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ORAL PRESENTATIONS

OP01 Joint analysis of multiple trio genomic datasets for the discovery of novel dominant epilepsy genes

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Background/Objectives: The epileptic encephalopathies (EEs) and epilepsy with co-morbid intellectual disability (ID) are groups of epilepsy characterized by refractory seizures and developmental regression. Both groups have been shown to have underlying monogenic causes. However, despite state-of-the-art testing, a significant proportion of people with these types of epilepsy do not receive a molecular diagnosis, suggesting yet-to-be-identified genetic causes. Our objective was to identify novel epilepsy with ID and EE genes through joint analysis of multiple trio genomic datasets.

Methods: We assembled WGS or WES datasets associated with EE or epilepsy with ID HPO terms. Datasets were from the FutureNeuro Research Centre, the Epilepsy Genetics Initiative, Epi4K, Undiagnosed Diseases Network, CSER,DDD and the UK 100,000 Genomes Project. A GATK4 pipeline was used for variant calling. A statistical model using DeNovoWEST was utilized to identify genes with a significant excess of de-novo variants (DNVs).

Results: A total of 1,811 trios/quads were included in the final analysis. We identified 14 genes with a significant excess of DNVs, of which 11 were established monogenic causes of epilepsy. We provided further evidence for 2 emerging epilepsy genes (NAV2 and PCDH7) and one potentially new epilepsy gene (CHML). All are brain-expressed.

Conclusion: Combining genetic and phenotypic data, we report the significant enrichment of DNVs across 1,811 trios/quads who underwent WES/WGS.

OP02 MEF2C Dysregulation and its Association with Neuropsychiatric Disorders and Cognitive Function in Human Neural Cells

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Myocyte Enhancer Factor 2C (MEF2C) is a transcription factor that plays a crucial role in neurogenesis and synapse development. Genetic studies have identified MEF2C as a gene that influences cognition and risk for neuropsychiatric disorders, including autism spectrum disorder (ASD) and schizophrenia (SCZ). Here, we investigated the involvement of MEF2C in these phenotypes using human-derived neural stem cells (NSCs) and induced neurons (iNs), which represented early and late neurodevelopmental stages. For these cellular models, MEF2C function had previously been disrupted, either by direct or indirect mutation, and gene expression assayed using RNA-seq. We integrated these RNA-seq data with MEF2C ChIP-seq data to identify dysregulated direct target genes of MEF2C in the NSCs and iNs models. Several MEF2C direct target gene-sets were enriched for SNP-based heritability for intelligence, educational attainment and SCZ, as well as being enriched for genes containing rare de novo mutations reported in ASD and/or developmental disorders. Analysis of single-cell RNA sequencing data revealed that several excitatory glutamatergic neurons in the hippocampus and cortex, including deep layer pyramidal cells, CA1 principal cells, and entorhinal cortex, were enriched for MEF2C direct-target genes. Overall, our results suggest that genes dysregulated as a consequence of either direct or indirect MEF2C disruption contribute to SCZ development and cognitive function from early stages of neurodevelopment. These genes are involved in a wide range of biological processes including neural/glial cell differentiation, cell migration, protein modification and catabolism in NSCs, as well as mitochondrial function and energy production in iNs.

OP03 Biological Insights into Sleep, Neurodevelopmental and Neuropsychiatric Conditions: Investigating the Overlapping Genetic Contributions Using Pathway-Based Polygenic Score Analysis

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It has been postulated that circadian dysfunction may contribute to the sleep problems commonly present in neurodevelopmental and neuropsychiatric conditions and even have a primary role in the pathophysiology of these conditions. Statistically significant correlations of genetic effects between numerous pairs of neurodevelopmental or neuropsychiatric and sleep phenotypes have been identified. We hypothesize that this overlapping genetic variation is enriched in certain biological pathways.

We used pathway-based polygenic score analysis to identify enriched pathways. We tested all pathways from the Reactome database that contained between 50 and 500 genes. We created polygenic scores for each tested pathway using summary statistics from the largest genome-wide association studies (GWAS) of autism, attention-deficit/hyperactivity disorder, schizophrenia (SZ) and bipolar disorder (BP). We tested the performance of these pathway-based polygenic scores, for each GWAS phenotype, in predicting chronotype and insomnia status of UK Biobank (UKB) participants.

The BP polygenic scores for the KEAP1-NRF2 and mRNA splicing-minor Reactome pathways were both statistically significant in predicting chronotype in UKB. The BP and SZ polygenic scores for a subset of the KEAP1-NRF2 pathway ranked highly in predicting insomnia in UKB. These results demonstrate that overlapping genetic variation between chronotype and BP is enriched in genes involved in the NRF2-KEAP1 pathway. Previous evidence has linked this pathway to the pathology of BP and SZ. Additionally, the expression of NRF2 is directly regulated by two core clock genes. Our results suggest that the NRF2-KEAP1 pathway could be involved in mediating the disrupted circadian rhythm phenotype of BP and SZ.

OP04 Investigating the role of rare microRNA-associated germline variants in the epileptic encephalopathies

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The epileptic encephalopathies (EE) are rare devastating forms of epilepsy with a largely monogenic genetic architecture. Although the molecular diagnostic rate of cases is about 40%, most screen negative on genomic testing. Rare damaging coding variants have been shown to be overrepresented in EE cases compared to controls. However, the role of rare variants within non-coding elements of the genome is understudied in the epilepsies. microRNAs are ~22nt non-coding RNAs which regulate mRNA expression through the 3'UTR. MicroRNAs are dysregulated in epilepsy patient samples and animal models. Using whole genome sequencing (WGS) data, we tested the hypothesis that rare microRNA-associated variation contributes to genetic risk for the EEs.

We assessed rare variant enrichment in 1,818 individuals (336 cases and 1,482 controls) through the 100,000 Genomes Project. We ran gene-set burden and collapsing analysis on ultra-rare variants (URV) across microRNA-encoding genes and 3 functional domains within 540 epilepsy associated genes, including conserved 3'UTRs, predicted microRNA-binding sites within 3'UTRs, and the coding sequence (CDS).

We found significant enrichment of URVs within conserved 3'UTRs in cases compared to controls. We also replicated previous findings on the enrichment of damaging URVs within the CDS. In addition, we found a signal for URV enrichment within seed and mature microRNA domains, which we will explore in a larger epilepsy cohort.

We have identified novel enrichment of rare variants outside protein-coding regions in EE cases using WGS data. These 3'UTR variants potentially regulate microRNA binding ability and will be characterised further.

OP05 Late Upper Palaeolithic genomes from the south of France.

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The genomic makeup of Europe from the end of the Last Glacial Maximum (LGM) is only beginning to be unravelled. In the Late Upper Palaeolithic of west Europe several distinct genetic ancestries have previously been reported. The first is associated with individuals from Magdalenian contexts in central Europe. The other, often named after the Palaeolithic Villabruna individual, represents the genetic ancestry which later formed the major ancestry fraction of the west European Mesolithic individuals. The processes by which these major genetic lineages of post-glacial Europe originated and admixed are only partially understood. The south-west of France is a key region in decoding these changes, as a region which may have been continuously occupied by modern humans since the Aurignacian period, which began 43,000 years ago. In this study we present six new shotgun sequenced genomes spanning a period of over 10,000 years, from the end of the LGM to the the beginning of the Holocene. Through the co-

analysis of these genomes with existing genetic data we present a framework for population movements, contact, and admixture during the late Upper Palaeolithic.

OP06 Blockchain and Artificial Intelligence-Enabled Stratified Trial System (BESTS) OP patient driven platform that leverages clinical and genomic data to accelerate clinical trial recruitment for precision therapies

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Background: With accelerating genomic discovery, the number of potential targets that might enable a precision approach is rising. Furthermore, clinical trials will become more personalised and stratified. However, recruitment of patients to studies is a significant barrier. We present BESTS, a cloud-based platform developed for collaborative use by patients, healthcare providers (HCPs) and clinical research organisations. Using artificial intelligence (AI), it allows patients to be matched to relevant trials via their health information, while retaining control and ownership of that data.

Methods: User-centred design and a combination of requirements gathering, ethnographic fieldwork, process mapping and prototyping was applied. Twenty-five participants representing HCPs, people with different conditions and caregivers engaged in interviews and workshops to elicit value propositions and user-requirements. From these, a specification of desired modules of functionality was established and guided design and build of initial prototype.

Results: BESTS value propositions for patients includes greater control around their data, reduced burden searching for suitable studies and access to genetic sequencing. Value propositions for HCPs includes easy identification of patients for trials and potential to demonstrate suitability as a trial site. A prototype was built containing four key modules: dynamic consent, enabled by blockchain technology; a genomics profile whereby patients can access whole genome sequencing; a clinical profile with condition-specific information and a dashboard to review clinical trial matches.

Conclusion: Privacy-by-design and PPI enables real-world effectiveness. Fears around digital technologies can be offset through transparency and informed consent. Accelerating trial recruitment will facilitate a faster introduction of treatments into care-pathways.

OP07 Using smMIPs-based panel sequencing to elucidate the genetic architecture of macular degenerations in an Irish cohort

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Macular degenerations (MD) represent a subtype of inherited retinal degeneration, with a high level of genetic heterogeneity, characterised by central vision loss and progressive degeneration of the macula and underlying retinal pigment epithelium. This study aims to sequence a cohort of Irish MD patients in an effort to provide a genetic diagnosis that enables patients to have greater clarity on disease prognosis and progression.

smMIPs-based targeted sequencing is an effective DNA sequencing methodology, often yielding high solve rates. An MD-smMIPs panel was employed, covering the exons and choice intronic regions of 105 inherited (i)MD and age-related (A)MD-associated genes, along with some known deep-intronic, non-coding and regulatory risk factor variants. Over 200 Irish MD patients were sequenced, with 20% of this cohort comprising MD patients that remained unresolved after a previous form of genetic screening. This study provides a diagnostic yield thus far of 32%. To date, 12 novel candidate disease variants have been identified in this MD cohort, in genes previously associated with iMD.

With the development of personalised medicine and novel gene therapies, it is increasingly important that we identify specific mutations in patients to enable an accurate diagnosis and implementation of optimal treatment plans. smMIPs targeted sequencing represents an effective first tier approach for providing MD patients with a genetic diagnosis. Continued analysis will undoubtedly identify further known and novel variants in MD-associated genes. Furthermore, this work may also reveal potential genetic overlaps between iMD and AMD that have not been elucidated as of yet.

OP08 Pinpointing where risks occur along a Clinical Genetics patient pathway; Data from 5 European centres

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Objectively pinpointing risks along the Clinical Genetics patient care pathway can identify areas where controls could improve safety and quality. This is critical as genetic and genomic testing becomes increasingly accessible via mainstream clinical services.

A 22-step process map was created spanning 5 stages along the Clinical Genetic patient journey: Patient and family history assessment, Clinical management of genetic testing, Sample processing and analysis, Result transmission, Result discussion. Participating clinical genetics teams completed a 6-week anonymised audit plotting risk events and near-misses using the process map. The frequency of risk events was calculated against the number of appointments offered over the 6 weeks.

Appointments with risks events ranged from 0.8% (Oulu) to 20.3% (Craiova). When risk events occurred, they frequently involved more than one map step, ranging from 20.0% (Craiova) to 52.4% (Belfast). Oxford had frequent events in the patient and family history assessment stage identified by the Genomic Practitioner at triage (mainstreaming risks), reducing the likelihood of risk in the downstream pathway. Oulu, where specialized genetic nurses support mainstreaming by managing the pretest counselling and organising the practical procedures, has a very low risk rate. Dublin was the only centre where secondary findings were identified (4 in total), which raises concern regarding quality of pre-test counselling in an Irish mainstream setting. Comparison of the patient journey risk-hotspots by centre permits identification of best practice strategies. Accessible, inter-connected IT infrastructure, staff resourcing and genomic education for mainstream clinicians were identified as possible means to reduce risk.

OP09 A 6 month pilot study for germline genetic testing for ‘BRCA’ and ‘Lynch’ in Cork University Hospital.

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Introduction: Germline cancer genetic testing is increasingly an important factor in delivering personalised cancer care. Increasing demands on genetic services in Ireland have resulted in the generation of significant waiting times for patients. In response, the Irish National Cancer Control Programme (NCCP) have developed a model of care for hereditary cancer which proposes the initiation of specified mainstream testing. In alignment with this, Cork University Hospital (CUH) has commenced a pilot cancer diagnostic service, funded jointly by the NCCP and CUH.

Methods: Over a 6 month period (10th Jan to the 10th June, 2023), patients who met the developed CUH ‘BRCA’ and ‘Lynch’ criteria were offered the choice to take part. Patients were offered an appointment with a Genetic Counsellor (AHCS) or a Consultant Geneticist.

Results: A total of 81 patients met the test criteria. Sixty nine per cent of patients requested clinic appointment with the remainder facilitated through a virtual option. Thirty nine patients received their results during this period: five likely pathogenic/pathogenic variants were identified [2x BRCA1, 2x BRCA2 and 1 MSH6]. One patient was identified as homozygous for a low/ moderate risk CHEK2 variant and 4 patients had variants of uncertain significance identified. The average time from referral receipt to an appointment was 22 days, the average time from referral receipt to result discussion with the patient was 57 days.

Conclusion: Through the development of strict criteria, a specific regional pathway for cancer diagnostic genetic services can be successfully delivered in a timely fashion.

OP10 A cascade-driven review of variant assessments comparing probands’ reports to updated assessments

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The Next Generation Sequencing (NGS) Laboratory at the Mater Misericordiae University Hospital has recently established cascade screening as part of the germline genetic testing diagnostic pipeline for Cardiology patients. This process involves targeted Sanger sequencing of a proband’s biological relative/relatives and subsequent variant assessment if an individual tests positive for the familial variant.

The NGS Laboratory follows the guidelines published by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP), ClinGen Sequence Variant Interpretation Working Group and the Association of Clinical Genomic Science (ACGS) for variant assessment and classification. However, variability exists within the implementation of variant interpretation between clinical laboratories, which can lead to discordance in classification. In addition, modern assessment of a variant could result in the potential upgrade or downgrade of its pathogenicity, which could have an impact on clinical management.

Here we will review the outcomes of cascade genetic testing in family members at the NGS Laboratory. We will demonstrate the importance of reassessing variants using new evidence and the application of the most recent variant interpretation standards from ACMG/AMP, ClinGen SVI and ACGS. Following this, we will discuss the insights gained during the process of variant reclassification and highlight the potential clinical and reporting impact.

POSTER PRESENTATIONS

P01 The utility of donor polygenic risks scores in predicting long term graft function.

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Background: Donor age and type (living vs deceased) are well established predictors of kidney transplant outcome. GWAS for traits including eGFR have demonstrated the effect of common genetic variation on kidney function. These GWASs can be used to calculate Polygenic Risk Scores (PRSs) at the individual level. We investigate the role of polygenic burden for multiple traits in kidney donors on transplant outcome.

Methods: We included 6,659 genotyped kidney transplant donors from 5 European ancestry cohorts. We calculated PRSs for Albuminuria, eGFR, hypertension, Kidney volume (KV), Intracranial aneurysm (IA), and stroke in the kidney donors using large published GWASs of European ancestry. We investigated the role of these PRSs on both transplant survival and transplant function.

Results: Standard deviation (SD) increases in donor hypertension and IA PRSs resulted in 7.8% and 8.1% increases in risk of graft failure respectively (p: 0.01, 0.008). SD increases in donor hypertension and IA PRSs result in a 0.69 and 0.70 mL/min/1.73m2 decease in recipient eGFR at 1-year post-transplant respectively (p: 0.005, 0.002). Similarly, a one SD increase in eGFR PRS results in a 1.6 mL/min/1.73m2 increase in eGFR at 1-year post-transplant (p: 2.0e-10). We found that those with high polygenic burden (top decile) for high eGFR had a mean eGFR at 1-year post-transplant of 56.2 vs 51.0ml/min/1.73m2 for those in the bottom decile.

Conclusions: These observations support the hypothesis that donor PRS has a significant impact on graft survival and function. These findings could have utility future transplant allocation decisions.

P02 A genetic perspective on the recent demographic history of Ireland and Britain

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Background: The demographic histories of the subtle but discrete genetic communities within Ireland and Britain are largely unclear.

Methods: We assembled genotype data from Irish and British individuals with ancestry from specific regions. Using networks of Identity-by-Descent (IBD) segment sharing, we detected regional genetic communities, and inferred demographic histories by estimating: (1) degrees of haplotypes shared across IBD length categories and estimated consanguinity, (2) changes in recent effective population size (N_e), (3) temporal patterns of migration rates, (4) temporal patterns of inferred European ancestry within Ireland and Britain, and (5) association of surnames with regional genetic communities in Ireland.

Results: The Orcadian, Manx, and Welsh communities show features of population isolation with elevated levels of IBD-sharing and ROH while the Irish communitites show cimilar levels of IBD shared. This is reflected in the Ne trajectories: recent population decline in the Orcadian, Manx and the Welsh communities while the Irish communities indicate a shared demographic growth. Temporal migration rate surfaces show changes in N-S migration barriers in Britain and Ireland over time and a stable migration corridor between N.E.Ireland and S.W.Scotland. There is a strong historical IBD-sharing signal from N.W. France and a more recent N-W Norwegian signal in Irish genetic groups and strong Germanic, Swedish and Norwegian contributions in the British groups.

Conclusions: We offer new insights into changes in the recent regional demographic history of Ireland and Britain over time. Through this, we can understand the driving forces of rare allele frequencies and disease risk association within these populations.

P03 Cell-type specific transcriptomic profiling in schizophrenia identifies changes in GABAergic neurons and oligodendrocytes at transcript level

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Schizophrenia is a complex neuropsychiatric disorder which affects approximately 1% of the population. There is an increasing focus on studying the molecular mechanisms of this disorder at cell-type resolution. Cell-type specific gene expression changes in schizophrenia are largely unexplored, particularly at the transcript-level. As such, we investigated disease-specific changes in gene expression across a range of cell-types.

RNA-seq profiled gene expression in prefrontal cortex tissue from schizophrenia cases (n=50) and controls (n=50). For each individual, four cell-types were isolated via fluorescence activated nuclear sorting (FANS), including GABAergic neurons , glutamatergic neurons , oligodendrocytes and microglia/astrocytes. Differential analysis at gene and transcript levels yielded marked differences in the genes implicated. The majority of the significant genes identified at transcript-level were not observed in the gene-level analysis, indicating the need to study differences in transcript expression at cell-type resolution. Different isoforms of KMT5A, a known schizophrenia risk gene, were implicated in GABAergic neurons and oligodendrocytes, and were not observed in traditional gene or transcript-level analysis. Cell-type specific imputed gene and transcript expression profiles for 870 individuals were created using the FANS data as a reference. This increased our power to identify disease associated expression changes in comparison to the FANS analysis and enabled a QTL analysis to link expression changes to genetic variants.

Overall, these analyses explored altered biology in schizophrenia on a cell-type specific basis. They placed particular emphasis on transcript changes which have been understudied at the cell-type level to date and may further our understanding of the neurobiology of schizophrenia.

P04 Determining the diagnostic yield of genomic testing from pulmonary fibrosis ascertained in Ireland

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Introduction: Idiopathic pulmonary fibrosis (IPF) is a fatal, progressive, irreversible lung disease. When IPF occurs in more than one first-degree relative it is termed familial pulmonary fibrosis (FPF). Patients with connective tissue disease (CTD) can develop inflammation and scarring in their alveolar cells, which may progress to pulmonary fibrosis. We compared the diagnostic yield of genomic testing when applied to IPF, FPF and CTD and catalogued the genetic landscape of pulmonary fibrosis mutations in Ireland.

Methods: We recruited and consented 112 patients to the study via the Respiratory and Rheumatology clinics at Beaumont Hospital, Dublin. To date, we have analysed whole-exome sequencing (WES) data of 26 patients with IPF, 23 with FPF and 63 with CTD-related ILD. WES was obtained from blood-derived DNA and processed using a GATK-V4.2 pipeline. A diagnostic assessment of the pathogenicity of each variant was conducted according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Results: We identified a pathogenic RTEL1 variant [NM_001283009: c.2920C>T] in a family with FPF. We identified a variant of unknown significance in RTEL1 [NM_001283009:c.1189C>G:p.Q397E] in another family with FPF. No pathogenic/likely pathogenic variants were identified in the IPF and CTD datasets, although we did identify variants of unknown significance in RTEL1, SFTPA1, NAF1 and ZCCHC8.

Discussion: These results indicate a diagnostic yield for FPF of 5.26% in the Irish population, although the sample size analysed to date is small. A lack of pathogenic variants in the IPF or CTD groups is consistent with the literature.

P05 A comparison of feature selection methodologies and learning algorithms in the development of a DNA methylation-based telomere length estimator

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Background: The field of epigenomics holds great promise in understanding and treating disease with advances in machine learning (ML) becoming increasingly important. Recently, DNA methylation (DNAm) measures have been utilised to detect disease and estimate biological traits such as aging. Given the challenge of high-dimensionality of DNAm data, feature-selection techniques are commonly employed to reduce dimensionality and identify the most important subset of features. In this study, our aim was to test and compare a range of feature-selection methods and machine-learning (ML) algorithms in the development of a novel DNAm-based telomere length (TL) estimator.

Results: We found that principal component analysis in advance of elastic-net regression led to the overall best performing estimator when evaluated using a nested cross-validation analysis and two independent test cohorts. This approach achieved a correlation between estimated and actual TL of 0.295 in our validation test set. Contrastingly, the baseline model of elastic-net regression with no prior feature reduction stage performed less well in general—suggesting a prior feature-selection stage may have important utility. Additionally, we observed that different DNAm-based TL estimators, with few common CpGs, are associated with many of the same biological entities.

Conclusion: The variance in performance across tested approaches shows that estimators are sensitive to dataset heterogeneity and the development of an optimal DNAm-based estimator should benefit from our developed methodological approach. Moreover, our methodology which utilises a range of feature-selection approaches and ML algorithms could be applied to other biological markers and disease phenotypes, to examine their relationship with DNAm.

P06 Adapted qPCR Methodology to Detect Oxidative Damage Associated with Induction of Telomere Attrition (TA) in Murine Tissue

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Numerous studies suggest that oxidative stress (OS) is associated with TA but rarely is telomeric oxidative damage (TOD) directly assessed. TOD alters shelterin binding, induces replication fork stalling and inhibits telomerase activity.

We adapted previously published methods to measure TOD, for use in murine tissue. We used C57BL/6J mice, with a naturally occurring nicotinamide nucleotide transhydrogenase (NNT) deficiency, previously used as a model of OS. Relative telomere length (RTL) was measured using mmQPCR and TOD was directly assayed using a formamidopyrimidine DNA glycosylase (FPG) enzyme-based qPCR method. This analysis compares reaction efficiencies before and after FPG treatment. FPG has a role in base excision repairs pathways, removing oxidised Purines (notably 8-Oxo Guanine). A reduction in the efficiency of the reaction indicates the presence of 8-oxo guanine in the telomeric tract ie TOD.

We adapted the assay specifically to investigate the longer murine telomeres. Namely reducing total template, increasing incubation time and adjusting qPCR parameters.

We show that both WT and nnt-/- kidney tissue has high RTL and low OS, testes has low RTL with high OS and BAT has average RTL and high OS. Using this improved method we have been able to show direct oxidative damage in a variety of mouse tissues and to demonstrate that TL and TOD do not always correlate. In light of our findings, care should be taken when interpreting data which use indirect biomarkers of oxidative stress to assess their role in TA. Additionally the nnt-/- mouse model, surprisingly did not show differential TOD.

P07 Diagnostic Yield of Broad Genomic Strategies: An Updated Analysis of The Irish Kidney Gene Project Registry

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Introduction: The prevalence of monogenic nephropathies is underestimated, despite over 700 genes being implicated. Herein, we provide an update on the diagnostic yield of various technologies (exome sequencing, targeted gene panel, and *MUC1* genotyping) employed by the Irish Kidney Gene Project (IKGP).

Methods: Between January 2014 and March 2023, clinic visit records were analyzed for clinical and genetic factors associated with resolved cases. ACMG-defined pathogenic or likely pathogenic variants were considered disease-causing.

Results: 593 IKGP families (976 individuals) have been sequenced to date, of which 58.5% have reached kidney failure, with an average age of 42.3 ± 16.5 years. We identified a disease-causing variant in 47.4% (281/593, following ACMG guidelines) of families, encompassing 52 distinct monogenic entities. Three phenotypes accounted for up to 82% of positive results in genes

related to 1) polycystic kidney disease (*PKD1* (number of families (n)=155), *PKD2* (n=23), *IFT140* (n=4)), 2) tubulointerstitial kidney disease (*UMOD* (n=6), *MUC1* (n=9), *HNF1B* (n=2), and *DNAJB11* (n=1)), and 3) COL4A-related disease (*COL4A5* (n=20), monoallelic *COL4A4* (n=1), *COL4A3* (n=8). Disease-causing variants identified in the remaining 42 genes comprised less than one-fifth of the solved families. A monogenic cause was identified in 31% (24/77) of families with CKD of unknown cause. In an adjusted model for age and sex, a family history of CKD predicted the genetic diagnosis independently [odds ratio: 4.7; 95% CI: 3.47–6.41, P <0.0001].

Conclusion: The use of broad genomic strategies for kidney diseases has a high diagnostic yield, especially in the presence of family history.

P08 A Novel Dominant ALG5 Pathogenic Variant in Two Unrelated Irish Families with Late-onset ADPKD and Atypical Tubulointerstitial Changes

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a monogenic disorder renowned for its clinical and genetic heterogeneity. Here, we investigated the genetic cause of the disease in two unrelated Irish families displaying a late-onset ADPKD phenotype with atypical tubulointerstitial changes.

Methods: Clinical and radiological assessments were performed. The available kidney biopsies were reevaluated. Whole-exome sequencing (WES) was employed following the exclusion of disease-causing variants using a custom-targeted gene panel of 227 nephropathy-associated genes and single-molecule real-time sequencing of the MUC1 gene.

Results: The clinical diagnosis was consistent in the majority of 23 affected individuals from two unrelated families with non-enlarged cystic kidneys and few or no liver cysts. Polycystic liver phenotype (>20 cysts) was present in two individuals. Although affected individuals displayed some degree of kidney impairment, five have progressed to end-stage kidney failure at an average age of 73.2±8.7 years. Extensive interstitial fibrosis and cystic tubular dilation were observed on biopsies of four affected individuals.

A novel missense variant in the ALG5 gene (c.235C>T, p.Arg79Trp) segregated with disease status in both investigated families. ALG5 was absent from the initial custom gene panel. The novel ALG5 variant was absent from the Genome Aggregation Database, and it is predicted to destabilize the protein as it is located in a conserved region. Therefore, this variant was classified as pathogenic per the American College of Medical Genetics and Genomics criteria.

Conclusions: This study expands the phenotypic spectrum of ADPKD loci by considering a novel ALG5 variant, which may inform clinical management.

P09 The impact of additional damaging rare variants on familial variability in autosomal dominant polycystic kidney disease

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Introduction: Evidence indicates that familial variability in autosomal dominant polycystic kidney disease (ADPKD), a known monogenic nephropathy, is influenced by undetermined molecular causes. We hypothesized that co-inheritance of additional damaging rare PKD1 or PKD2 variants (ADRV) with a pathogenic variant may cause familial variability.

Methods: Targeted gene-panel identified primary pathogenic variants in familial cases of clinically diagnosed ADPKD. ADRVs were investigated using the following criteria: 1) rare (allele frequency <0.01), 2) exonic or splicing region missense variants, and 3) SIFT and PolyPhen predicted to be detrimental to protein formation. All AV were deemed as variants of uncertain significance. We

compared disease progression to end-stage kidney failure (ESKF) in families with ADRV (≥1 member with ADRV per family) and families with only primary variants.

Discussion: A total of 115 families with ADPKD (338 individuals, 55.9% female, 53.8% progressed to ESKF) were included. Thirty-one (26.9%) families (52 individuals) had at least one patient with an ADRV. Those with non-truncating PKD1 variants and ADRV had a lower mean age of ESKF than those without additional variants (46 ± 10.1 vs. 52.35 ± 11.6, p = 0.041). The mean age of ESKF was not different between families with truncating PKD1 and PKD2 variants. In a multivariate Cox mixed-effects model, we identified an independent effect of the additional variants on familial disease progression [multivariate shared frailty model p = 0.0015].

Conclusion: Our findings suggest that co-inheritance of additional rare damaging variants in families with PKD1 non-truncating variants may explain familial variability in ADPKD.

P10 Copy Number Variant Analysis Using Sequencing Data Improves Diagnostic Yield for Autosomal Dominant Polycystic Kidney Disease

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by clusters of kidney cysts, leading to kidney enlargement and functional decline. While pathogenic variants in PKD1 and PKD2 genes are known causes of ADPKD, copy number variants (CNVs) in these genes are not routinely included in genetic diagnostic tests. When included, additional testing is via multiplex ligation-dependent probe amplification (MLPA), which is separate to NGS diagnostic pipelines. Here we set out to call pathogenic CNVs for ADPKD using NGS data.

Methods: 14 patients (5 families) from the Irish Kidney Gene Project with no molecular diagnosis (NMD) following whole exome sequencing (WES) (n=11) or WES plus targeted gene panel (n=3) were analyzed for CNVs in PKD1 and PKD2 using the GATK germline CNV caller pipeline (GATK gCNV). The results were verified using MLPA. Further testing is underway for other NMD families.

Results: CNVs in PKD2 were called from the NGS data in 5/14 patients (2/5 families). All five were confirmed by MLPA; 3 in one family with an exon 5 heterozygous deletion, and 2 in another family with a large heterozygous deletion encompassing PKD2. No families had CNVs in PKD1 detected by GATK gCNV or MLPA. CNV calling increased the diagnostic yield in a cohort of 379 patients from 89% to 91%.

Discussion: These results indicate that NGS data can be used for CNV detection alongside the routine SNP and insertion/deletion analysis. Inclusion of CNV calling from NGS could improve the diagnostic yield of genetic testing of ADPKD.

P11 ACMG-guided diagnostic yield in genetic generalized and non-acquired focal epilepsy

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Background: Epi25 is a collaborative of >200 partners from 40 research cohorts, focused on the genetics of epilepsy. However, to date, analysis has focused on ultra-rare risk variants, as distinct from pathogenic variants. No formal cohort-level genomic diagnostics have been conducted using internationally recognized guidelines for variant pathogenicity assignment. Here we applied American College of Medical Genetics and Genomics (ACMG) guidelines to individuals diagnosed with genetic generalized (GGE) and non-acquired focal epilepsy (NAFE) in the Epi25 dataset.

Methods: We identified GGE and NAFE patients by their phenotypes and family history. Intellectual disability was an exclusion criteria. We shortlisted variants from exome data that satisfied the following genetic criteria; (i) gnomAD MAF <0.001, (ii) exclude non-coding and synonymous variants, (iii) limit to genes on the Genomics England PanelApp list. Shortlisted variants were classified using ACMG criteria for pathogenicity.

Results: Our results provide a diagnostic yield of up to 2% (9/441) in GGE and up to 7.3% (33/450) in NAFE. We identify a diagnostic yield of 0.6% (1/157) in juvenile myoclonic epilepsy, 1.6% (2/124) in childhood absence epilepsy onset <9yrs, 2.3% (2/86) in epilepsy generalized tonic clonic seizures alone and 5.4% (4/74) in juvenile absence epilepsy patients. The highest yield genes for NAFE were DEPDC5 and SCN1A.

Conclusion: These data suggest a modest but significant diagnostic yield in common epilepsies without ID. Further data are required to solidify these findings but, on completion, will represent a comprehensive assessment of exome sequencing diagnostic yield in patients with NAFE and GGE.

P12 European Health Data Space: implications for genetics research in Ireland

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Genetic and genomics research has a culture of data sharing, but the sharing of this data requires the navigation of complex ethical and legal rules. In recent years, researchers have been critical of the General Data Protection Regulation (GDPR) for hampering the sharing of data for research. This is in part due to the fragmented implementation of the GDPR across the European Union (EU) Member States and the differing rules on the secondary use of data.

In May 2022, the European Commission published the draft regulation for the European Health Data Space (EHDS). It is part of the European Commission's plans to build a strong European Health Union and to realise the potential that data holds for the economy. The draft regulation is aiming to address some of the elements of the GDPR that are perceived to be hampering data sharing by proposing (amongst other purposes) one legal framework to facilitate access to electronic health data across all Member States for eight specified purposes that includes "purposes that would benefit the society such as research, innovation, policy-making, patient safety, personalised medicine, official statistics or regulatory activities".

While such a framework is clearly needed to enable data sharing, the proposed regulation conflicts in part with Irish legal and ethical principles, including the Health Research Regulations 2018. This paper will reflect on the EHDS and its potential impact on data sharing for genetics research in Ireland.

P13 Investigating the genetic basis of cognitive function

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Rare protein truncating variants in ADGRB2, KDM5B, GIGYF1, ANKRD12, SLC8A1, RC3H2, CACNA1A and BCAS3 have an impact on adult cognitive function. The aim of this study was to investigate if common variants at these genes also influence cognitive function, specifically the domains of general IQ, episodic memory, working memory, attentional control and social cognition. SNPs were selected at each gene for analysis if they represented eQTL in brain tissues, missense variants or variants that have been associated with cognitive function or schizophrenia from GWAS. Genotypic data for these SNPs and phenotypic data for the cognitive domains were extracted from our Irish psychosis case-control (1,540 = 1005 cases and 535 controls) and analyzed using linear regressions. Twenty-three LD independent SNPs were analyzed across all genes. No SNPs were associated after the Bonferroni correction. Among the nominally significant results, two missense variants (rs7243088 and rs34996750) at ANKRD12 were associated with IQ and social cognition respectively. In addition, eQTL SNP rs12607307 was associated with IQ and working memory, where the G allele was associated with poorer cognitive function and increased gene expression. At CACNA1A eQTL SNP rs2302080 was associated with IQ and working memory (C allele was associated with poorer cognitive function and increased gene expression). At SLC8A1 eQTL SNP rs62149405 was associated with IQ and social cognition (T allele was associated with poorer cognitive function and decreased gene expression). We detected some evidence that common variants at these genes are associated with cognitive function but further analysis is required in larger samples.

P14 Nonsense SERPINA1 Variants and Alpha-1 Antitrypsin Deficiency

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Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder that can cause lung, liver, and skin disease. The most common pathological mutation is Z (p.Glu342Lys, rs28929474), present in 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.

23,500 Irish individuals have been screened following American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines in a national targeted detection programme. Serum AAT quantification is by turbidimetry. AAT phenotyping by isoelectric focusing allied to confirmatory allele-specific genotyping when required. Rare and novel mutations are identified by SERPINA1 gene sequencing.

We have identified a large number of rare mutations in a national targeted detection programme for AATD. These include nonsense or null (Q0) mutations that produce no detectable AAT protein in routine laboratory quantitative assays. Overall, a total of 6 different Null mutations have been detected, Q0amersfoort, Q0bolton, Q0lisbon, and Q0porto, in addition to 2 novel mutations Q0dublin and Q0cork (Ferrarotti et al, 2014).

Our study underlines the importance of multiple approaches to investigating AATD, including phenotyping, allele-specific genotyping, and SERPINA1 sequencing (Franciosi et al, 2019). As testing for AATD increases, it is likely that additional nonsense mutations will be discovered.

P15 Congenital Mismatch Repair Deficiency (CMMRD) Diagnostic and Screening Challenges

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We present a case of a 32 year old man, who was diagnosed aged 30 with a carcinoma of the transverse colon showing microsatellite instability. Despite no family history in keeping with Lynch Syndrome, germline genetic testing confirmed homozygous PMS2 variants yielding a diagnosis of CMMRD. Subsequently he was diagnosed with a colonic tubulovillous adenoma with associated polymorphic EBV positive lymphoproliferative disorder.

CMMRD is a rare cancer predisposition syndrome caused by biallelic pathogenic variants in the mismatch repair pathway. PMS2 biallelic variants are the most common cause of CMMRD. Diagnosis based on family history alone can be difficult due to the reduced penetrance of PMS2 in comparison to other genes in the mismatch repair pathway. This syndrome is not fully understood with diagnostic criteria first published by Wimmer et al in 2014.

Current recommendations come from the European Consortium ‘Care for CMMR-D’ and were published by Vasen et al in 2014. Screening for haematological based cancers remains difficult; clinical examination and blood count biannually is recommended and consideration to be given to optional abdominal ultrasound. These guidelines are best aimed at identifying lymphoma and leukaemia.

This case expands the phenotype of CMMRD and highlights the current challenges. Wimmer criteria should be considered in young onset cancers and more research is needed to understand the complete phenotype and efficacy of the current screening programme.

P16 Investigating Mitochondrial Genomics and Age-Related Diseases: A Comprehensive Analysis

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Ageing is the leading risk factor for most chronic human diseases, including Alzheimer's, coronary artery disease, diabetes, and common malignancies. The decline of mitochondrial respiratory capacity and the increased production of reactive oxygen species is a well-established aspect of the ageing process, establishing variation in mitochondrial DNA as a crucial area of study in the ageing process. While previous studies have identified several candidate biomarkers, the small datasets have produced results that are often non-replicable or disputed between studies.

Our goal is to determine the impact of somatic and inherited mitochondrial genetic variation on biological ageing and disease. We aim to achieve this by developing a new analysis pipeline for mitochondrial genetic data and leveraging the extensive data from UK Biobank. This dataset includes comprehensive genetic and phenotypic information, such as genome-wide genotype data for all 500,000 participants obtained through an Affymetrix array and whole-exome and whole-genome sequencing data for eligible individuals. Additionally, single-variant analyses, gene-gene interaction analyses, haplogroup analyses, mitochondrial copy number, and heteroplasmy analyses will provide valuable insight into the role of mitochondrial genomics in biological ageing and disease and contribute to the existing knowledge base in the field.

P17 Identification of autism-associated copy number variations: bioinformatic filtering pipeline optimisation in whole genome sequencing family data

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Autism Spectrum Disorder (ASD), commonly referred to as autism, is a neurodevelopmental condition diagnosed in 1 in every 100 children worldwide and that is characterized by impairments in social communication and restrictive, repetitive behaviours (RRBs). Today, autism diagnosis relies on the psychiatric assessment. Despite autism’s strong association with genetic factors, the established diagnostic criteria do not include condition-associated genetic biomarkers. Consequently, inaccurate and gender-biased diagnoses of autism are still very frequent. Advances in next generation sequencing technology and bioinformatic tools have corroborated the instrumental role that Copy Number Variations (CNVs) - a type of rare genetic variants that include the duplication and deletion of genomic segments (>50bp) - play in the etiology of autism. Therefore, and considering the current lack of widely accepted bioinformatic workflows for the detection of CNVs, this project aims to implement a filtering strategy for WGS data from a multiplex family cohort to accurately identify autism-associated CNVs. The proposed filtering pipeline presents a combinatorial approach, using four different CNV calling algorithms (CNVpytor, ERDS, LUMPY and Manta) and tests a total of 62 individuals from 11 autism-affected multiplex families. We found that an average of 2985.8 deletions and 211.3 duplications were detected per individual in the cohort. Furthermore, after implementing a CNV accepting criteria based on family and relatedness information, an average of 3,614.4 total CNVs were identified per pedigree. All identified CNVs were compared to a list of 49 neurodevelopmental condition-associated CNVs (ND-CNVs), out of which 14 were preliminary detected in the cohort.

P18 Rare variant burden analysis in polycystic kidney disease

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Background: Polycystic kidney disease (PKD) affects 12 million individuals worldwide. Although genomics has been transformative in PKD diagnostics, there is considerable unexplained variance in disease severity. We hypothesise that PKD is the result of a combination of previously established monogenic causes but also polygenic factors. In this study we performed rare variant burden among Irish PKD patients in order to determine the role of polygenic burden as a modifier of PKD risk and prognosis.

Methods: Patients were recruited via the Inherited Kidney Disease Clinic at Beaumont Hospital. Targeted panel and whole exome sequencing data from 480 PKD patients and whole genome sequencing data from 134 Irish controls from ALS study were analysed and processed a GATK4-based bioinformatics pipeline and annotated using ANNOVAR. Variant filtering and sub-setting were subsequently conducted using custom-built scripts in R. Burden testing was performed using SAIGE-GENE software. Analysis focused on variants within two gene lists (i) genes known to cause ADPKD, ARPKD and Polycystic Liver and Renal cysts (n=14) and (ii) cystic kidney disease genes (defined by Genomics-England PanelApp) (n=74).

Results: After processing and filtering the raw genomic sequence, 97 variants were obtained for gene list 1 and 137 variants for gene list 2. Rare variant burden results between unsolved PKD cases and controls and between cases with differing PKD severity will be presented.

Conclusion: Rare variant burden may improve our understanding of how multiple genes influence PKD diagnosis and progression.

P19 Characterisation of diverse global ancestries within the UK Biobank

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The UK Biobank (UKBB) is a large dataset containing in-depth phenotype and genotype data of over 500,000 UK participants. Studies leveraging the UKBB routinely analyse a subset of the participants with homogenous European ancestry, labelled by the UKBB as “White British” according to self-identification and genotype-based principal component analysis. Thus, by analysing 78,620 participants without the “White British” label there is an opportunity to characterise the non-UK ancestries present in the UKBB using population genetic approaches.

Here we characterised world-wide ancestry in the UKBB by identifying the primary ancestry groups as well as a large group of individuals with inter-continental admixture. To identify continental ancestries, an individuals’ continental ancestry proportions were estimated using the ADMIXTURE algorithm and reference populations from the 1000 Genomes and Human Genome Diversity Projects. Applying the dbscan algorithm to these ancestry components in the UKBB yielded six broad ancestry clusters. These were further divided by applying community detection to a network of Identity-By-Descent sharing. With this haplotype sharing data we further characterised sub-continental communities by demographic history, such as population size and isolation.

We find that the UKBB is a repository of diverse ancestries primarily from Europe, Africa, and Asia. The ancestry and immigration history of this world-wide ancestry reflects the demographic history of Britain and the Commonwealth in the 20th century. The population structure identified in this study can serve as a control for population history and facilitate the detection of rare functional variation in diverse ancestry groups.

P20 A cloud-based bioinformatic tool to enable automated diagnostic analysis of raw genomic sequence data from people with rare monogenic diseases

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Introduction: In recent decades, whole genome and whole exome sequencing have been increasingly used both for clinical diagnostic purposes and for research. However, one of the biggest barriers to realising the potential of these methods is the need for expertise and experience in bioinformatics and computer science in order to process the raw genomic sequence and make it accessible and ready for analysis for researchers and clinicians. In order to deal with this problem, we present a cloud-based bioinformatic tool for raw genomic sequence analysis. This tool simplifies the existing complexity of raw genomic germline sequence processing and enables fast and easy automated analysis of a large number of samples for identifying potentially pathogenic variants.

Methods: This tool was built based on GATK4 algorithms and deployed using Cromwell Azure technology. An R script was added to create a unique feature that allows dynamic variant filtering using gene panels to obtain a shortlist of variants for American College of Medical Genetics (ACMG) classification in accordance with the patient's phenotype.

Results: A proof of concept of this tool will be presented, performed using patient-derived whole genome and whole exome sequences of epilepsy and renal disease patients.

Conclusion: This tool can support faster and more effective clinical decision-making and can be integrated into a variety of clinical and research settings.

P21 An Audit of the number of Robertsonian Translocations found after follow-up of Acrocentric Trisomies in Pregnancy Loss Samples in the past 8 Years

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In September 2021, the Northern Ireland regional genetics team based in Belfast City Hospital made a procedural change to the cytogenetic testing of pregnancy loss samples. Prior to this date, both parents of all pregnancy loss samples relating to trisomies of acrocentric chromosomes 13, 15, 21, or 22 were offered karyotype blood testing to identify potential Robertsonian translocations. However, following September 2021, such testing is now solely carried out on trisomy 21 pregnancy loss samples. Motivated by this procedural change, we have collated and analysed parental testing results from 2015 until June 2023, to understand the general characteristics of this data. Of the available parental karyotype data, which was noticeably incomplete during the COVID-19 pandemic, 4 parental translocations were identified during the period considered. Only 2 relating to trisomy 13 pregnancies would have explained the loss of the pregnancy. In the other 2 cases the parental translocation was an incidental finding which did not explain the loss of the pregnancy. This would affirm the relative fatality of non-'trisomy 21' Robertsonian translocations, in comparison to chromosome 21 trisomy This analysis also highlighted the relative heightened incidence of trisomy 21 pregnancy losses, compared to the other acrocentric trisomy chromosome losses considered.

P22 The Effect of Post-Weaning Social Isolation and Chronic Celecoxib Administration on Gene Expression in the Mouse Hippocampus

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Two risk factors for neuropsychiatric disorder are early life stress and chronic inflammation. Here we model these factors in mice using post-weaning social isolation (SI) and chronic anti-inflammatory administration. We investigate how these factors alter gene expression in the hippocampus and investigate the biological relevance of these changes. A total of 32 female C57Bl6 mice were split between chronic celecoxib-treated (CEL) and vehicle-treated controls. Half of the animals were also subject to post-weaning SI from postnatal day (PD) 21 for a total of 40 days for an n = 8 per group. RNA was extracted from the hippocampus and subject to paired-end RNA-seq. Differentially-expressed genes (DEGs) were defined at FDR < 0.05 using DEseq2. SI induced a total of 55 DEGs in the hippocampus, while CEL administration induced 355 DEGs. Five genes (Adamtsl5, Neurod1, Hrasls, Kcnab3, Cdh6) were differentially-expressed by both factors. The most significantly-enriched GO terms for SI DEGs were gamma-aminobutyric acid:sodium symporter activity (GO:0005332), calcium ion binding (GO:0005509). For CEL administration, the top GO terms were neuron part (GO:0097458), neuron projection (GO:0043005) and locomotory behaviour (GO:0007626). Neither set were enriched for common risk genes contributing to neurodevelopmental or neuropsychiatric disorder. When cell type enrichment analysis was performed, SI-induced DEGs were enriched in a population of astroeppendymal cells, while CEL-induced DEGs were enriched in four populations of medium spiny neurons (MSNs). Overall, both factors induced transcriptomic changes in the brain. These changes were related to neurodevelopment and some showed concordance with human psychiatric disorders through cell type enrichment analysis.

P23 Review of variants assessed with updated PP3 guidelines from ClinGen

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The accurate interpretation and classification of genetic variants are crucial for effective diagnosis and management of inherited diseases. The American College of Medical Genetics (ACMG) and Association for Molecular Pathology (AMP) guidelines provide a standardized framework for variant interpretation, with subsequent refinements by various expert groups. These guidelines incorporate the recommended use of computational predictors as "supporting" evidence for variant pathogenicity or benignity. However, the lack of consensus among the suite of predictive tools available, hinders the consistency of application within these recommendations. Updated guidelines, provide defined threshold ranges for different computational predictors and identifies the most robust tool, REVEL, with multiple points of usage from BP4_verystrong to PP3_strong. As these updates are recent changes, the impact that these changes may have on variant assessment and patient care has yet to be fully determined. This study aims to address this issue by evaluating the impact of computational tools on missense variants in genetic testing for Cardiology patients

attending the Inherited Cardiac Conditions clinic at the Mater Misericordiae University Hospital. The Next Generation Sequencing (NGS) Laboratory at MMUH has conducted a re-assessment of missense variants using the new ClinGen recommendations for PP3/BP4 criteria. The study compares the original and updated variant interpretations with the outcomes obtained when incorporating computational tools. The findings of this study hold significant implications for the accurate interpretation and reporting of missense variants in genetic testing. Establishing the clinical relevance for computational tools will enhance variant classification accuracy and improve patient care.

P24 The Genomic Data Infrastructure Ireland Project

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Launched as a European Member States' declaration in 2018, the 1+ Million Genomes (1+MG) initiative aims to facilitate secure access to genomic and associated clinical data across Europe for improved research, healthcare and health policy making. In 2020, the Beyond 1 Million Genomes (B1MG) project was announced and supports 1+MG by coordinating agreement on genomic infrastructure set-up, legal/technical guidance, data standards and data access best practices. In 2022, the Genomic Data Infrastructure (GDI) project was announced to facilitate creation of the infrastructure needed to realise the 1+MG initiative.

The overall aim of the GDI project is to provide a secure cross-border federated network of national genome collections across Europe. The GDI Ireland (GDI-IE) project aims to establish the Irish infrastructure linked to GDI, with public and patient involvement and trust at its core.

Via six related areas of activity, GDI-IE will facilitate Ireland's participation in 1+MG: (1.) Promoting the establishment of the Irish 1+MG mirror group. (2.) Developing a national plan for realisation of Irelands participation in 1+MG. (3.) Creating a proof of concept genomic infrastructure. (4.) Determining the Irish specific governance system required to ensure security. (5.) Performing a feasibility study for an Irish genome project and (6.) The development of training initiatives for the next generation of genomic clinicians and scientists.

Here we outline how GDI-IE is enabling the development of a sustainable and secure genomic data-access infrastructure in Ireland, laying the foundation for data infrastructure that can grow to underpin national level genomics in Ireland.

P25 Proposed model for erythrocyte derived Microvesicles (eMV) as delivery vectors and potential impact on THP-1 cells

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Background: Human erythrocytes secrete Microvesicles (eMV). Its biogenesis has been described as a part of erythrocyte senescence/eryptosis and is involved in cellular communication. eMV profiling may identify new diagnostic markers, therapeutic targets, environmental interactions and signalling pathways. This research proposes an eMV vector role on THP-1 cells.

Methods: Flow cytometry and fluorescent-tagged antibodies were used to determine the "surfaceome" of eMV, western blotting for protein determination, protease determination using capture antibodies on nitrocellulose membrane, and Gene Ontology (GO) analysis for the presence of human proteins/genes comparisons between erythrocyte and eMV. THP-1 cells were challenged with eMV, and microscopic observation of cell growth was undertaken.

Results: eMV were taken up by THP-1 cells via receptor-ligand interaction. eMV were found to contain many proteins including CD36, CD58, CD63, and CD47. Protein Kinase C (PKC) and various down-regulating "has-mir" and "has-let" genes were identified.

Conclusions: eMVs inhibit THP-1 cells proliferation and tetraspanins CD36, CD58 and CD63 allow receptor-mediated endocytosis fusion with THP-1 cells. Once inside the cell, eMV release their content, including miRNAs. CD47 can protect against phagocytosis. The actions of identified eMV content, key transporting molecules including miRNAs, PKC, has-mir and has-let genes detected may explain the observed effect on the recipient cell proliferation and overall fate. PKC is linked to inhibition of cell proliferation, G-protein mediated events, and various down regulator has-mir and has-let genes. The resultant data was used to create a schematic summary of eMV biogenesis, content, communication mechanisms and potential impact of eMV on THP-1 cells.

P26 First instance of a pathogenic ARL3 variant in an Irish inherited retinal degeneration cohort.

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A family of 6 individuals presented with autosomal dominant retinitis pigmentosa (adRP). A likely causative variant in ARL3 was identified through smMIPs-based sequencing of 113 genes associated with RP and Leber congenital amaurosis. Subsequent cascade analysis identified the variant in all affected family members.

ARL3, a small G-protein regulated by RP2 involved in enriching lipidated proteins to outer segments of photoreceptors, was first associated with adRP in 2016, with only two dominant variants reported. One is presented here: ARL3 c.200A>T p.(Asp67Val), where a hydrophilic negatively charged residue is replaced with a hydrophobic neutral residue. This is a highly conserved residue within the nucleotide binding domain, with mutation to Val predicted through AI-based AlphaFold protein-modelling to affect binding to GTP analogue mGppNHp. Moreover, the variant has been shown to confer constitutive GTPase activity to ARL3 (Travis et al., 2023). Additionally, in silico pathogenicity tools strongly support the pathogenicity of the variant.

Interestingly, this dominant variant has previously been reported only once, in a family of Ashkenazi Jewish ethnicity (Ratnapriya et al., 2021). The family presented in our study are not of Ashkenazi Jewish ancestry. We are currently exploring whether these cases are the result of a single founder mutation or dual mutational events. ARL3 variants are a rare cause of adRP, with few cases and only two variants reported world-wide. ARL3 variants can also cause recessive RP, with <10 variants reported. Notably, the case study presented here is the first instance of ARL3-associated retinal degeneration in our Irish IRD cohort.

P27 The Development of an Alkaptonuria Clinic for Adults in Ireland

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Alkaptonuria (AKU) is a rare genetic disorder resulting in abnormal tyrosine metabolism characterised by the deposition of homogentisic acid, leading to ochronosis, spondylo-arthropathy, arthritis and aortic valve disease. Traditionally it was diagnosed in childhood due to the identification of discoloured urine, but with genetic/genomic analysis, it is now detected more efficiently. Nitisinone has been licenced for use in Ireland as a treatment for AKU. Patients on this drug require frequent medical, biochemical and dietetic monitoring.

Due to a lack of an adult services for patients with AKU in Ireland, patients travelled to the National Alkaptonuria Centre in Liverpool. Travel restrictions imposed during the COVID-19 pandemic resulted in the need to develop an Irish service in the National Centre for Inherited Metabolic Disorders, Mater Misericordiae University Hospital (NCIMD-MMUH).

Results: The first Irish National Alkaptonuria Clinic was held at NCIMD-MMUH in March 2022. Four patients attended the service, three as outpatients and one was admitted to restart Nitisinone. This clinic has been repeated at 6 monthly intervals since and the patient number has grown to 6, of which 4 are currently on nitisinone.

Clinic development involved:

1. Metabolics including Genetic Counselling
2. Ophthalmology
3. Rheumatology
4. Orthopaedics
5. Pain clinic
6. MMUH Laboratory -urine and blood metabolite panels

Conclusion / Discussion: This clinic has allowed close monitoring of patients with AKU, including their clinical and biochemical condition, and the safe initiation of treatment without having to travel abroad. This saved the state money as the treatment abroad scheme was no longer required.

P28 Biallelic likely pathogenic variants in RPE65 in a patient with Retinitis Pigmentosa.

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Receiving a genetic diagnosis is of paramount importance for patients with inherited retinal diseases (IRDs) to ensure their eligibility in clinical trials and benefit from therapeutics such as Luxturna. Here we present a case of a patient with two RPE65 variants which have been confirmed in trans. This patient presented at age six with difficulty seeing in low light and at forty years of age, best corrected visual acuity was remarkably well preserved unlike arLCA and arRP.

The proband underwent whole exome sequencing which identified two coding variants in RPE65 NM_000329.2:c.1445A>G,p.Asp482Gly and c.329A>G,p.Asp110Gly. Through rigorous data filtering and utilisation of in silico prediction tools, the p.Asp482Gly variant was investigated further as a potential splice-altering candidate. Midigene plasmids were constructed containing the genomic region of interest and transfected into HEK293T cells. 48 hours post-transfection, mRNA was harvested and wildtype and mutant transcripts analysed by RT-PCR, gel electrophoresis and Sanger sequencing.

Midigene functional analysis revealed a splice defect caused by the p.Asp482Gly variant but not the p.Asp110Gly variant. However, the latter has been reported previously both homozygously and in trans with pathogenic variants in several cases.

It is widely accepted that aberrant splicing plays an important role in the pathogenesis of some IRDs. However, it's essential to conduct functional studies to verify splicing defects and reclassify variants as pathogenic/likely pathogenic. Of particular note, this patient's phenotype is not characteristic of the corresponding genotype which highlights the need for future modifier studies to reveal complex genotype-phenotype correlations in IRDs.

P29 A comparative review of popular DNA methylation microarray analysis pipelines for human intervention studies

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DNA methylation, the most widely studied epigenetic mechanism, plays an essential role in health and is altered in many diseases. Illumina Infinium HumanMethylation BeadChip arrays have emerged as cost-effective tools for quantifying genome-wide DNA methylation. Many packages are available within the R/Bioconductor environment that perform some or all steps of an epigenome-wide association study (EWAS), including quality control, normalisation and identification of differentially methylated sites and regions. For novice users, it can be difficult to navigate these packages to achieve their desired research goals. Two packages, *ChAMP* and *RnBeads*, provide a complete start-to-finish pipeline for methylation array analysis which is capable of being executed in a single line of code, making them "one-stop shops" for DNA methylation analysis. As such, they may be of particular interest to R novices. This review compares these two packages in detail through the reanalysis of previously published methylation datasets from human studies, including studies of coeliac disease and folic acid intervention. Here, we highlight the main differences between these pipelines which lead to variability in results. We found that *ChAMP* provides a more customisable pipeline with a shorter run time, though it is somewhat limited by its inability to adjust for covariates. *RnBeads* has a greater number of features overall, with more options for normalisation and exploratory analysis, and it implements a powerful method for removing surrogate variables. Our findings highlight the impact that the choice of microarray analysis pipeline has on reported results in EWAS.

P30 A rare case of X-linked osteoporosis with fractures due to a splice variant in the *PLS3* gene

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Background: Osteogenesis imperfecta (OI) is a rare, heritable, disorder of bone formation traditionally caused by pathogenic variants in the *COL1A1* and *COL1A2* genes. OI predisposes affected individuals to frequent, low impact fractures. More recently, additional genes have been implicated in OI and osteoporosis. Among them is *PLS3*, which encodes the protein plastin 3 and is involved in the formation of F-actin bundles. While the pathogenesis has not yet been clearly elucidated, pathogenic variants in *PLS3* have been recently shown to be a rare case of X-linked OI.

Case: A forty-one-year-old male patient attended for assessment of dysmorphic features in the context of a previously investigated cardiomyopathy. The patient reported a history of enamel hypoplasia and a significant fracture history without any obvious predisposing factors to osteoporosis. He was born to nonconsanguineous parents and there was no family history of fragility fractures, or of cardiomyopathy. Examination showed a blue-grey tint to both sclerae, highly arched palate, and increased thoracic kyphosis.

A connective tissue disease, multi-gene, panel identified a pathogenic splice site variant in the *PLS3* gene. Subsequent dual energy X-ray absorptiometry confirmed severe osteoporosis (Z-score lumbar spine of -4.4; Z-score hip of -1.9).

Conclusion: Here we describe a case of the recently characterised X-inked OI due to a pathogenic variant in *PLS3*. Further investigations are ongoing into a potential underlying cause for this patient's cardiomyopathy, as *PLS3* variants have not previously been associated with significant heart disease. We also aim to follow treatment response to bisphosphonates going forward.

P31 Prevalence and Spectrum of Lysosomal Storage Disorders: Insights from the Adult National Centre of Inherited Metabolic Disorders

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Background: Lysosomal storage disorders (LSDs) are a major group of genetic disorders that usually result in a deficiency of a specific lysosomal enzyme leading to the accumulation of substrates that cause multi-organ progressive disease. Although individually rare, collectively they are relatively common.

Patients with LSDs require significant multidisciplinary input and the adult National Centre of Inherited Metabolic Disorders (NCIMD-Mater) has developed a highly specialised LSD clinic/service which allows patients access to physicians (including metabolic physicians, cardiologists, nephrologists), nurses, genetic counselling, psychology and social work sometimes in one visit. A registry is currently under development to track patient demographics, natural history and outcome of treatments.

Methods: A retrospective audit was performed on patients attending the NCIMD- to look at the spectrum and prevalence of LSDs.

Results: One hundred seventy patients with 19 different LSDs attend the NCIMD-MMUH specialised LSD service. The largest groups are sphingolipidoses (68.8%) and mucopolysaccharidoses (MPS) (26.5%). In comparison, the most common diseases are Fabry Disease (59.4%), Hurler syndrome (14.1%) and Gaucher Disease (5.3%), with an estimated prevalence among the adult Irish population (≥15 years) 1:41000, 1:172000 and 1:460000 respectively. N215S, the most common GLA variant identified in our FD patients, usually causes a cardiac-predominant phenotype.

Conclusions: Identifying the spectrum and prevalence of patients with LSDs attending NCIMD-Mater is essential for planning the specialised LSD clinic/service as this group requires significant multidisciplinary input. It also informs toward the carrier frequency in the ROI. It is hoped the LSD registry under development will become a National Registry.

P32 The effects of an ultrarare variant in ATP6V0A1 on lysosome function, autophagy and nutrient sensing

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The Vacuolar H+ ATPase is a multi-subunit proton pump involved in the acidification of lysosomes during autophagy. ATP6V0a1, a gene implicated in neurodevelopmental and neurodegenerative disease, encodes the a1 subunit of this proton pump. Whilst these disorders predominantly affect the nervous system, milder phenotypes may be associated with hypotonia and movement phenotypes. We investigated the role of ATP6V0a1 in human muscle and neuronal cells by siRNA-mediated knockdown and overexpression of variant discovered in patients. Myotube morphology, lysosomal function, mTOR signalling and autophagy levels were significantly affected as a result of knockdown or variant overexpression. NFkB activation was also significantly reduced following ATP6V0a1 knockdown which may be associated with lysosome sensing of pro-inflammatory cytokines as a result of ineffective lysosomal acidification by Vacuolar H+-ATPases. Differentiation potential was negatively influenced by ATP6V0a1 knockdown or variant expression. Together, these data support the critical nature of ATP6V0a1 function in muscle and neuronal homeostasis. Next, we aimed to develop allele-specific gene therapies for people suffering from ATP6V0a1-associated disease, validation of allele-specific primers was performed. The sequences and chemistry of allele-specific siRNAs was tested which provides basis for the development of allele-specific siRNA therapies for patients in the future.

P33 The phenylalanine hydroxylase genotype and the expected responsiveness to sapropterin dihydrochloride in the adult Irish population

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Background: Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism resulting from a deficiency of phenylalanine hydroxylase that catalyzes the hydroxylation of phenylalanine to tyrosine with the help of a cofactor (tetrahydrobiopterin; BH4).

Ireland has one of the world's highest incidences of PKU; currently, ~ 400 patients attend the National Centre for Inherited Metabolic Disorders (NCIMD), Mater Misericordiae University Hospital (MMUH). Sapropterin dihydrochloride, a synthetic form of BH4, is a genotype-specific treatment that has recently been added to the precision genomic medicine program at NCIMD, MMUH. To service the plan for the roll-out of this treatment, all patients with PKU were genotyped, including prediction around sapropterin dihydrochloride responsiveness.

Methods: A study, analyzing the PAH genotype of patients (>18 years) with PKU attending the NCIMD, was performed along with sapropterin dihydrochloride responsiveness analysis.

Results: Two hundred eighty-three patients had PAH genotyping performed. One hundred and four different genotypes were identified in the population, with the R408W/R408W (13.78%) being the most common. The most frequent allelic variants were R408W (34.63%), F39L (12%), I65T (10.78%), L348V (5.48%) and IVS12+1G>A (4.78%). Sapropterin dihydrochloride responsiveness was predicted as likely in 12%, unlikely in 47% and difficult to predict in 41% of patients accurately.

Conclusion: The up-to-date PAH genotype landscape in the adult Irish PKU population is presented, detailing percentages of patients who will likely respond to sapropterin dihydrochloride. A large number will require a trial period to investigate responsiveness; information important for service planning as NCIMD continues to develop a precision genomic medicine program.