp22.11. However, G banded chromosomal analysis of metaphase cells failed to identify a translocation. Subsequently Illumina CytoSNP 850k array analysis and FISH analysis using an Empire Genomics probe for the 6q21 region confirmed the presence of a duplication of this region and showed that the duplicated material had been inserted into the short arm of the X chromosome.

Utilising the initial NGS data we designed primers to cover one of the breakpoints on Xp22.11 and confirmed by bi directional Sanger sequencing that the duplicated material interrupts the *PHEX* gene in exon six of twenty-two. This interruption is predicted to result in an abnormal protein product which would be targeted for nonsense mediated decay. This insertion was also confirmed in our proband's mother who had a clinical diagnosis of hypophosphatemic rickets.

In conclusion we have shown the utility of molecular and traditional cytogenetic techniques in determining the underlying genetic cause of hypophosphatemic rickets in a local family.

P33

Evaluating the diagnostic yield of commercial gene panels in autism

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Autism is a prevalent neurodevelopmental condition, highly heterogenous in both genotype and phenotype. A genetic diagnosis of autism may allow for genetic counselling for affected individuals and their families; opportunity to take part in targeted research or to receive anticipatory medical advice.

Genetic diagnosis in autism is limited by the ability to robustly determine the relevance of putatively pathogenic genetic variation (Myers et al. 2020; Schaaf et al. 2020).

As a result, the development of effective gene panels to aid autism diagnosis is challenging. Despite this, commercial gene panels are available and marketed for use in autism diagnosis (Hoang, Buchanan, and Scherer 2018). Here we estimate the clinical utility of 18 commercial gene panels through secondary analyses of clinically relevant variation identified and characterised by whole exome sequencing in the Simon's Powering Autism Research Knowledge cohort (Feliciano et al. 2019). We determine the diagnostic yield of each panel as the proportion of individuals sequenced, for which a relevant genetic variant was identified, corresponding with the genes contained on that panel (ranging from 0.22% to 10.02%). We also quantify the relevance of the genes included in each panel as the proportion of targeted genes with evidence supporting autism association (ranging from 43.41% to 100%) (Abrahams et al. 2013).

Considering the low diagnostic yield of the panels investigated, we infer that while gene selection for inclusion in autism panels is relevant, these gene lists are not extensive enough to justify use in autism diagnosis and are currently of limited clinical utility.

P34

Validation of the MRC Holland P062-D2 multiplex ligation-dependant probe amplification (MLPA) methodology to detect Copy number variants (CNV's) in the LDLR gene, associated with Familial Hypercholesterolaemia.

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Familial hypercholesterolaemia (FH) is a common autosomal dominant disorder which is predominantly related to genetic variants within the LDLR gene. This locus has a high frequency of Alu repeat elements and consequently copy number variations (CNV's) account for over 10% of the detectable FH pathogenic variants in *LDLR*, including single exon or multi-exon deletions and duplications. The current gold standard for CNV detection in *LDLR* is multiplex ligation dependent probe amplification (MLPA).

St James's Hospital Biochemical Genetics Laboratory, NGS analysis has reported 210 *LDLR* variants to date, representing a diagnostic rate of 36%.However, to enhance this service an *LDLR* MLPA assay (SALSA MLPA Probemix P062 LDLR MRC Holland) was developed and validated. Verification included an assessment of reproducibility (CV=100%), repeatability (CV=100%) and clinical performance characterisation (100% sensitivity and specificity) which led to INAB accreditation under ISO 15189. Protocols were subsequently established to select patients for MLPA analysis based on DLCN score and negative NGS scan.

The combination of NGS and selected MLPA analysis has led to a definitive diagnosis in 38% of FH patients. Overall, 9 LDLR CNVS were detected in 13 unrelated FH patients, including 7 single or multi-exon deletions, and 2 duplications (increased dosage), including two novel CNV's; multi exon deletion of exons 3-11 and duplication of exon 16.

Overall, the verification of this method has proved to be an effective adjunct in establishing a genetic diagnosis of FH, particularly in NGS negative patients who have a high phenotypic risk.

P35

Genetic characterisation of copy number variants (CNVs) by identifying genomic breakpoints in large whole exon and multi-exon deletions in the LDLR gene, associated with Familial Hypercholesterolaemia.

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Familial hypercholesterolaemia (FH) is a relatively common autosomal dominant disorder due primarily to variants in *LDLR,* which predisposes to premature CVD. The most cost-effective strategy for identifying FH is genetic cascade screening in kindreds with an identified proband. Over 10% of FH-causing variants are attributed to copy number variants (CNV's) and MLPA is commonly used to detect these complex rearrangements in the *LDLR*. However, limitations of this method include the inability to determine the exact breakpoint sequence where the deletion/duplication occurs and its expense as a sole cascade screening method within large FH family groups. Thus, characterisation of CNV breakpoints not only provides insights into FH pathogenesis but can also facilitate development of less complex and more cost-effective cascade-screening assays.

A strategy combining both short- and long-range PCR techniques and Sanger sequencing was applied to elucidate the nature and extent of breakpoints in known LDLR CNVs. More specifically, a novel breakpoint in a heterozygous deletion of exon 6 was initially identified using a short-range PCR tiling strategy. Subsequently, this variant was used to validate long-range PCR assays for use in the identification of breakpoints in two multi-exon CNVs - heterozygous deletions of exon 4-6 and exons 15-18. This PCR-based approach revealed breakpoints incorporating *Alu* sequences in the flanking intronic DNA suggesting a non-allelic homologous recombination (NAHR) mechanism.

The addition of the breakpoint sequences to NGS FH sequencing panels could increase the detection rate of CNVs in the FH patient cohort in a cost effective manner.

P36

Evaluation of Inherited Retinal Disease patients following negative result from panel testing

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Introduction: First-tier screening of inherited retinal degenerations (IRD) with next generation sequencing (NGS) has a diagnostic yield of ~70%[1]. Whole exome/genome sequencing (WES/WGS) may detect further variants, resolving up to 79% of pedigrees[2] however they come with increased cost and need for capacity to manage secondary findings. Deep phenotyping is required to assess which genetic testing modality is most appropriate.

Methods: Patients enrolled on the Target 5000 study who had negative result after NGS techniques[1,3] were reassessed by reviewing their records (clinical examinations, multi-modal imaging, electrodiagnostics). This was performed by 3 clinicians in a masked fashion.

Results: 67 patients from 50 pedigrees were identified.

72% (n=48) retained a clinical diagnosis of IRD. 4% (n=2) were referred to the metabolic service for further investigation. 25% (n=17) were deemed non-IRD (4 uveitis, 1 neuro-ophthalmology, 12 AMD).

Of those 48 clinically IRD patients, 8% (n=4) were resolved by further sequencing during the process, 10% (n=5) patients had a single variant associated with autosomal recessive disease and will undergo single gene sequencing for the second variant. 3 pedigrees (n=15) have undergone WGS and 1 pedigree has been resolved. The remaining 48% (n=23) will be reassessed by the clinical genetics team to determine the most appropriate additional genetic testing modalities (e.g., SLA array, WES or WGS).

Conclusion: After reassessment, further genetic testing was not necessary in 28% of patients by either identifying an alternative diagnosis or referring them onto an appropriate specialty. A care pathway has been developed for the resolution of these patients.

P37

A Study of Plexiform Neurofibromas in Neurofibromatosis type 1 patients in Northern Ireland

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Plexiform neurofibromas, arising from the nerve sheath, are the most frequent tumours associated with Neurofibromatosis type 1 (NF1). They cause a variety of complications, including disfigurement, with is often associated with loss of self-esteem, pain, and functional impairment. They can also undergo malignant change. Surgical resection is difficult as the lesions grow along nerve sheaths and,

consequently, regrowth is common post-operatively. Medical treatment, such as MEK inhibitors, have recently been trialled, with good results. We have characterised plexiform neurofibromas in our NF1 cohort of patients. There are >500 NF1 patients known to the Regional Genetics Centre in Northern Ireland, with around 20% having a plexiform neurofibroma. Descriptive statistics were carried out in this group to ascertain the commonest locations, presenting age and symptoms, and proportion of patients requiring surgery.

P38

Dermatological Manifestations of Fabry's Disease in Ireland and towards Investigating a Genotype-Phenotype Correlation

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Introduction: Fabry's disease (FD) is a rare, x-linked lysosomal storage disorder that results in accumulation of globotriaosylceramide. Dermatological changes, primarily angiokeratomas, are the earliest objective manifestations of the disease; however there is still a considerable delay in diagnosis. We are unaware of any established genotype-phenotype correlation in FD

Aim: To review the dermatological manifestations in FD patient cohort in the national Centre for Inherited Metabolic Diseases (NCIMD) to investigate:

1. The type of dermatological manifestations present in the Irish Fabry's Disease Cohort
2. Time from onset to diagnosis

Methods: A retrospective review of all adult patients with FD who attend the National Centre for Inherited Metabolic Disorders-Adult Service (NCIMD) in Dublin was conducted noting the dermatological manifestations, age of onset and genotype.

Statistical analysis was conducted using SPSS version 25.

Results: Out of 80 patients attending NCIMD, 41 (51%) had skin changes. Angiokeratomas were present in 25 (31%) patients, edema in 19 (24%) patients and hypo/hyperhidrosis in 11 (14%) patients.

Only 4/11 probands with dermatological manifestations were diagnosed based on the presence of them. The average age of onset of angiokeratomas was 21 years for females and 15 years for males. The average time lag from symptom onset to diagnosis was 8.5 years for females and 9.5 years for males.

Conclusions:

- Angiokeratomas are important but underappreciated early diagnostic feature of FD.
- These manifestations are highly non-specific what can lead to delay in diagnosis.
- All 41 patients have had *GLA* genotyping and we are currently investigating for a genotype-phenotype correlation.

P39

Pitfalls in the Application of Genetic Variant Interpretation Guidelines

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The first major milestone of modern-day genetic variant assessment was the 2015 publication of the American College of Medical Genetics guidelines for variant interpretation. These guidelines were established to add structure to types of evidence that were used to classify variants, on a spectrum from benign to pathogenic. The sources of data considered include population, computational, functional and segregation.

Despite the diverse sets of data incorporated into the recommended variant assessment, there are still several gaps that exist which inevitably lead many variants to the classification of unknown significance. Variants of incomplete penetrance pose complications for using segregation and population data, as those carrying the variant may not be affected as expected. Furthermore, this may also cause a higher than expected allele frequency in the control population. One such variant in the Irish population is a *PRPF31* heterozygous whole gene deletion, resulting in retinitis pigmentosa, a condition which causes progressive blindness.

Another shortcoming of the guidelines concerns the interpretation of splice variants. Although canonical splice site variants are considered, many other intronic variants such as non-canonical, near-exonic and deep-intronic variants have also been shown to be pathogenic. Recently, a deep-intronic variant associated with Stargardt Disease was found to be enriched in the Irish population, *ABCA4*-NM_000350.2:c.4539+2028C>T.

These knowledge gaps can be addressed by research groups whom the clinical genetics community are particularly reliant upon for generation of functional data such as novel enzyme assays, splice-site analyses and bespoke validation experiments. These will prove invaluable in advising future guidelines in genomics.

P40

Management of SADS Biobank in Next Generation Sequencing Laboratory at the Mater Misericordiae University Hospital

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Sudden cardiac death (SCD) is the most common cause of death in Western countries with an incidence of ~1.34:100,000 for the ages 7 - 64, with 5 - 8% of those showing no evidence of any structural cardiac abnormality or any coronary disease at autopsy in Europe. If sudden death cannot be explained even after post mortem, it is considered as Sudden Arrhythmic Death Syndrome (SADS), which is a preventable condition when diagnosed in advance. The SADS Study is a collaborative work with the Steering Committee on Adult Sudden Death of the Irish Heart Foundation, University College Dublin and the Health Service Executive. The collaboration has two main functions; 1) tissue collection from deceased patients with a suspected unexpected sudden cardiac death and 2) clinical and genetic screening of family members. The SADS biobank is centralized in the Next Generation Sequencing (NGS) Laboratory at the Mater Misericordiae University Hospital (MMUH) and allows for genetic studies to test for channelopathies and cardiomyopathies. The Family Heart Screening Clinic at MMUH performs protocol-driven screening tests for family members of SADS victims who attend the clinic through referral from hospital, general practitioner or pathologists, or self-referral for inheritable cardiac diseases.

Since its establishment in May 2015, the biobank has received 261 samples. Following receipt of individual consent organized through the Family Heart Screening clinic, genetic testing has taken place on 42 cases (16%). The management of the SADS biobank in the NGS Laboratory will be described in this process.

P41

Diagnostic yield of panel testing in a cohort of Inherited Retinal Degeneration (IRD) patients in Northern Ireland

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Introduction: Genetic testing for IRD has evolved rapidly with next generation sequencing. The addition of new genes to diagnostic panels increases the likelihood of detecting disease-causing variants and variants of uncertain significance (VUS).

Aim: Review panel results from patients referred to the IRD clinic to determine the distribution of clinically actionable variants (pathogenic/likely pathogenic, P/LP) and VUS.

Methods: Data was collected by reviewing molecular diagnostic reports from probands tested 2019-2020.

Results: We reviewed panel screening results from 153 patients. The panels ranged in size from single gene (ABCA4, USH2A) to large retinal dystrophy panels. Overall molecular yield was 64.1%; 87 patients (56.9%) had a molecular diagnosis after testing, 11 patients (7.2%) had VUS with the potential to be reclassified as likely pathogenic. 38 patients with Stargardt disease had a relatively high yield of molecular diagnoses with 32 (84%) testing positive for two P/LP variants in the ABCA4 gene. Out of 47 rod cone dystrophy patients, molecular yield was 72.3%; 27 (57.4%) had P/LP variants/partial or whole gene deletions and 7 (14.9%) had VUS. Four cone dystrophy patients were tested, one had a molecular diagnosis (25%) and one had a VUS. Out of three macular dystrophy patients tested, one had a molecular diagnosis (33.3%).

Conclusion: Panel testing has allowed over half of the patients in this cohort to receive a molecular diagnosis. Although our numbers were small, the low diagnostic yield seen in cone dystrophy and macular dystrophy testing corresponds to that found in other groups.

P42

PorphyriaDB - a cloud-driven genetic database for the acute hepatic porphyrias.

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The acute hepatic porphyrias (AHPs) are autosomal-dominant genetic disorders that can manifest with acute neurovisceral attacks causing serious morbidity, and pathological variants in the haem biosynthetic pathway genes *HMBS*, *PPOX* and *CPOX* underpin this group of disorders. Our laboratory runs a de facto Irish national molecular diagnostic service for the acute porphyrias, which has enabled the identification of AHP genetic susceptibility in >90% of Irish kindreds. Access to up-to-date classifications of mutations is a key requirement in reporting on the pathogenicity of genetic variants identified during molecular diagnostic analysis. Therefore, although genetic confirmation is a central requirement for definitive diagnosis of AHP susceptibility, to date there is no genetic variant database available providing comprehensive reference information, including in-silico and functional characterisation of AHP-related genetic variants, to enable this process.

In an effort to automate our diagnostic pipeline, we curated an in-house genetic reference database for annotation of missense variants in HMBS, PPOX and CPOX. To ensure reproducibility, transparency and

accessibility to the broader porphyria community, we employed a backend cloud-native infrastructure for database curation (PorphyriaDB.com). The result is a secure and scalable system that can nevertheless be updated by means of a simple spreadsheet or CSV file. It was built on Amazon Web Services (AWS) using an Infrastructure as Code (IaC) approach, enabling future similar databases to be deployed with minimum expense and effort. The database incorporates prediction scoring of variants, based on established prediction tools and meta-predictor algorithms, benchmarked against functionally validated mutations associated with the aetiopathogenesis of AHP.

P43

Heterozygous deletion of *PRFP31* resulting in Autosomal Dominant Retinitis Pigmentosa - Therapeutic Implications

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Retinitis Pigmentosa (RP) is a group of inherited retinal degenerations. Autosomal dominant RP (adRP) is genetically highly heterogeneous. At least 30 genes have been implicated as causative, one of which is *PRPF31*. The Inherited Retinal Degenerations Service at the Royal Victoria Eye and Ear Hospital, Dublin, Ireland has, in collaboration with the Ocular Genetics Unit at Trinity College Dublin, been engaged in Next Generation Sequencing (NGS) of patients attending the Service since 2011. This genotyping exercise has more recently been extended to cover the island of Ireland, Target 5000, and to include whole genome sequencing (WGS). Resulting from this on-going study, a patient with adRP was ascertained and clinically characterised over a seven-year period. WGS identified an approximately 26kb heterozygous deletion of the entire *PRPF31* gene, together with the adjacent *TFPT* gene and the promoter of *NDUFA3. PRPF31* is an important component of the spliceosome, involved in pre-RNA splicing. *PRPF31* variants are estimated to account for 10% of adRP. Most are single base changes or deletions. Total deletion of the gene has been uncommonly reported. Many autosomal dominantly inherited retinopathies are due to the dominant negative effects of the pathogenic gene variant driving the disease process. Gene replacement alone is unlikely to result in benefit and a strategy of 'Suppression and Replacement' may be required to achieve a therapeutic effect. Total deletion of *PRPF31* suggests haploinsufficiency as the causative mechanism in this patient, raising the possibility that gene replacement alone may, in fact, be a therapeutic option.

P44

The Spectrum of Gene Mutations Associated with Hypertrophic Cardiomyopathy in an Irish Cohort

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Introduction: Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder. It affects 1:500 people and is associated with cardiac hypertrophy and sudden death. It is inherited in an autosomal dominant fashion. Up to 60% of affected individuals carry a mutation in a sarcomere gene. Rarer aetiologies include mitochondrial defects, lysosomal storage disorders and other phenocopies. We sought to catalogue the genetic landscape of HCM in an Irish cohort.

Methods: A retrospective analysis of the clinical database of an inherited cardiac conditions clinic was undertaken. All patients with 'gene positive' hypertrophic cardiomyopathy were reviewed. All ACMG Class 4 and 5 variants were recorded. Class 3 variants in candidate genes were also recorded, although not actionable.

Results: The results of genetic testing for 254 HCM patients were reviewed. 238 patients (94%) had a single gene variant. 13 patients (5%) had digenic disease. The remaining 3 patients (1%) had polygenic disease.

MYBPC3 was the most commonly implicated gene in sarcomeric HCM with 116 patients (45.6%) carrying a Class 4 or 5 mutation. MYH7 mutations were found in 51 patients (20%). Troponin mutations were found in 20 patients (6.8%). Although classified as a VUS, there was an overrepresentation of FHOD3 mutations with 20 patients (7.8%) carrying a variant. In 15 patients (5.9%) it was the only associated gene variant. 41 patients (16%) had pathogenic mutations in PRKAG2, LAMP2 and mitochondrial genes.

P45

X Marks the Spot : X-Inactivation As A Cause of Severe Danon Disease in Females

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Background: A 22 year old female patient presented to hospital in acute heart failure with ventricular arrhythmias and cardiogenic shock. Echocardiography revealed severe concentric left ventricular hypertrophy and systolic dysfunction. Her clinical history was notable for mild intellectual disability, anxiety and depression but no skeletal muscle weakness. There was no family history of cardiac conditions or sudden death. Cardiac transplantation was performed.

Genetic Analysis: Genetic testing was performed using an extended panel for mutations associated with hypertrophic cardiomyopathy. This revealed a Class 4 mutation in the lysosomal associated membrane protein-2 gene (LAMP2 c.742-1G>C). She was diagnosed with Danon disease, a rare X-linked autosomal dominant condition causing severe cardiac hypertrophy, neuropsychiatric problems and skeletal myopathy. Cascade family testing demonstrated that her mother was also a gene carrier but clinically unaffected.

As in other X-linked conditions, severe clinical presentations such as this are unusual in females. In view of the phenotypic variability, X-inactivation studies were performed on both the proband and her mother. The results demonstrated that the proband had 86% inactivation of her paternal X allele. This skewed inactivation resulted in disease severity comparable to a male.

Discussion: X-inactivation, or Lyonization, is an important and overlooked cause of X-linked disease expression in heterozygous females. The concept that female carriers of pathogenic mutations are mosaics should be considered in all cases and evidence of skewed X-inactivation should be sought. Rates of X-inactivation may be tissue specific. The traditional concept of X-linked disorders only causing severe phenotypes in males needs to be abandoned.

P46

Removing the uncertainty from variants of unknown significance: a modified variant classification approach

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Background: The Next Generation Sequencing (NGS) Laboratory at the Mater Misericordiae University Hospital uses the guidelines from American College of Medical Genetics (ACMG) and ClinGen group to assess and classify genetic variants. The number of class III Variant of Uncertain Significance (VUS) in diagnostics reports are increasing given the number of variants that are being discovered. There is an excessive need to decrease the uncertainty in clinical reporting and to provide a conclusive, specific and accurate answer to clinicians and their patients. The strength of certain ACMG criteria can be modified based on available information, which can result in the upgrade or downgrade of the classification of a variant.

Methods: The NGS Laboratory has undertaken a review of the ACMG criteria to which modified strengths can be applied, to better understand the evidence required to change the classification from a VUS for or against pathogenicity.

Results: The PP2 criteria (Cosegregation with disease in multiple family members) can be upgraded from supporting evidence to medium/strong evidence, based on the number of segregations in the family. Also, criteria PS3 (well established *in vitro* or *in vivo* functional studies) can be downgraded from strong to moderate/ supporting, based on the type of assay and control data used. This approach will be discussed with case studies, which resulted in a change of classification from a VUS. The presented cases provide examples where additional available information can be used to address the increasing identification of VUS.

P47

Complex phenotype of ARCN1 gene related disorder

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Monoallelic pathogenic ARCN1 gene variants cause autosomal dominant ARCN1-related disorder, associated with consistent phenotype of short stature and rhizomelia, with microcephaly, microretrognathia and developmental delay in the 6 previously reported cases. Other less common manifestations include seizures, joint laxity, cleft palate, need for tracheostomy, cataracts, dental anomalies and transient defects in N-glycosylation.

To our knowledge we report 7th case worldwide who presented originally with antenatal detection of shortened long bones in the context of a family history of short stature and maternal Insulin Dependent Diabetes Mellitus (IDDM), the complexities of diagnostic and research pathways and evolving clinical phenotype over 15 years in one patient. The patient history including posterior subcapsular cataracts, PDA, failure to thrive, short stature, nail and enamel hypoplasia, mild learning difficulties, joint laxity, microcephaly, micrognathia, abnormal skeletal features and evolving dysmorphism will be presented. Diagnostic genetic testing confirmed the patient to be heterozygous for the pathogenic ARCN1 frameshift gene variant previously detected on research; impacts on reproductive counselling including prenatal options such as pre-implantation genetic diagnosis (PGD), empowerment and knowledge for the patient and family.

We further delineate the ARCN1 phenotype, an emerging disorder of developmental delay and skeletal manifestations and provide possible expansion of the phenotype of an underreported disorder.

This case demonstrates the efficacy of routine diagnostic use of trio whole exome sequencing (WES) in complex phenotypes with impact on the diagnostic pathway, potential management and treatment options and increasing knowledge on evolving rare phenotypes.

P48

Genetic analysis of over 100 inherited retinal disease probands using whole genome sequencing and *in vitro* splice assays.

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Purpose: Inherited retinal diseases (IRDs) are a major cause of visual impairment globally. These disorders are genetically heterogenous with >270 genes associated to date. As 30-40% of IRD cases remain genetically unexplained following preliminary sequence analysis, we aimed to obtain a genetic

diagnosis using whole genome sequencing (WGS) where the genetic cause of disease was not found using target capture or whole exome sequencing.

Methods: WGS was employed on 103 previously unresolved cases. After initial prioritization, we performed an in-depth interrogation of all non-coding and structural variants in genes where one likely pathogenic coding or non-canonical splice site variant was detected. Functional analysis of putative splice-altering variants was performed using *in vitro* splice assays.

Results: We identified the genetic cause of disease in 28 patients who underwent WGS. Causative coding variants were observed in genes such as *CEP78*, *FAM161A* and *HGSNAT*. Pathogenic structural variants were detected in *PRPF31* and *RPGRIP1* as well as a CAG repeat expansion in *ATXN7*. In 18 monoallelic cases, we found an additional candidate non-coding variant which was predicted to disrupt the splicing process *in silico*. We established a genetic diagnosis in 10 cases as they carried pathogenic splice defects.

Conclusions: WGS is a powerful tool to identify causative non-coding and structural variants. This study highlights the importance of sequencing and functional analysis of non-coding regions beyond non-canonical splice-sites. Studies such as this are particularly relevant given recent advances in splice modulating therapeutics, appropriate access to which will only be possible given an accurate genetic diagnosis.