Ulster Med J 2020;**89(1):**47-63

Abstracts

22nd Meeting of the Irish Society of Human Genetics

Friday 20th September 2019 Stranmillis University College, Belfast.

ORAL PRESENTATIONS:

OP01. The Genetic Landscape of Scotland and the Isles.

Edmund Gilbert[1,2], Seamus O'Reilly[3], Michael Merrigan[3], Darren McGettingan[3], Veronique Vitart[4], Peter K Joshi[5], David W Clark[5], Harry Campbell[5], Caroline Hayward[4], Susan M Ring[6,7], Jean Golding[8], Stephanie Goodfellow[9], Pau Navarro[4], Shona M Kerr[4], Carmen Amador[4], Archie Campbell[10], Chris S Haley[4,11], David J Porteous[10], Gianpiero L Cavalleri[1,2*], James F Wilson[4,5*]. *equal contribution

[1.] Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin, Ireland. [2.] FutureNeuro Research Centre, Royal College of Surgeons in Ireland, Dublin, Ireland. [3.] Genealogical Society of Ireland, Dún Laoghaire, Ireland. [4.] MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, Scotland. [5.] Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland. [6.] Bristol Bioresource Laboratories, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK. [7.] Medical Research Council Integrative Epidemiology Unit at the University of Bristol, Bristol, UK. [8.] Centre for Academic Child Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK. [9.]Isle of Man, UK. [10.] Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, Scotland. [11.] The Roslin Institute and Royal (Dick) School of Veterinary Sciences, University of Edinburgh, Edinburgh, Scotland.

The genetic structure within southern Britain and Ireland is well described, however large swathes of Scotland in particular have yet to be characterised. In addition, Scotland and Ireland experienced Norse Viking invasions around the turn of the 1st and 2nd millennia. However, the extent to which these movements impacted the genetic landscape of both Scotland and Ireland is poorly understood. Thus we; i) assembled genotype data for 2,554 individuals from across the entire archipelago with geographically-restricted ancestry (including the Isle of Man and Shetland for the first time), ii) compared population structure in Scotland to the rest of Britain and Ireland, iii) modelled the proportion of Norwegian ancestry in northern Britain and Ireland, and iv) compared this modern structure to ancient Gael and Norse DNA. Extensive geographic structuring is revealed in Scotland; from broad scales such as a NE to SW divide in mainland Scotland, to very fine structure in the Northern Isles of Scotland. We document Norwegian ancestry in the north of Scotland, within Orkney and Shetland (reaching its maximum in Shetland) which falls to minimal frequency outside of the north of the country. We find the best proxies of ancient Icelandic Gaels in to be the north-west of Britain and Ireland, specifically the Hebrides and Donegal. Therefore the genetic diversity of these regions will allow better understanding of Viking movements and the founding of Iceland.

OP02. Interrogating and correcting fine-scale genetic structure in large (>36,000 samples) GWAS datasets using scalable haplotype sharing methods

RP Byrne[1], W van Rheenen[2], JH Veldink[2], RL McLaughlin[1]

[1.] Smurfit Institute of Genetics, Trinity College Dublin. [2.] Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht.

We leveraged a powerful and scalable haplotype painting algorithm, the Positional Burrows Wheeler Transform (pbwtPaint), to explore the co-ancestry of 36,052 individuals of European descent from a recent amyotrophic lateral sclerosis (ALS) genome-wide association study (GWAS). The resulting haplotype sharing matrix revealed both striking broadscale genetic structure between samples from different countries and subtle genetic structure within each country. This approach captured population structure within the dataset at a far higher resolution than standard methods using unlinked single nucleotide polymorphism data, making it an appealing option for correcting subtle confounding in GWAS. We explored this possibility by fitting principal components (PCs) of this haplotype sharing matrix as covariates in a logistic regression model GWAS, and comparing metrics of statistical inflation and confounding against a model using standard independent marker PCs as covariates. We observed that both the λ_{GC} and LD-score regression intercept were significantly closer to 1 when using PCs of the haplotype sharing matrix, signifying lower inflation and confounding from population structure. Notably, the GWAS analysis that was corrected using haplotype sharing PCs as covariates retained the power to detect all major hits from the original meta-analysis of the data, suggesting that it does not suffer from loss of power to detect true associations. We also detect an additional hit at the established ALS locus *TBK1*, which was sub-threshold in the original analysis, but has since been detected in larger ALS GWAS, implying that this method imparts greater power than traditional approaches in some scenarios.

OP03. Investigating the genetics of cognitive resilience in healthy ageing using the UK Biobank (n = 333,737)

Joan Fitzgerald[1], Laura Fahey[1], Laura Whitton[1], Gary Donohoe[1], Derek W Morris[1]

[1]The Cognitive Genetics & Cognitive Therapy Group, The School of Psychology and Discipline of Biochemistry, The Centre for Neuroimaging & Cognitive Genomics, National University of Ireland Galway, Galway, Ireland

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

Background: Age-related cognitive decline results in increased difficulty in performing tasks that require memory or rapid information processing. Cognitive resilience is the ability to withstand the negative effects of stress on cognitive functioning. The polygenetic contribution to cognitive resilience requires large data sets for analysis. In addition, longitudinal data is needed to identify individual differences in cognitive performance over time. The UK Biobank cohort of over 500,000 participants over the age of 40 offers the potential to advance research on the genetics and biology of cognitive resilience.

Methods: We created a longitudinal cognitive resilience phenotype by combining the phenotypic cognitive parameter of current reaction time with a proxy phenotype of education years (EY). We used this resilience phenotype, in genome-wide association studies (GWAS) to identify genes and gene sets that influence the biological pathways involved in resilience. To remove the influence of the EY on the analysis we compared genetic data on participants that displayed resilience to those that showed expected cognitive decline.

Results: GWAS outputs analysis showed 273 significantly enriched genes for participants that demonstrated resilience. Genotype–tissue expression was significant in brain tissue, particularly in the anterior cingulate cortex, frontal cortex, and hippocampus. Biological Pathway analysis includes synapse, post synaptic density and neuron guidance.

Conclusion: This analysis shows an association between cognitive resilience and enrichment of neuronal activity. Confirmatory examination of these findings in datasets with strong longitudinal cognitive data, such and the Health and Retirement Study, is on-going.

OP04. Genome-wide DNA methylation analysis for type 1 diabetes

LJ Smyth, C Wooster, J Kilner, F Kee, I Young, B McGuinness, AP Maxwell, GJ McKay, AJ McKnight with the

GENIE consortium and NICOLA Collaborative Group

Genetic Epidemiology Research Group, Centre for Public Health, Queen's University Belfast

Introduction: Type 1 diabetes (T1D) is a polygenic disease characterised by autoimmune inflammatory destruction of the pancreas and subsequent hyperglycaemia. Several GWAS have identified loci associated with T1D risk, but recent evidence suggests that epigenetic changes in DNA methylation may have a causal role in T1D.

Methods: To identify potential methylation-based biomarkers of T1D, blood-derived DNA from 250 individuals with ≥15 years duration of T1D was compared to 391 controls with no evidence of diabetes. All individuals were from the British Isles. DNA was bisulphite treated using the EZ DNA Methylation Kit (Zymo). The Infinium HD Methylation Assay MethylationEPIC BeadChips (Illumina) were used to determine the methylation status of >850,000 CpG sites, gene bodies and promoters.

Results: MethylationEPIC data was analysed using GenomeStudio v2011 and Partek Genomics Suite v7.0. Comparing T1D with controls identified 1,706 CpG sites with significantly different ($p<10^{-8}$) levels of methylation (≥±2 fold change). Genes including *HLA-DRB1*, *HLA-DQA1* and *PLEKHA1* have been previously linked to T1D and contained ≥2 differently methylated CpG sites ($p<10^{-8}$). High concordance (R^2=0.994) between duplicate samples (n=7) was observed. The cellular metabolic process pathway was the top-ranked pathway ($p=1.8x10^{-10}$) with the strongest enrichment score.

Discussion: This study suggests that epigenetic factors play a role in T1D and has affirmed previously reported loci. Use of the MethylationEPIC array has provided the opportunity to report on previously unexplored regions of the methylome. Blood-derived methylation signatures may have utility as minimally invasive biomarkers for T1D.

OP05. Development of OPA1 Gene Therapy for Dominant Optic Atrophy

DM Maloney[1], N Chadderton[1], S Millington-Ward[1], GJ Farrar[1]

[1]School of Genetics and Microbiology, Trinity College Dublin

Dominant Optic Atrophy (DOA) is an inherited blinding disease that primarily targets the retinal ganglion cells (RGC) and largely involves disrupted mitochondrial bioenergetics leading to cellular dysfunction. DOA has an estimated prevalence of between 1in 10,000 to 1 in 30,000, making it one of the most common optic neuropathies. Around 90% of DOA cases are caused by mutations in the OPA1 gene. OPA1 is a dynamin-related GTPase that plays a crucial role in the maintenance of the mitochondrial network of the cell, with OPA1 mutations causing characteristic fragmentation of the mitochondrial network. Due to alternate splicing there are several distinct OPA1 isoforms that show unique expression patterns in different tissues.

Here, OPA1 isoforms 1 and 7 are identified as being predominantly expressed in the human retina by interrogating publicly available RNA-seq data. The potential of OPA1 isoform 1 and 7 for use in gene therapy approaches was then investigated using codon-optimised versions of both OPA1 isoforms. This was achieved by ectopically expressing each isoform in OPA1-null mouse embryonic fibroblast (MEF) cells. Of note, cells expressing either of these OPA1 isoforms showed significant improvement in a range of different mitochondrial biomarkers. Rescued cells showed restoration of a wild-type tubular mitochondrial network, along with a significant increase in the rate of mitochondrial fusion. Rescued cells also showed significantly increased metabolic activity in Seahorse XFe96 assays when compared to OPA1-null MEF cells, showing restoration to wild-type MEF cell levels. These data represent an important step forward in the development of OPA1 based gene therapies for DOA.

OP06. Who needs rare disease services in Ireland? Constructing a list of high-prevalence rare diseases for Ireland to inform service needs.

DM Lambert[1], S Nguengang-Wakap[2], A Olry[2], A Rath[2], D Murphy[1], SA Lynch[1], EP Treacy[1]

[1]National Rare Diseases Office, Dublin, [2]INSERM, US14-Orphanet, Paris, France

Introduction: Rare diseases (RDs) are a public health priority but their scarcity and diversity leads to a lack of knowledge and expertise. Accurate epidemiological information about RDs is necessary to inform public policy, but without an Irish rare disease registry, there is a dearth of primary data.

Methods: Collaborative work with Orphanet Coordination derived a global point prevalence of RDs from the 'Orphanet Epidemiological File' (www.orphadata.org) by selecting RDs described by 'point prevalence' from predefined geographic regions, and summing point prevalences. In the National Rare

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

Disease Office, expert opinion and disease-specific publications were used to adapt a 'high prevalence' list for Ireland.

Results: Globally, 'point prevalence' describes 5,304 RDs (85.9%). The minimum cumulative point prevalence of RDs is 3.5-5.9% of the population. While globally 84.5% RDs analysed (n=3585) had a point prevalence of <1/1,000,000; greater than 95% of the population burden of RDs was attributable to 390 diseases with a prevalence >1/100,000. To construct a comparable Irish 'high-prevalence' list, 191 RDs with known prevalence >1/100,000 across all countries were drawn from the global list. A further 147 diseases with possible prevalence >1/100,000 in Ireland due to ethnic, environmental or founder-effect are currently under consideration for inclusion.

Conclusion: 3.5%-5.9% is the first evidence-based estimate of the global population prevalence of RDs. Creation of an Irish list of high-prevalence RDs permits development of care pathways and systems that address the needs of the majority of Irish people with RDs. Implementation of RD codification in eHealth Ireland will provide more accurate data.

OP07. Birth incidence and survival in an 11 year cohort of liveborn babies with a fatal foetal abnormality in the Republic of Ireland

E Gunne[1], DM Lambert[2], C McGarvey[3], K Hamilton[3], EP Treacy[2], SA Lynch[1,2]

[1.] Children's University Hospital, Temple Street, Dublin; [2.] National Rare Disease Office, Mater Misericordiae University Hospital, Dublin; [3.] National Paediatric Mortality Register, Dublin.

The Health (Regulation of Termination of Pregnancy) Act legalized termination of pregnancy (TOP) in Ireland from January 2019, allowing TOP past 12 weeks of pregnancy for *'a condition affecting the foetus that is likely to lead to the death of the foetus either before, or within 28 days of, birth'*, as defined in the Clinical Guidance Pathway by the Institute of Obstetrics and Gynaecology (2019). Accurate information about survival can aid decision-making regarding TOP in couples with an antenatal diagnosis of fatal foetal anomaly.

Retrospective analysis of anonymised death records (2006-2016), from the National Paediatric Mortality Registry from the Central Statistics Office was undertaken. During this time TOP was unobtainable as it was contrary to the Irish Constitution, allowing natural history data to be sought. Rare disease diagnoses and survival times were assigned from narrative records, and compared to national annual birth rates.

Survival curves constructed for diagnoses of anencephaly, trisomy 13, trisomy 18 and bilateral renal agenesis showed that 88.5%, 35.0%, 38.1% and 89.1% respectively were deceased by 24 hours. Survival time range and median were calculated for severe skeletal dysplasias, hydranencephaly and triploidy whose occurrences were rare, with all deaths occurring in the neonatal period. Birth incidences ranged from 1 in 5,300 to 1 in 388,000.

Potentially fatal fetal anomalies were not included as their variable prognosis is better informed by case-by-case antenatal ultrasound rather than diagnostic label. This analysis did not capture the rate of intrauterine death associated with these conditions, and was confounded by TOPs performed outside the jurisdiction.

OP08. The Molecular Basis of Acute Porphyria and familial Porphyria Cutanea Tarda in the Republic of Ireland – an update

[1]S Savage, [1]E Rasheed, [1]A Rashid, [1]E Keogh, [1]B MacNamara, [1]C Collison, [1]N Brazil, [2]S Whatley, [1]VEF Crowley

[1] Biochemistry Department, Central Pathology Laboratory, St James's Hospital, Dublin 8 [2] Cardiff Porphyria Centre, Department of Medical Biochemistry, University Hospital of Wales, Heath Park, Cardiff

Introduction: The acute hepatic porphyrias, including acute intermittent porphyria (AIP), variegate porphyria (VP) and hereditary coproporphyria (HP) along with familial Porphyria Cutanea Tarda (fPCT) are autosomal dominantly inherited disorders affecting key enzymes in the haem biosynthetic pathway. Clinically these disorders may manifest as photosensitive skin lesions (VP, HP and PCT) and/or acute neuropathic episodes (AIP, VP and HP). All demonstrate variable penetrance and expressivity. Thus, while biochemical investigations, including blood, urine and faecal porphyrin analysis, are critical for the diagnosis of active porphyric disease, these investigations may not be sensitive enough to identify presymptomatic variant carriers. Hence molecular genetic analysis has become an important component in kindred follow-up for identifying porphyria susceptibility.

Methods: The Biochemistry Department, St James's Hospital, Dublin, has established a molecular diagnostic service based on direct nucleotide sequencing to facilitate diagnosis of genetic susceptibility to AIP, VP, HCP and PCT respectively.

Results: To date over 30 different genetic variants linked with a porphyria phenotype have been identified in different kindreds including non-Irish. The spectrum of variants includes missense, nonsense, splice-site and small insertions and deletions e.g. *HMBS* (R26C, R26H, IVS4+1G>A), *PPOX* (IVS4-1G>A, Q435X, W427X, A150D, Q375X) and *CPO* (R332Q, R332W, c.1291-1292 ins TG). In addition, novel variants have been identified in collaboration with Cardiff Porphyria Centre.

Conclusion: This unique insight into the molecular basis of porphyrias in the ROI indicates that acute porphyrias and fPCT are genetically heterogeneous. Furthermore, the variant scanning assay in St James's Hospital has identified pathogenic variants in >93% of confirmed porphyria kindreds

OP09. European Reference Networks: potential for rare disease research and patient care in Ireland

DN Murphy[1], DM Lambert[1], SA Lynch[1], J Turner[1], EP Treacy[1].

[1] National Rare Diseases Office, Dublin, Ireland

Between 5,000 and 8,000 rare diseases impact roughly 30 million people in the EU, and up to 300,000 in Ireland. Diagnosis and treatment of rare diseases is extremely difficult due to low prevalences, scattered patient populations and scarcity of national expertise. Collaboration across countries is essential. European Reference Networks (ERNs) concentrate resources through the centralisation of knowledge and experience of clinicians and researchers across Europe. They comprise virtual networks involving healthcare providers who collaborate via a dedicated IT platform. A fundamental principle of this initiative is that the knowledge and experience travel, not the patient.

Centres of Expertise (CoE) are the physical structures that connect patients to the ERNs. Each CoE is specialised in a particular disease or group of diseases, with the purpose of delivering timely diagnosis and appropriate treatments. With such a vast number of rare diseases and CoEs in Europe, the immediate challenge is mapping out the appropriate care pathway for each patient on

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

a national basis. Orphanet Ireland has identified 72 Irish CoEs, connected to 22 of the 24 existing ERNs. We have attempted to determine the appropriate Irish CoE and ERN for the 345 most prevalent rare diseases (affecting more than 1 in 100,000). Of these, we successfully assigned 331 to ERNs (3 of which are ambiguous as they affect more than one organ or system), and 248 to CoEs within Ireland. The elaboration of Irish care pathways in collaboration with the CoEs and ERNs is predicted to enhance diagnosis, clinical research and treatment access.

OP10. Mitochondrial Disease Mimics

Samantha Doyle[1], Zaza Abidin[1], Suranga Senanayake[1], Stephanie James[1], Mei Yap[2], Caroline Hart[3], Ellen Crushell[2,4], Shane Smyth[5], Andrew Green[6,7], Eileen Treacy[1,8], Tim Lynch[5], Gregory Pastores[1], Aoife Laffan[5], James O'Byrne[1]

[1]National Centre for Inherited Metabolic Disorders, Mater Misericordiae University Hospital, Dublin, Ireland. [2]Department of Neurology, Dublin Neurological Institute, Mater Misericordiae University Hospital, Dublin, Ireland. [3]National Centre for Inherited Metabolic Disorders, Temple Street Children's University Hospital, Dublin, Ireland. [4]University College Dublin, Belfield, Dublin, Ireland. [5]Department of Neurology, Mater Misericordiae University Hospital, Dublin, Ireland. [6] Department of Clinical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland. [7]School of Medicine and Medical Science, University College Dublin, Dublin, Ireland. [8]Department of Paediatrics, Trinity College, Dublin, Ireland

A diagnosis of primary mitochondrial disease was traditionally arrived at on the basis of clinical and biochemical features including abnormal respiratory chain analysis on muscle biopsy and/or identification of other "mitochondrial disease markers". With the increased availability of genetic testing, in particular massive parallel sequencing, alternative primary diagnoses which result in secondary mitochondrial dysfunction are being identified

We present a cohort of six cases who previously had a diagnosis of mitochondrial disease. Alternative primary diagnoses have recently been identified which includes Andersen-Tawil syndrome (gene: KCNJ2), COL4A1-related brain small-vessel disease (gene: COL4A1), cardio facio cutaneous syndrome (gene: BRAF), autosomal recessive spinal cerebellar ataxia-10 (gene: ANO10), facio scapula humeral muscular dystrophy (gene: DUX4) and IGSF1 deficiency syndrome (gene: IGSF1).

Conclusion: The reported cohort highlights the important point that many genetic conditions may mimic mitochondrial disease and, although the phenotype and biochemical tests may indicate mitochondrial disease, we suggest that genetic confirmation is required to secure a diagnosis. Establishment of an accurate diagnosis is important, not just prognosis and planning of management and treatments regimes, but also for appropriate genetic counselling and the identification of other at-risk family members for possible cascade analysis. The link between many of these primary diagnoses and secondary mitochondrial dysfunction is poorly understood but reporting such cases will allow these pathways to be elucidated and understood.

POSTER PRESENTATIONS:

P01. Early retinal remodelling in a mouse model of juvenile retinal degeneration

A Palfi[1], A Yesmambetov, GJ Farrar[1]

[1]Dept. Genetics, Trinity College Dublin

Mutations in TULP1 are causative of inherited retinal degenerations (IRD). The retina of Tulp1-/- mice is characterized by rapid loss of photoreceptors while much less is known about the changes in the inner retina. Using histology analysis we investigated early remodelling events in Tulp1-/- retinas at postnatal days (p) 5, 8 and 14 (n=3-5). Apart from wt controls, we used Rho-/-, Rds-/- retinas as disease controls. Qualitative and quantitative morphological analysis on microscope images from these samples was performed. In agreement with previous work, we detected minor alterations in thickness of the retinal layers in IRD mice between p5-14. However, using various retinal markers we identified significant cellular and subcellular alterations. In the outer plexiform layer, the photoreceptor synapses were compromised, while the horizontal cell processes invaded the photoreceptor layer in IRD mouse retinas. In the inner nuclear layer, expression of a number of markers, such as PAX6, CTBP2, MAP2 was different between IRD mouse and wt retinas. Additionally, the morphology of Muller glia cells was also altered. Apart from the large number of TUNEL+ cells in the outer nuclear layer in IRD mouse retinas TUNEL+ cells were also detected in the inner nuclear layer in Tulp-/- but not in the other retinas at p14. Our data suggest compromised photoreceptor synaptic development/function in IRD mouse retinas. Delayed development of a number of cellular markers in the inner retina suggests that degeneration in Tulp1-/- retinas is different from that of Rho-/- and Rds-/-.

P02. Detection of putatively pathogenic rare, inherited CNVs from family whole genome sequencing data

CM Ormond[1]*, NM Ryan[1]*, EA Heron[1], M Gill[1], AP Corvin[1]
*equal contribution

[1]Neuropsychiatric Genetics Research Group, Dept. of Psychiatry, Trinity College Dublin.

We seek to identify rare copy number variations (CNVs) which may be contributing to disease risk in families with a high load of psychiatric illness. Calling CNVs accurately from short read sequencing data is complex; to date no single CNV caller is capable of detecting all classes (deletions, insertions, translocations, etc.) or sizes of CNVs with high specificity and sensitivity. However, studies have shown that CNV detection can be improved by looking at consensus calls across multiple algorithms. We propose that incorporating family data can also give better control for false positive rates across callers.

Based on this hypothesis we have developed a novel ensemble approach that combines two classes of CNV caller: paired-end/split read methods (Manta and LUMPY) and read depth methods (ERDS and CNVnator), as well as Mendelian inheritance patterns, to improve precision and recall of CNV detection from family data. This pipeline incorporates a rigorous filtering strategy aimed at identifying rare, pathogenic, segregating CNVs within each pedigree. We have used validated CNVs from the gold-standard CEPH 1463 pedigree to assess the performance of our ensemble approach and to compare it against each of the individual component tools.

P03. Improving the State of Polygenic Prediction: Are Neural Networks Applicable to Genetic Data?

CM Kelly[1], RP Byrne[1], MA Doherty[1], JC Hengeveld[1], RL McLaughlin[1]

[1.] Dept. of Genetics, University College Dublin. [2.] Dept. of Genetics, University College Cork.) [1.] Smurfit Institute of Genetics, Trinity College Dublin

Deep Learning using Artificial Neural Networks (ANNs) has

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

been gaining traction due to its widespread success in generating accurate prediction models from complex input data such as audio and image information. It is of current interest to explore whether this technique can be applied to handle genetic data as input. It remains an open question as to whether the sheer size and sparsity of information represented within genotype matrices may be amenable to the complex transformations performed by ANNs.

Polygenic prediction has also been seeing improvements recently, however, the explained variance for all traits remains stubbornly lower than the theoretical maximum as represented by its estimated heritability (h^2). This discrepancy may partially be due to the strictly linear methods employed by conventional GWAS and Polygenic Risk Score (PRS) calculation. As it is well established that complex non-linear interactions are ubiquitous in determining the outcome of biological processes, it is reasonable to suspect that some of the variation of a trait is as a result of these epistatic interactions that are not well modelled by the methods currently employed in genetic prediction.

This project aims to investigate the potential of deep learning's known ability to handle and exploit non-linear information in improving on current genetic prediction methods. Both real and simulated genotype and phenotype data are used to determine the feasibility and accuracy of this method using PRS as a benchmark. This may not only be useful from a clinical perspective but could also give insight into a trait's genetic architecture.

P04. The role of common genetic variation in presumed monogenic forms of epilepsy

C Campbell[1,2], C Leu[3], N Delanty[1,5], D Lal[3,4] and GL Cavalleri[1,2]

[1] Futureneuro Centre, RCSI Dublin, [2] Department of Molecular and Cellular Therapeutics, RCSI Dublin, [3] Genomic Medicine Institute, Lerner Research Institute, Cleveland Clinic, [4] Stanley Medical Research Institute, Broad Institute, [5] Neurology Department, Beaumont Hospital

Background: The developmental and epileptic encephalopathies (DEEs) are a group of severe epilepsies which co-present with intellectual disability, and occur in cases without a family history of epilepsy. Their severe phenotype means that DEEs are thought to be primarily monogenic, caused by highly damaging rare mutations. Currently, analysis of exome sequence data can identify a causative mutation in around 40% of DEEs. Little is known about the genetic architecture of the remaining DEEs which screen-negative after genomic analysis. Here, we used a method known as polygenic risk scoring (PRS) to test whether the burden of common genetic variation is relevant to the development of the DEEs.

Methods: Exome and GWAS data on DEE cases (n=745), and population controls (n=75,000) were obtained from the DDD cohort and Ukbiobank, respectively. Damaging mutations in known epilepsy genes were bioinformatically inferred. PRS were calculated using the most recent ILAE GWAS of epilepsy and compared between i) DEE cases and the general population, and ii) DEE cases with and without damaging mutations.

Results: DEE cases with and without inferred damaging mutations were found to have elevated PRS for epilepsy. We did not detect a significant difference in PRS between DEE cases with and without damaging mutations.

Discussion: This research provides the first evidence that common genetic variation contributes to the development of the DEEs. Our results suggest common genetic variation contributes to DEE status irrespective of the presence of a highly damaging rare genetic variant. Further work in additional cohorts is required to extend these results.

P05. Investigating the role of microRNAs in the hypoxic response in prostate cancer

CZ Angel[1], CJ McNally[1,2] , DJ McKenna[1]

[1]Genomic Medicine Research Group, Ulster University, Northern Ireland.[2] Randox Laboratories, Diamond Road, Crumlin, Co. Antrim, BT29 4QY

Hypoxia is a well-established driver of aggressive behaviour in prostate cancer (PCa). However, the reasons for this are not completely characterised and the role of microRNAs (miRNAs) in the hypoxic response remains unclear. In this study, we investigated the expression and functional role of miRNAs in response to hypoxia in prostate cancer.

Three models of PCa hypoxia were utilised (i) *in vitro* culture at 0.1% oxygen (ii) 3D spheroid culture and (iii) an *in vivo* tumour xenograft experiment. miRNA expression was measured by RT-qPCR. miRNA functionality was assessed by RT-qPCR, Western blots and bioassays. Bioinformatics analysis of prostate cancer clinical data in The Cancer Genome Atlas (TCGA) repository was also performed.

The miRNAs miR-210 and miR-21 were upregulated by hypoxia in our various models. The subsequent effect on their respective networks of target genes and cell behaviour was investigated. miR-210 and miR-21 expression is positively associated with markers of hypoxia and tumour aggressiveness in clinical samples, suggesting they may have value as novel biomarkers in this disease. Random forest analysis of TCGA data revealed that addition of miR-21 and miR-210 levels to Gleason score could predict treatment response with >90% accuracy.

We provide evidence that miRNAs play a role in the progression of PCa through hypoxia-related mechanisms. In particular, miR-210 and miR-21 appear to contribute to the hypoxic response involved in PCa progression. We propose that miRNA profiling of these and other miRNAs has great value for improving diagnostic, prognostic, and potentially therapeutic approaches for this disease.

P06. The ancient population genetics of Portugal

EM Breslin[1], LM Cassidy[1], R Martiniano[2], V Mattiangeli[1], AM Silva[3], DG Bradley[1]

[1]Smurfit Institute of Genetics, Trinity College Dublin, [2] Department of Genetics, University of Cambridge, Downing Street, Cambridge. [3]Laboratory of Prehistory, Research Center for Anthropology and Health, Department of Life Science, University of Coimbra.

The field of ancient population genetics has advanced rapidly since the development of high-throughput next-generation sequencing (NGS) and the discovery that the petrous part of the temporal bone is a rich reservoir for aDNA, allowing the generation of whole genome sequences for ancient individuals. Portugal occupies a unique position in Europe; located on the edge of mainland Europe and facing both the Atlantic and the Mediterranean, it was connected to two major maritime, trade and migration routes as well as experiencing influx from central Europe throughout its prehistory. However, many open questions remain about demographic and selection processes acting on populations at key transition points in European prehistory, such as the early Bronze Age migrations from the Pontic Steppe, the potential source for the R1b Y-chromosome haplogroup which now dominates in European populations. In this study we present whole genome sequences from ancient Portuguese

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

individuals (0.1-2.9X), covering a period of over 3000 years as well as a wide geographic region. We observe changes in both mitochondrial and Y-chromosome haplogroup frequencies over time, reflecting changing demographic processes acting on Iberian populations. We use principal component analysis (PCA), outgroup *f*-3 statistics, Patterson's D-statistic and ADMIXTURE analysis to investigate questions such as hunter gatherer admixture in the Neolithic and Steppe introgression in the subsequent Bronze Age.

P07. The Epilepsiome Project: revising the Human Phenotype Ontology for epilepsy and seizures

H.Kearney [1,2], G.Balagura [3], D. Lewis-Smith [4], S. Ganesan [5], J. Gan [5], P.D. Galer [5], Y. Wang [6], NCK Tan [7], N.J. Lench [8], C.A. Steward [8], R. Krause [9], P. Robinson [10], N. Delanty [1,2], G.L. Cavalleri [1,11], I. Helbig [5]

[1] FutureNeuro Research Centre, Royal College of Surgeons in Ireland, Dublin, Ireland. [2] Department of Neurology, Beaumont Hospital, Royal College of Surgeons in Ireland, Dublin, Ireland. [3] Dipartimento di Neuroscienze, riabilitazione, oftalmologia, genetica e scienze materno-infantili (DINOGMI), Università degli Studi di Genova, Italy. [4] Epilepsy Genetics Research Group, Institute of Neuroscience, Newcastle University, UK. [5] Division of Neurology, Children's Hospital of Philadelphia, USA. [6] Department of Neurology, Epilepsy Center, Children's Hospital of Fudan University, Shanghai, China. [7] Department of Neurology, National Neuroscience Institute, Singapore. [8] Congenica Ltd, Wellcome Genome Campus, Cambridge, UK. [9] Luxembourg Centre for Systems Biomedicine, Université du Luxembourg, Luxembourg. [10] Jackson Laboratory for Genomic Medicine and the Institute for Systems Genomics, University of Connecticut, USA. [11] Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland.

Rationale: The phenotypic features in a person with epilepsy are often complex with regards to seizure presentations, which is acknowledged by the most recent revision of the seizure classification by the International League Against Epilepsy (ILAE). We provide updated seizure-related human phenotype ontology (HPO) terms to facilitate a deep phenotypic interpretation of heretofore unexplained genetic epilepsies.

Methods: The Epilepsiome project is a Task Force of the Genetics Commission of the ILAE and represent the link to the gene curation efforts within the ClinGen Epilepsy Clinical Domain Working Group (CDWG). Within the efforts to align terminology used in the diagnostic space, the Epilepsiome Project revised HPO terms for epileptic seizures. The updated classification was built through an online portal and consensus was achieved through biweekly conference calls.

Results: Focal, generalised and neonatal HPO seizure terminologies were constructed according to the most recent ILAE classification and aligned with the existing HPO structure. This ontology allows capture of clinical information at various levels of detail and aims to preserve the onset, awareness and motor/non-motor nature of each seizure type, using multiple parentages. We integrated other frequently observed seizures currently not included in the ILAE, which required a separate branch within the ontology due to biological peculiarity of their age of onset, their clinical significance or genetic architecture.

Conclusions: Improvements in HPO terms for epileptic seizures will enable a more versatile seizure ontology leading to deep phenotyping of people with epilepsy to improve associations with genomic data in both a research and diagnostic setting.

P08. Modulation of a prodegenerative pathway as a potential therapy for retinal degeneration.

Finnegan LK[1], Chadderton N[1], Palfi A[1], Millington-Ward S[1], Kenna P[2], Carty M[3], Bowie AG[3], Farrar GJ[1]

[1] The School of Genetics & Microbiology, Trinity College Dublin, Dublin 2, Ireland; [2] Royal Victoria Eye and Ear Hospital, Dublin 2, Ireland; [3] The School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin 2, Ireland.

Approximately 300 million people suffer from some form of blindness, from monogenic inherited retinal degenerations to complex diseases such as AMD. Due to the vast heterogeneity of genetic forms of blindness, it is challenging to develop gene-specific therapies for each disease. Fortunately, many of these conditions display mechanistic commonalities, with key pathways being implicated in many diseases. By targeting these, in principle we can develop therapies that may be applicable to a wider group of patients. One such pathway involves the degeneration of neurons in response to injury or stress. Pro-degenerative proteins can promote degradation of the axons of damaged neurons, leading to eventual cell death. A knockout mouse model has been used to assess whether the absence of one such gene and encoded product may be neuroprotective against rotenone-induced insult to the retina. Optokinetic response (OKR) measurements suggest that the lack of the encoded product is functionally beneficial, with knockout mice performing significantly better than wild-type mice following rotenone treatment (0.241±0.052 c/d and 0.08973±0.03750 c/d respectively; $p<0.0001$). These data will be complemented by histological and MRI studies to explore the extent of the beneficial effects that may be provided by this approach. Importantly, the preliminary data thus far from this mouse work suggest the potential benefit of modulating this cellular pathway to ameliorate retinal pathologies. Further studies are underway to explore the extent of the therapeutic value of this strategy to provide benefit in the context of retinal degenerations.

P09. Identifying the Genetic Candidates of Previously Unresolved Inherited Retinopathies in Ireland.

L Whelan[1], A Dockery[1], PF Kenna[1,2], D Keegan[3], G Silvestri[4,5], M Khan[6], SS Cornelis[6], C-M Dhaenens[6,7], P Humphries[1], GJ Farrar[1], FPM Cremers[6], S Roosing[6].

[1]The School of Genetics & Microbiology, Trinity College Dublin, Dublin 2, Ireland. [2]The Research Foundation, Royal Victoria Eye and Ear Hospital, Dublin 2, Ireland.[3]The Mater Misericordiae University Hospital, Dublin 7, Ireland. [4]Department of Ophthalmology, The Royal Victoria Hospital, Belfast BT12 6BA, Northern Ireland, UK. [5]Centre for Experimental Medicine, Queen's University Belfast, Belfast BT7 1NN, Northern Ireland, UK. [6]Dep. of Human Genetics and Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, The Netherlands. [7]Univ Lille, Inserm UMR-S 1172, CHU Lille, Biochemistry and Molecular Biology Department-UF Génopathies, F-59000 Lille, France.

Purpose: *Target5000* aims to genetically characterise approximately 5000 people in Ireland with an inherited retinal degeneration (IRD). Thus far, over 1,000 IRD patients have been sequenced for variants in 260 IRD genes. One arm of the project focuses on improving detection of candidate variants by whole genome sequencing (WGS), by analysing non-coding mutations and performing functional analysis.

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

Approach: IRD patients are clinically diagnosed by *Target5000* ophthalmologists. When informed consent is given, the *Target5000* study employs target capture next generation sequencing (NGS), with a positive candidate detection rate of 68%. To improve detection rates, whole-gene or WGS was employed on a case-dependent basis to identify pathogenic intronic variants not previously captured.

Results: One common form of IRD is ABCA4-associated Stargardt disease (STGD1), often caused by deep-intronic variants. Thus far, 36 'unresolved' STGD1 and cone-rod dystrophy cases have undergone targeted ABCA4 whole-gene sequencing, positively identifying a candidate in ~50% of cases. A variant in intron 30 resulting in a pseudoexon inclusion was particularly frequent and found in 5/16 (likely) solved cases. Furthermore, 40 patient samples have undergone WGS.

Conclusions: An objective of *Target5000* is to provide actionable outcomes empowering patients with genetic diagnoses and potentially future access to clinical trials or approved treatments, where appropriate. The results presented highlight the significant value of a target capture NGS strategy as a preliminary diagnostic measure, with remaining elusive cases undergoing more extensive genetic analysis. This methodology improves variant detection rates and progresses the goal of fully elucidating the genetic architecture of IRDs in Ireland.

P10. Genes regulated by BCL11B during T-cell development are enriched for de novo mutations found in schizophrenia patients.

Laura Fahey[1,2], Gary Donohoe[1], Pilib Ó Broin[2], Derek Morris[1]

[1]Cognitive Genetics and Cognitive Therapy Group, Centre for Neuroimaging & Cognitive Genomics, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Galway, Ireland. [2]School of Mathematics, Statistics and Applied Mathematics, National University of Ireland Galway, Galway, Ireland.

Schizophrenia (SCZ) is a common but severely debilitating adult-onset mental illness. Abnormal neurodevelopment contributes to SCZ risk, but evidence also supports a role for immune dysfunction in SCZ. *BCL11B* is associated with SCZ in GWAS and is a transcription factor involved in regulating the differentiation/development of cells in both the brain and the immune system. Here, we use functional genomics analysis of *BCL11B* to investigate the contribution of neuronal and immune processes to SCZ pathophysiology. We generated three gene-sets that contain the targets of BCL11B in (i) brain striatal cells(n=220 genes), (ii) Thy3 developing T-cells (n=74 genes) and (iii) Thy4 developing T-cells(n=560 genes). For each gene-set, the BCL11B targets were identified using an integrated analysis of differential gene expression data and ChIP-seq binding data. We tested each gene-set for enrichment of genes associated with SCZ using MAGMA and GWAS data. Enrichment of SCZ de novo mutations was tested with denovolyzeR using data from exome sequencing of SCZ trios (n=1,024). MAGMA analysis did not identify evidence of enrichment of SCZ genes in our gene-sets. Analysis of de novo mutations did identify that the Thy4 gene-set was enriched for genes containing protein altering mutations (p=0.0007). When this gene-set was divided up into genes that were either up- or down-regulated upon *BCLL1B* knockout, the enrichment signal was coming from the up-regulated genes (p=0.0002). Pathway analysis of these up-regulated genes identified 'Interferon alpha/beta signalling' and 'Cytokine signalling in immune system' as biological pathways that are enriched for these genes. These analyses, leveraging a GWAS-identified SCZ risk gene and functional genomics datasets, indicate that de novo mutations in immune pathways contribute to SCZ risk.

P11. The biochemical characterisation of a novel missense variant in Fumarase Hydratase identified in an Irish patient with breast cancer

Úna M McVeigh[1], Terri P McVeigh[2], Nicola Miller[1], Derek W Morris[3], Michael J Kerin[1], Andrew Flaus[3]

[1] Discipline of Surgery, Lambe Institute for Translational Research, NUI Galway, Ireland; [2] Cancer Genetics Unit, The Royal Marsden NHS Foundation Trust, London, United Kingdom; [3] Centre for Chromosome Biology, NUI Galway, Ireland.

Fumarase hydratase (FH) catalyses the reversible conversion of fumarate to L-malate during the Krebs cycle. FH has also been identified as a tumour suppressor and contributes to the DNA damage response. Monoallelic variants give rise to the rare tumour predisposition syndrome hereditary leiomyomatosis and renal cell cancer (HLRCC). Variants in *FH* have recently been implicated in tumours of the CNS, bladder, and breast. We identified a novel p.Gly58Ser variant of FH in a breast cancer patient through a targeted resequencing study of an Irish cohort of patients with breast cancer (n=91) and healthy controls (n=77). The variant is predicted to be damaging/pathogenic *in silico* by four independent missense prediction algorithms. Inspection of 3D structures shows that Gly58 is located near the active site and could disrupt a secondary structural element. To test the effect of the mutation directly, we recombinantly expressed and purified wild type and Gly58Ser mutant human FH as well as a mutant Ala308Thr which is known to disrupt activity. We then compared their enzymatic properties with respect to tetramerisation, pH dependence, substrate affinity and activity. Our results show that the Gly58Ser variant significantly impairs enzymatic function of FH. This study illustrates how screening of an Irish patient cohort can reveal novel mutants amenable to detailed structure-function analysis that can be directly tested for biochemical effects.

P12. A randomized controlled trial of folic acid intervention in pregnancy highlights a putative methylation-regulated control element at *ZFP57*

RE Irwin[1], SJ Thursby[1], M Ondičová[1], K Pentieva[2], H McNulty[2], RC Richmond, A Caffrey[2], DJ Lees-Murdock[1], M McLaughlin[3], T Cassidy[3], M Suderman[4], CL Relton[4], CP Walsh[1]

[1] Genomic Medicine Group. [2] Nutrition Innovation Centre for Food and Health, School of Biomedical Sciences. [3] Psychology Institute Ulster University, Coleraine, Northern Ireland, United Kingdom. [4] MRC Integrative Epidemiology Unit, Bristol Medical School, University of Bristol, Bristol, UK.

Maternal blood folate concentrations during pregnancy have been previously linked with DNA methylation patterns, but this has been done predominantly through observational studies. We showed recently in an epigenetic analysis of the first randomized controlled trial (RCT) of folic acid supplementation specifically in the second and third trimesters (the EpiFASSTT trial) that methylation at some imprinted genes was altered in cord blood samples in response to treatment. Here, we report on epigenome-wide screening using the Illumina EPIC array (~850,000 sites) in these same samples ($n=86$). The top-ranked differentially methylated promoter region (DMR) showed a gain in methylation with folic acid (FA) and was located upstream of the imprint regulator *ZFP57*. Differences in methylation in cord blood between placebo and folic acid treatment groups at this DMR were verified using pyrosequencing.

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

The DMR also gains methylation in maternal blood in response to FA supplementation. We also found evidence of differential methylation at this region in an independent RCT cohort, the AFAST trial. By altering methylation at this region in two model systems in vitro, we further demonstrated that it was associated with *ZFP57* transcription levels. These results strengthen the link between folic acid supplementation during later pregnancy and epigenetic changes and identify a novel mechanism for regulation of *ZFP57*.

P13. AAV-oph*Ndi1*: a potential therapy for Leber Hereditary Optic Neuropathy (LHON).

N Chadderton[1], A Palfi[1], M Carrigan[1], S Millington-Ward[1], D Maloney[1], K Hanlon[1], P Humphries[1], PF Kenna[1] and GJ Farrar[1].

[1]School of Genetics and Microbiology, Trinity College Dublin, Dublin 2, Ireland.

LHON is a debilitating mitochondrially inherited eye disorder characterised by rapid, painless loss of central vision in one eye, typically followed by loss of vision in the second eye within months. It is caused by mutations in five of the mitochondrially encoded subunits of Complex I. LHON affects approximately 1 in 30,000 individuals, predominantly males. Currently, gene therapy for the ND4 mutation is showing great promise in clinical trials. However, there is growing evidence that mitochondrial dysfunction may be involved in a wide range of neurodegenerative disorders and the transkingdom approach proposed here may also be applicable to these. The therapy under development uses a nuclear yeast gene, NADH-quinone oxidoreductase (*Ndi1*), that encodes a single subunit complex I equivalent and as such is mutation independent.

We have previously shown the potential of AAV2/2-*Ndi1* to protect retinal ganglion cells (RGCs), the cells primarily affected in LHON, in a rotenone-induced murine model of LHON. Subsequently, we have optimised *Ndi1* codon usage using *in silico* analyses to enhance expression in mammalian cells and to potentially reduce immunogenicity, creating oph*Ndi1*. Here we demonstrate that oph*Ndi1* functions more efficiently than *Ndi1*. When evaluated in the LHON mouse model, intravitreal injection of AAV2/2-oph*Ndi1* significantly reduced RGC death and led to a preservation of retinal function as assessed by optokinetics (OKR). This benefit was attained using significantly less AAV2/2-oph*Ndi1* than AAV2/2-*Ndi*.

oph*Ndi1* holds great therapeutic promise for this debilitating mitochondrial disorder and could be applicable to other conditions where mitochondrial dysfunction may play a significant role.

P14. Investigating DHFR2's growing pool of RNA isoforms

N Bookey [1], P Drago [1], A Parle-McDermott [1]

[1] School of Biotechnology, Dublin City University

The complex folate one-carbon metabolism (FOCM) interlinks with homocysteine metabolism with the help of vitamin B2, B6 and B12 to maintain normal cell functions: purines and thymidylate synthesis, glycine and other amino acids synthesis, methylation reactions.

DHFR is the only FOCM enzyme capable of reducing dietary folic acid to Dihydrofolate, and further reduce it to Tetrahydrofolate, the actual methyl-group donor. For a long time, DHFR was thought to be the only reductase of its family to have an active role in FOCM, until a second one was discovered: DHFR2.

DHFR2 is a retrogene, derived from a DHFR RNA copied back into the genome. It has two main isoforms, both harbouring the whole ORF in a single exon. These isoforms could translate into functional proteins even though the endogenous form of the enzyme has not been detected so far. Additional isoforms have been predicted, with some containing the entire DHFR2 ORF and others possibly having regulatory functions.

We performed several PCR assays on cDNA aiming to detect all possible isoforms in different cell lines. Other than confirming the two main transcripts presence, distinct new variants were detected in different cell types. They differ slightly from the predicted isoforms, especially at the 5' and 3' ends. In one case, a new exon has been identified, establishing a brand new transcript. Ultimately, as a result of the differential expression of each transcript due to tissue type and differentiation status, a targeted full-length sequencing approach is the logical next step.

P15. CRISPR/Cas knock-out cell lines to give new insight on DHFR2 function and its interplay with DHFR

P Drago [1], N Bookey [1], A Parle-McDermott [1]

[1] School of Biotechnology, Dublin City University

All organisms possess a version of DHFR, from bacteria to humans, but just primates, *H. sapiens* included, present a second active Dihydrofolate Reductase. DHFR has a key role within Folate One-Carbon metabolism, as it reduces Dihydrofolate into Tetrahydrofolate, a methyl group shuttle involved in glycine, purines and thymidylate biosynthesis. Accordingly, its function is essential for DNA synthesis, making DHFR a crucial regulator in cell proliferation and death.

DHFR2 (Dihydrofolate Reductase 2) is a retrogene derived from the reverse transcription of DHFR RNA back into the genome (3q11.2). The recent discovery of DHFR2 being active has opened up to a whole new set of questions, relative to DHFR/DHFR2 function and localisation, their interlinks and subcompartmentalization.

DHFR2 protein has not been detected so far, and its similarity with DHFR (92% homologous), makes it a huge challenge to identify endogenous levels of its protein. To solve this issue, we have engineered two HepG2 cell populations by CRISPR/Cas creating both a DHFR and DHFR2 knock-out lines. The DHFR-negative line will definitively allow the sole DHFR2 isolation and identification. It will also make clear if DHFR2 is able to compensate for the lack of DHFR, replacing its cytosolic function. Instead, the DHFR2-negative line will give us information about the importance of DHFR2 as part of the folate metabolism and its relevance in cell proliferation.

P16. Retinoic Acid Receptor Specificity in Glioma Growth Suppression

PM. Flynn[1], A. Toulouse[1], N. Bermingham[2], M. Jansen[2], CK. Hand[3],

[1] Dept. of Anatomy & Neuroscience, School of Medicine, University College Cork. [2]Dept. of Neuropathology, Cork University Hospital. [3]Dept. of Pathology, School of Medicine, University College Cork.

Primary brain tumours have an incidence of 8/100,000/year in Ireland. 80% of these tumours are adult diffuse infiltrating gliomas, and the majority are high grade, causing death within two years. Obstacles to treatment include impossibility of complete surgical resection, outward convection pressures, first-pass metabolism, the blood brain barrier, and the existence of cancer stem cells, reigniting malignant growth following treatment.

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

Retinoic acid and its synthetic analogues, the retinoids, are potent, lipophilic differentiation agents capable of crossing the blood brain barrier. They have recently been considered as potential adjuvant therapy to trigger the terminal differentiation of glioma cells. Retinoids act via a family of nuclear retinoic acid receptors (RARs) that stimulate the expression of target genes. Three genes exist for RARs (*RARA*, *RARB*, *RARG*). Each gene encodes multiple functional isoforms differing in the N-terminus active protein domain. Most studies examining their expression in tumours have focused on the common regions, not differentiating between the various isoforms. Previous studies highlighted tumour suppressive functions for some RARB isoform (RARB2) while others (RARB1) were shown to stimulate proliferation. Considering the potential therapeutic benefit of retinoids and the mixed functions of RAR isoforms, we wish to determine the role of specific isoforms in controlling glioma growth. To date, our results show that expression of specific isoforms is associated with growth suppression while others are associated with increased proliferative rates. We propose that differential manipulation of RAR isoforms may be key in targeting tumour suppression

P17. Detecting pathogenic repeat expansions from genome sequence data

RL McLaughlin[1]

[1] Smurfit Institute of Genetics, Trinity College Dublin

Repeat expansions are an important class of genetic variation in neurological diseases and may represent a convergent aetiological molecular mechanism. However, the identification of novel repeat expansions using conventional sequencing methods is a challenge due to their typical lengths relative to short sequence reads and difficulty in producing accurate and unique alignments for repetitive sequence. However, this latter property can be harnessed when using paired-end short read sequencing data to infer the possible locations of repeat expansions and other structural variation.

Here we present REscan, a fast and lightweight command line utility that infers the possible locations of repeat expansions from paired-end short read sequencing data by reporting the proportion of reads orientated towards a locus that do not have an adequately mapped mate. A high number for this statistic relative to a population of data indicates the location of a possible repeat expansion for experimental follow-up. We validate this approach using whole-genome sequence data for 259 cases of amyotrophic lateral sclerosis, of which 25 are positive for a large hexanucleotide repeat expansion in C9orf72, and show that REscan has good discriminative accuracy in identifying repeat expansions from paired-end sequence data. Application genome-wide may infer the locations of other repeat expansions and accelerate the discovery of novel disease-relevant genetic variation.

P18. Genetic risk factors in mitochondrial DNA associated with diabetic kidney disease – GWAS discovery and meta-analysis.

RD Skelly[1], LJ Smyth[1], J Cole[2], AP Maxwell[1], AJ McKnight[1] with the GENIE and DNCRI consortia,

[1] Epidemiology and Public Health Research Group, Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom [2] Broad Institute, Cambridge, MA, USA

Diabetic kidney disease (DKD) affects ~40% of persons with diabetes and is the leading cause of chronic kidney disease and end-stage renal disease (ESRD) globally. Mitochondrial dysfunction is implicated in the pathophysiology of DKD. Previous research reported SNPs in nuclear genes, which influence mitochondrial function, are significantly associated with DKD. Furthermore, these genetic and functional data prompted further investigation of SNPs affecting mitochondrial function for association with DKD.

Initial analyses were performed using DNA samples from the All Ireland / Warren 3 Genetics of Kidneys in Diabetes UK Collection (UK-ROI) which comprised 1,804 white individuals with T1D, diagnosed before 31 years of age, whose parents and grandparents were born in the British Isles. Genotyping was performed using HumanOmni1-Quad array (n=1,051,295 SNPs directly typed), with data imputed to the Haplotype Reference Consortium for SNPs in mitochondrial DNA (mtDNA, n=225 total SNPs) and 2,526 nuclear-encoded mitochondria genes (NEMGs) (n=2,880,249 total SNPs).

PLINK was used to investigate association with DKD, ESRD and estimated glomerular filtration rate (eGFR) in the UK-ROI with follow-up in up to 19,406 individuals from up to 17 independent collections. The SNP that showed most evidence for association with decreased eGFR after adjusting for covariates was MitoG11915A (P =0.0003) which is a synonymous variant found in the mitochondrial gene *MT-ND4*. In NEMGs there were 8 SNPs in 4 genes associated with DKD related phenotypes.

In conclusion, mtDNA variants and SNPs in NEMGs are associated with DKD in T1D. Further research is needed to explore the functional impact of these variants.

P19. Exploration of a tissue specific promoter for retinal ganglion cells

S Millington-Ward[1], N Chadderton[1], A Palfi[1], M Berkeley[1], K Hanlon[1], P Humphries[1], PF Kenna[1] and GJ Farrar[1].

[1.] Smurfit Institute of Genetics, Trinity College Dublin, Dublin 2, Ireland.

Cell-specific promoters restricting gene expression to retinal ganglion cells (RGCs) and optic nerve may be advantageous when designing gene therapies for disorders such as Leber Hereditary Optic Neuropathy and glaucoma. To identify potential candidates within the ~4.7kb packaging constraint of AAV we analysed the upstream region of genes, 2.5kb from transcriptional start sites, which were believed to be both highly expressed and enriched in the RGCs. Sequence conservation across mammals was used as a proxy for putative promoter function. The lead promoter element was from neurofilament heavy (NEFH), in which we identified two highly conserved regions (F and A). These were used in differential configurations to drive EGFP expression from AAV2 vectors (AAV2-A-EGFP, AAV2-FA-EGFP and AAV2-FspacerA-EGFP). Promoter-driven expression profiles in murine retina were compared to expression from a 2.5kb upstream human NEFH (AAV2-2.5NEFH-EGFP) and a 2.2kb upstream murine Nefh promoter (AAV2-2.2Nefh-EGFP), following both intravitreal and subretinal injection. RNA and histological data (in retinal cryosections and wholemounts) are presented and immunohistochemistry was performed on EGFP and using RGC and amacrine cell-specific antibodies.

Our results demonstrate that AAV-2.5NEFH-EGFP, AAV-2.2Nefh-EGFP and interestingly AAV-A-EGFP represent novel promoters that mediate robust and highly preferential gene expression in RGCs and optic nerve, with additional expression seen in some amacrine cells. Notably conserved element A is only ~300bp and as such represents a versatile promoter for driving expression in RGCs and optic nerve from AAV, where cargo capacity is restricted.

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

P20. The Contribution of Second-hits in CNV Carriers to Putative Psychiatric Traits

Thomas Dinneen[1], Richard O'Cónail[1], George Kirov[2], Lorna M. Lopez[1], Louise Gallagher[1].

[1]Department of Psychiatry, Trinity College Dublin. [2]MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff, UK.

Background: Copy Number Variants (CNVs) are large genomic deletions/duplications of >1kb, spanning regions that can encompass one or many genes. Though a common form of structural variation, pathogenic CNVs, of population freq. <1%, represent significant risk loci for Neuropsychiatric Disorders (NPDs). NPD-CNVs are associated with phenotypic pleiotropy. Recent reports indicate that the concomitant inheritance of polygenic 'second-hit' variants may underlie this behavioural and neurological pleiotropy. Here we define second-hits as independent single-nucleotide polymorphisms (SNPs) in brain-expressed genes significantly associated with NPDs.

Methods and Results: Using the UK Biobank cohort (n=500,000), we will test whether there is an enrichment of second-hits in brain expressed genes in NPD-CNV carriers vs non-NPD-CNV carriers. We will generate polygenic risk scores (PRS) for autism, schizophrenia, cognition, mood disorders, cross disorder and epilepsy. We will compare the concordance of an individual's PRS to their respective psychiatric profiles and compare NPD-CNV to non-NPD-CNV carrier's results. Psychiatric profiles will be based on self-reported psychiatric illness/symptoms, cognitive scores, educational attainment, health outcomes and other available proxies for psychiatric symptoms in the UK Biobank. Sex differences will also be investigated. Results of these tests will be reported.

Discussion: This study tests the hypothesis that second-hit variants contribute to the phenotypic pleiotropy in CNV carriers. Our research will ultimately improve our understanding of NPD-associated CNVs for researchers, clinicians and genetic counsellors.

P21. Opposite expression patterns of Spry3 and p75NTR in cerebellar vermis suggest a male-specific mechanism of autism pathogenesis.

Z Ning[1], JM Williams[1], R Kumari[1], PV Baranov[1], T Moore[1]

[1]School of Biochemistry and Cell Biology, University College Cork, Cork, Ireland

Autism is a genetically complex neurobehavioral disorder with a population prevalence of more than 1%. Cerebellar abnormalities, including Purkinje cell deficits in the vermis, are consistently reported and rodent models of cerebellar dysfunction exhibit features analogous to human autism. We previously analysed the regulation and expression of the pseudo autosomal region 2 gene SPRY3, which is adjacent to X chromosome-linked TMLHE, a known autism susceptibility gene. SPRY3 is a regulator of branching morphogenesis and is strongly expressed in Purkinje cells. We previously showed that mouse Spry3 is not expressed in cerebellar vermis lobules VI-VII and X, regions which exhibit significant Purkinje cell loss or abnormalities in autism. However, these lobules have relatively high expression of p75NTR, which encodes a neurotrophin receptor implicated in autism. We propose a mechanism whereby inappropriate SPRY3 expression in these lobules could interact with TrkB and p75NTR signalling pathways resulting in Purkinje cell pathology. We report preliminary characterisation of X and Y chromosome-linked regulatory sequences upstream of SPRY3, which are polymorphic in the general population. We suggest that an OREG-annotated region on chromosome Yq12 ~60 kb from SPRY3 acts as a silencer of Y-linked SPRY3 expression. Deletion of a β-satellite repeat, or alterations in chromatin structure in this region due to trans-acting factors, could affect the proposed silencing function, leading to reactivation and inappropriate expression of Y-linked SPRY3. This proposed male-specific mechanism could contribute to the male bias in autism prevalence.

P22. A genomic exploration of population structure in the Ladakhi, a high-altitude Himalayan population

Sushil Bhandari[1], Sara Hillman[2], Edmund Gilbert[1], Padma Dolma[4], Mitali Mukerji[5], Bhavana Prasher[5], Hugh E. Montgomery[3], Gianpiero L Cavalleri[1]

[1.] Department of Molecular and Cellular Therapeutics, The Royal College of Surgeons in Ireland, Dublin 2, Ireland [2.] Maternal and Fetal Medicine Department, UCL Institute for Women's Health, London, UK [3.] UCL Institute for Human Health, London, UK, [4.] Sonam Norboo Memorial Hospital, Leh Ladakh, India. [5.] Institute for Integrative Biology and Genomics, New Delhi, India

The Ladakhi people dwell in the Jammu and Kashmir regions of India, between the Karakoram and Himalayan mountain ranges, at ≥3400 meters altitude. The Ladakhi share similar linguistic, cultural and religious practices with Tibetans. However, relative to Tibetans, the Ladakhi are very poorly studied at the level of population structure and genetic selection. In this context, we set out to conduct a genomic survey of population structure in representative samples of the Ladakhi people.

Methods: We genotyped 310 Ladakhi DNA samples using the Illumina Global Screening Array gene chip. We merged the Ladakhi with data from 800 individuals representing different reference language groups including; Sino-Tibetan (Tibetans, Sherpa, Han), Indo-European (Indo-Aryan, Hazara), Austroasiatic (Munda) and Burusho (a linguistic isolate in Jammu-Kashmir). We performed ADMIXTURE, principal component analysis (PCA), fineSTRUCTURE and ChromoPainter analysis on the combined autosomal data.

Results: In PCA plots, the Ladakhi population cluster together with Sherpa and Tibetans, forming a distinct Himalayan group, different from other mainland populations of South and East Asia. ADMIXTURE analysis at k=4 suggests ancestry proportions in the Ladakhi to be approximately 50% Highlander (Tibetan/Sherpa) and 50% Indo-European. These results suggest contemporary Ladakhi people are the admixed of Tibetans and Indo-Europeans.

Conclusions: Our results suggests a considerable component of the Ladakhi genome descends from ancestral highlander populations residing on the Tibetan plateau for the last 35,000 years, with subsequent admixture with neighbouring Indo-European populations.

P23. Towards estimating the incidence of rare diseases in a paediatric population, born in Ireland in the year 2000.

EA Gunne[2], C McGarvey[2], K Hamilton[2], A Ward[1], E Treacy[3], D Lambert[3], SA Lynch[1, 2&3]

[1] Dept. of Genetics, Our Lady's Children's Hospital Crumlin, [2] Temple Street Children's University Hospital, [3] National Rare Disease Office, Mater Hospital.

Background: The EU recognises rare disease (RD) as life threatening with delays in establishing a diagnosis and treatment. The Irish National Plan for RDs (2014) recommended epidemiological studies of RD prevalence to improve both cost efficiencies and care of patients with RD's.

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

Objective: To derive the incidence of paediatric RD and the number of paediatric RD mortality cases through analysis of records held at two major tertiary paediatric hospitals, for children born in the year 2000.

Methods: Cases were identified using electronic/manual records from: the National Paediatric Mortality Registry office; Clinical, Cytogenetics and Molecular genetics database; Radiology and the Hospital In-Patient Enquiry system (HIPE). In addition a detailed analysis of national death registration information for RDs from 2006-2016 was undertaken along with a 2year study (2015-2016) of inpatient RD deaths.

Results: There were 54,789 livebirths in 2000. Genetics records identified 801 cases of RDs Ongoing HIPE searches identified 1381 cases. Mortality data revealed that of all deaths on the Register (2006-2016), (n=4044) aged 0-14, 58.56% (n=2368) had a RD diagnosis with age distribution; Neonates, 56% (1140/2050), Post-neonates, 58% (450/778), Children aged 1-14 years, 64% (778/1216). Of the total (n=234) inpatient deaths with a RD from 2015-2016, 52.6% (n=123) were cared for at the two major centres.

Conclusion: This study to-date has identified > 2,200 RD patients presenting by age 17 giving a minimum incidence of 4% for paediatric RDs. We expect the final figure to be higher when we complete analysis of all the HIPE and sub-specialty data from these major centres.

P24. Next generation diagnostics in Irish polycystic kidney disease patients

KA Benson[1], S Murray[2], SR Senum[3], C Kennedy[2], K Yachnin[4], N Gangadharan[1], PC Harris[3], GL Cavalleri[1], P Conlon[2]

[1] Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland [2] Department of Nephrology, Beaumont Hospital, Dublin, Ireland. [3] Nephrology and Hypertension, Mayo Clinic, Rochester MN, US [4] Region Norrbotten, Kiruna Hospital, Kiruna, Sweden

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease. ADPKD is primarily caused by variants in *PKD1* and *PKD2*. Sequencing of *PKD1* is difficult due to multiple pseudogenes. There is unexplained variance in the age-of-onset of PKD, even within families.

Aim: 1) Establish a targeted NGS panel to improve molecular diagnosis of PKD and 2) characterize large 'super-families' for the study of new ADPKD genes and genetic modifiers.

Methods: NGS was performed using a custom Roche SeqCap targeted panel (273 genes) and Illumina NextSeq. Bioinformatics was performed using an in-house GATK pipeline. Pathogenicity was assigned using American College of Medical Genetics and Genomics guidelines and Mayo Clinic PKD in-house methods. Gap-filling Sanger sequencing was utilized in unsolved cases.

Results: 172 PKD patients were sequenced with average coverage 189X. A molecular diagnosis meeting pathogenicity criteria was obtained in 82% (141/172) of patients following gap-filling Sanger of *PKD1* and *PKD2* (n=41). 46 of the PKD-causing variants we detected were novel. We identified 13 rare, diagnostic PKD variants shared across multiple affected individuals recorded clinically as having no known familial relationship. Second-degree relatedness was confirmed *via* clinical follow-up. These families form the basis for the assembly of PKD 'super-families'.

Conclusions: NGS is suitable for sequencing of PKD genes including *PKD1*, although some gap filling by Sanger is required for complete coverage. We have identified 13 potential ADPKD 'super-families' using genomic data for further study. These results are improving diagnostics of ADPKD in the Irish renal clinic.

P25. A Large Deletion on Chromosome X Causes Choroideremia by Whole Gene Deletion of CHM in Irish Patients.

A Dockery[1], L Whelan[1], M Carrigan[1], J Zhu[2], N Wynne[3], G Silvestri[4,5], D Keegan[2], PF Kenna[1,3], GJ Farrar[1].

[1] The School of Genetics & Microbiology, Trinity College Dublin, Dublin 2, Ireland. [2] The Mater Misericordiae University Hospital, Dublin 7, Ireland.[3] The Research Foundation, Royal Victoria Eye and Ear Hospital, Dublin 2, Ireland.[4] Department of Ophthalmology, The Royal Victoria Hospital, Belfast BT12 6BA, Northern Ireland, UK.[5] Centre for Experimental Medicine, Queen's University Belfast, Belfast BT7 1NN, Northern Ireland, UK.

Purpose: *Target5000* is a genetic study to detect and characterise variants associated with inherited retinal degenerations (IRD). Choroideremia is an X-Linked recessive chorioretinal degenerative condition with progressive atrophy of several key cells of the retina and the surrounding blood retinal barrier. Here we describe a novel deletion in the CHM gene found in two Irish pedigrees. This 500kb deletion represents the largest yet detected IRD-associated deletion in Ireland.

Approach: As part of the Irish IRD registry, *Target5000*, patients with inherited retinal degenerative conditions are recruited. Target capture sequencing was employed to investigate variation in 254 IRD-associated genes. Upon detection of the deletion in CHM, PCR analysis was used to elucidate the full extent of the deletion.

Results: Two members of a large X-linked Retinitis Pigmentosa pedigree clinically presented with choroideremia and tested negative for the segregating RPGR variant found in other affected members of this pedigree. Both males were sequenced and found to possess large deletions spanning the CHM gene, totalling 500kb.

This deletion has also been detected in a second Irish pedigree since its discovery. Two additional males and two carrier females from this second pedigree were all found to be severely affected with progressive choroideremia.

Conclusions: Typically, female carriers of CHM mutations show mild stationary signs with no symptoms, while males are severely affected. In this instance, females were more severely affected than expected with advanced signs of degeneration and progressive visual decline. This is possibly due to random X-inactivation and the severity of CHM gene deletion.

P26. Epilepsy alone cohort and routine genetic testing – is it needed?

C McKenna[1], M Humphreys[1], S McNerlan[1], T Dabir[1]

[1] Northern Ireland Regional Genetics Service, Belfast

Only a small proportion of epilepsy is secondary to syndromic conditions and/or mutations in a single gene. The cost of array comparative genomic hybridization (CGH) is ~£300, and the cost of epilepsy gene panel testing ranges from £525-£1,300. Both investigations risk identifying benign copy number variants or variants of unknown significance. We aimed to identify patients who have had an array CGH and/or gene panel test requested for epilepsy, in the absence of an additional phenotype ("epilepsy only"), and to determine the diagnostic yield of these investigations.

Array CGH requests and gene panel tests for epilepsy were reviewed between January 2013 and June 2018. We excluded those patients

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

with learning difficulties, global developmental delay, dysmorphic features and congenital abnormalities. Requests were extracted from a departmental database, which includes a clinical summary provided by the clinician. We reviewed the medical records for further clinical information relevant to phenotype. Diagnostic yield included all copy number variants identified on array CGH and pathogenic/ likely pathogenic variants detected on gene panel tests.

We identified 40 array CGH requests for patients with "epilepsy only" phenotype. Only one of these yielded a copy number variant, and the clinical significance of this variant was uncertain. We identified 15 gene panel requests for patients with "epilepsy only". Again, only one of these requests identified a likely pathogenic variant in *SCNA1*, a gene associated with Dravet Syndrome. Based on the low diagnostic yield we would not recommend routine array CGH or gene panel testing in individuals with "epilepsy only".

P27. To screen or not to screen; Three cases of *RET* duplication.

C McKenna[1], G Rea[1], M Humphreys[1], S McNerlan[1], PJ Morrison[1]

[1] Northern Ireland Regional Genetics Service, Belfast

RET is a proto-oncogene which encodes a receptor tyrosine kinase. Loss of function mutations in *RET* are associated with Hirschsprung disease, while gain of functions mutations cause Multiple Endocrine Neoplasia Type 2 (MEN2). Patients with MEN2 have an increased risk of medullary thyroid cancer and phaeochromocytoma. Screening recommendations for patients with MEN2 include annual calcitonin from 6 months and annual metanephrine from 8 years.

We report three unrelated patients with duplications at 10q11.21 which include *RET*. Patient A is 7 years old and has a history of autism and dysmorphic features. Parental studies are pending. Patient B is 2 years old and has a history of developmental regression and autism. The duplication was inherited from her unaffected mother. Patient C is 51 years old and has a diagnosis of neurofibromatosis type 1; Her array also identified a deletion at 17q11.2 which includes *NF1*. None of the patients have a personal or family history of *RET* associated cancers or Hirschsprung disease.

While intragenic duplications, which create an additional cysteine residue, have been identified in patients with MEN2, whole gene duplications of *RET* have not been reported. Therefore it is difficult to determine whether these patients are at risk of *RET* associated disease and whether any screening is required. It is possible that we will see increased reporting of duplications involving oncogenes, such as *RET,* following their inclusion in the ACMG recommendations for reporting of secondary findings. This will present a challenge for clinicians to provide accurate disease risk estimates and screening recommendations.

P28. The Northern Ireland Cohort of Neurofibromatosis type 2 patients & clinical correlation of their Genetic Severity Score

DE Donnelly[1], L Jeffers[1], PJ Morrison[1]

[1] Dept Clinical Genetics, Belfast City Hospital, Belfast

Neurofibromatosis type 2 is a rare, autosomal dominant, cancer predisposition syndrome caused by mutations in the NF2 gene on chromosome 22. Birth incidence is around 1 in 33,000. Patients typically present in the second decade of life with hearing loss due to the characteristic tumour of acoustic neuroma, which is often bilateral. Other intracranial tumours, such as meningioma, schwannomas or ependymomas, can also occur. Treatment is generally surgical, but this carries many risks, including acquired hearing loss, facial nerve palsy or significant loss of function. The average life expectancy is around 45 years of age. There are many important predictors of severity, e.g. age of onset of symptoms, which can provide useful prognostic information. Genotype-phenotype correlations are well recognised and, in 2017, a revised Genetic Severity Score [1] was devised for NF2. All patients with NF2 in Northern Ireland are followed up at the Regional NF2 clinic in Belfast and we estimate that we have almost complete ascertainment. We have measured the Genetic Severity Score for each patient and assessed its correlation with clinical symptoms. We hope to continue this work by calculating the Score for newly-diagnosed patients, so that it can guide management, aid future research and give patients some prognostic information. [1]. Halliday D et al, Genetic Severity Score predicts clinical phenotype in NF2. *J Med Genet*. 2017;**54(10):**657-664.

P29. The Collar Bone is connected to the Pancreas: a Cytogenetic Explanation

E Sasaki[1], H Kelly[1], B Hayes, K Ryan[1], E Carolan, D Betts[1], A Green[1,2]

[1]Dept. Of Clinical Genetics, Children's Health Ireland [2]School of Medicine and Medical Science, University College Dublin

A male infant was born at 28 weeks after spontaneous rupture of membranes, weighing 700g (0.4^{th} – 2^{nd} percentile), and transferred to the neonatal unit. There had been antenatal concerns over soft markers with short femurs and an absent nasal bone, and amniocentesis was carried out. At birth he was noted to be dysmorphic, with a broad open fontanelle, and required ventilation. Chest X ray showed absent clavicles, a relatively small thorax, and small scapulae. After birth, it transpired that the baby's father and paternal grandmother had absent clavicles, short stature and poor dentition. A diagnosis of autosomal dominant cleidocranial dysostosis was made.

The infant's course was complicated by sepsis. Despite adequate treatment of sepsis he failed to wean from insulin and was subsequently diagnosed with neonatal diabetes. Neonatal diabetes is a rare disorder with a number of different genetic causes.

Microarray and G banding analysis produced a unifying explanation and mechanism for these two apparently unconnected phenotypes.

On microarray the baby had a 143kb deletion within chromosome 6p21.1 that included part of the *RUNX2* gene, which is mutated in cleidocranial dysostosis. He also had a 12.8 Mb duplication of chromosome 6q23.2-24.2, containing a large number of genes that included *PLAGL1* and *HYMAI*. Paternally derived duplications of 6q24, involving those genes, are associated with transient neonatal diabetes mellitus, and one would therefore infer that the 6q duplication is paternally derived, and that the baby's neonatal diabetes is likely to be transient.

The baby also had an unrelated 251kb deletion within 2p16.3 involving the *NRXN1* gene. Such deletions are associated with a variable degree of developmental disorders in children and adults. G band analysis pre and postnatally showed that there was an unbalanced insertion of the duplicated 6q chromosome material into 6p21.1, presumably at the site of the *RUNX2* deletion.

One would therefore expect that the baby's father with cleidocranial dysostosis carries an insertion of 6q23.2-24.2 into 6p21.1, causing his, and likely the baby's grandmother's cleidocranial dysostosis. Parental microarray and G band analysis is under way.

This rare combination of chromosome 6 rearrangement and distinct clinical disorders has not previously been reported in the literature.

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

P30. The Significance of Genetic screening in PKU adult cohort & the introduction of Sapropterin dihydrochloride

A Sheerin[1], L Grabowsky[1], S James[1], S Senanayake[1], Z Abidin[1], J O'Byrne[1], E Treacy[1], G Pastores[1]

[1] The National Centre for Adult Inherited Metabolic Disorders, Mater Misericordiae University Hospital, Dublin.

Introduction: The largest cohort of patients at The National Centre for Adult Inherited Metabolic Disorders (NCIMD) have Phenylketonuria (PKU). The NCIMD manages patients transitioned from Paediatric services upon reaching adulthood. Improved treatments have extended life expectancy and increased quality of life for patients with PKU; however diet and supplements remained the only means of treatment for life until the recent introduction of Sapropterin dihydrochloride.

Aim: To analyse the genotype of the PKU cohort in attendance at The NCIMD with a focus on responsiveness to Sapropterin dihydrochloride.

Method: The data are collated from when the Adult unit was first established in 2013 until the end of May 2019. Exclusion criteria include patients over the age of 53 and patients who have two negatively indicated genotypes for the use of Sapropterin dihydrochloride. Genotypes are recorded in a secured database on-site and descriptive analyses were performed.

Results: The total number of patients examined is 282; 104 were male (36.8%) and 178 were female (63.1%). The total samples processed and available for analysis were 148 (male= 46, 31%; female= 102, 68.9%). The frequency of Saptopterin dihydrochloride responsiveness in both alleles was observed (responsive= 15, 10%; unresponsive= 48, 48.33%; uncertain= 85, 57%). The most common alleles recorded were R408W (41.1%), F39L (13.8%), 165T (11.2%), and L249F (3.8%).

Conclusion: Due to the uncertainty surrounding Sapropterin dihydrochloride responsiveness for various common mutations in the Irish PKU cohort, there is a need for greater genetic and metabolic collaboration. Analysis and treatment may be impacted by time elapsed from sending samples to receiving results.

P31. *POT1*: An emerging oncological phenotype

C McKenna[1], G Rea[1], V McConnell[1]

[1] Northern Ireland Regional Genetics Service, Belfast

Patients with mutations in protection of telomeres 1 (*POT1*) gene are an emerging phenotype and to date 21 families, involving 69 confirmed POT1 gene mutation carriers have been reported in literature. Somatic mutations in *POT1* are also reported in chronic lymphocytic leukaemia, cutaneous T-cell lymphoma and lung tumours. As there are so few reported cases of patients with *POT1* mutations it is difficult for clinicians to counsel patients as to which cancers are more likely to occur in mutation carriers, and what screening, if any, is indicated.

In this four- generation pedigree we describe the oncological burden of three individuals with a known mutation in *POT1* and three first degree affected, deceased relatives who are presumed to be gene carriers. Cancers present in this family reflect some cancers which have previously been described in patients with *POT1* mutations, including melanoma, sarcoma, oligodendroglioma and lymphoma. However, our pedigree also includes disease phenotypes not previously described in the *POT1* cohort, including atypical pancreatic cancer, desmoid tumour, ovarian cystadenofibroma, lipomas and other dermatology cancers.

At present dermatology follow-up is recommended in confirmed *POT1* gene mutation carriers described in this pedigree as evidence suggests an increased lifetime risk of melanoma however, additional screening recommendations are very difficult currently with few *POT1* families ascertained. Our family extends current knowledge on phenotype in *POT1* families reported in literature with the hope that, in the future, it will be possible to offer patients more targeted screening and more accurate disease risk estimates.

P32. Schwannomatosis – the Northern Ireland Cohort

DE Donnelly, L Jeffers, PJ Morrison, C McKenna

[1] Dept Clinical Genetics, Belfast City Hospital, Belfast

Schwannomatosis is a rare, autosomal dominant, cancer predisposition syndrome that can lead to schwannomas, which mainly occur in the spinal and peripheral nerves. As acoustic neuromas can occur, the condition can be mistaken for Neurofibromatosis type 2 (NF2). It is, however, important to differentiate between these 2 disorders, as the prognosis is generally poorer for NF2; the average life expectancy in NF2 is around 45 years of age, whereas in schwannomatosis, it is around 75 years. This prognostic information in useful in guiding clinical management and is also helpful for patients. Most schwannomatosis patients will have mutations in the LZTR1 and SMARCB1 genes. In Northern Ireland, our schwannomatosis patients are followed up at the Regional NF2 clinic in Belfast and we estimate that we have almost complete ascertainment. Here we present the findings of genetic analysis of this cohort and summarise their clinical symptoms.

P33. Dying to see you?

L Bradley[1], SA Lynch[1,2]

[1] Children's Health Ireland (CHI), at Crumlin, Ireland. [2]. Children's Health Ireland, at Temple Street, Ireland

Introduction: The Department of Clinical Genetics at CHI provides services for individuals affected by or at risk of a genetic condition in the Republic of Ireland. There are currently 3,283 referrals waiting to be seen, of whom 930 are waiting longer that the HSE standard of 18 months.

A negative consequence of a long waiting list is that patients die whilst waiting. Resulting harm includes: 1) no diagnosis 2) no genetic testing, no DNA stored, 3) family unaware of a hereditary disorder, denied screening, 4) relatives having unnecessary screening as no predictive test for family, 5) future pregnancy options limited if paediatric proband undiagnosed. As of 13/06/2019, we have recorded 33 deaths on our waiting list. We began to systematically collect data on deaths since March 2018. This study concentrates on these cases; n=15/33.

Aims: To identify the consequences to the relatives of these 15 referrals.

Results: Nine were adult cancer genetic referrals, 5/9 diagnostic, 3/9 predictive, and a further case had NF2. Only 1/9 had DNA stored. Two adult patients had a cardiac family history (Marfan syndrome, cardiomyopathy) respectively. Neither had DNA stored. Four paediatric patients had multiple malformations secondary to a chromosomal or genetic syndrome. In 3/4 a diagnosis had already been reached. The fourth case, who died unexpectedly of unrelated causes, had no DNA stored.

Summary: 11/15 patients who died did not have DNA stored, precluding diagnosis and risk calculation for their relatives. As

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

each extended 3 generation Irish family has ~64 relatives, lack of diagnosis has far reaching consequences.

P34. Interventions to improve psychosocial well-being in female *BRCA*-mutation carriers following risk-reducing surgery: A Cochrane Systematic Review.

L Jeffers[1], J Reid[2], D Fitzsimons[2], PJ Morrison[1,4], M Dempster[3]

[1] Department of Medical Genetics, Northern Ireland Regional Genetic Service, Belfast City Hospital, Belfast, UK. [2] School of Nursing and Midwifery, Queen's University Belfast, Belfast, UK,[3] School of Psychology, Queen's University Belfast, Belfast, UK, [4] Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, UK.

Background: Women who carry a pathogenic variant in either a BRCA1 or BRCA2 gene have a high lifetime risk of developing breast and tubo-ovarian cancer. To manage this risk, women may choose to undergo risk-reducing surgery to remove breast tissue, ovaries and fallopian tubes. Surgery should increase survival, but can impact women's lives adversely at a psychological and psychosexual level. Interventions to facilitate psychological adjustment and improve quality of life post risk-reducing surgery are needed.

Aim of Review: To examine psychosocial interventions in female BRCA carriers who have undergone risk-reducing surgery and to evaluate the effectiveness of such interventions on psychological adjustment and quality of life.

Methods: We searched the Cochrane Central Register of Controlled trials (CENTRAL) in the Cochrane Library, MEDLINE via Ovid, Embase via Ovid, CINAHL, PsycINFO, Web of Science and Scopus up to April 2019.

Results: We identified two studies; one randomised controlled trial and one nonrandomised study.

Conclusions: The effect of psychosocial interventions on quality of life and emotional well-being in female BRCA carriers who undergo risk-reducing surgery is uncertain given limited high quality evidence. Next Generation Sequencing, along with targeted cancer treatments, increasing knowledge around the biology of cancers and the results of the 100K Genome Project will open up genetic testing to many more women. For as long as surgical interventions remain the dominant risk-reducing option for management of women with a deleterious BRCA gene, health professionals have a responsibility to ensure there is provision to holistically manage the outcomes of such surgery.

P35. An Irish male with bilateral Fibular Aplasia Tibial Campomelia and Oligosyndactyly (FATCO) syndrome

Michaela Pentony[1], Lisa Bradley[2], Pamela O' Connor[1]

[1] Department of Neonatology, Coombe Women and Children's University Hospital [2] Department of Clinical Genetics, Our Lady's Children's Hospital Crumlin

Introduction: FATCO (Fibular Aplasia, Tibial Campomelia and Oligosyndactyly) syndrome is a rare descriptive diagnosis first defined by Courtens *et al*. in 2005, who recognised a comparable pattern of malformations with his own case and 4 others described in the literature. Aetiology remains unknown, however defects involved in *SHH* (Sonic hedgehog) gene expression have been proposed.

Case Description: We report on a term male infant born with severe malformations. On examination, there was absence of the left radius and ulna, bilateral anterior angulation of lower limbs with skin dimpling overlying. Both ankle joints were dysplastic and there was oligosyndactly of both feet. Right upper limb was normal. X-rays of the limbs revealed dysplastic tibiae, absence of both fibulae, a right foot containing 3 ossified metatarsals with 2 formed digits, and a left foot with a single ossified metatarsal and two soft tissue digits with small bony elements. The infant had no other associated anomalies, and is developmentally appropriate at 1 year. Management included Symes amputation, prosthetics and following genetic referral FATCO syndrome was suggested as the best fitting diagnosis. Whole genome sequencing of the infants blood is currently being performed.

Discussion: This is an important case to report as there are very few descriptions in the literature, In keeping with the majority of reports, this case appears to be sporadic and development is normal. Our case is male, keeping with preponderance. Treatment aims at optimising functionality of limbs and stabilisations of joints.

P36. Natural history of a fibrous cephalic plaque and sustained eight decade follow-up in an 80 year old with tuberous sclerosis complex type 2.

Claire W Kirk[1], Deirdre E Donnelly[1], Rachel Hardy[1], Charles W Shepherd[1], Patrick J Morrison[1]

[1]Tuberous Sclerosis Clinic, Belfast City Hospital, Belfast BT9 7AB.

Introduction: Fibrous cephalic plaques (FCP) are a characteristic manifestation of tuberous sclerosis complex (TSC) and occur in one third of cases. Their natural history and long term course is unknown, as is the outcome of long term follow-up of TSC cases in old age.

Phenotype and methods: We describe an 80 year old with TSC due to a c.2784dupC TSC2 mutation, who was diagnosed in infancy with an FCP and was regularly followed up at the TSC clinic over 8 decades with regular epilepsy treatment and renal monitoring.

Results: Regular clinical photography and clinical records document the plaque at different ages. The FCP naturally resolved at 74 years. Facial angiofibromas also faded with time in the last decade. His epilepsy and renal abnormalities remained under control with careful surveillance and monitoring.

Discussion: Natural aging in the eighth decade causes progressive laxity of collagen and leads to natural resolution of FCPs. This novel finding with a unique 80 year follow up yields valuable insights into the aging changes within FCPs and facial angiofibromas as the pathways linking facial angiofibromas and FCP's through the TGF-β1 pathway are now being elucidated.

Conclusion: We present a clinical odyssey showing the natural progression and history of FCPs in TSC and comment on the mechanistic pathways allowing potential interventions in this disfiguring condition. TSC cases can be successfully managed and complications – particularly in the brain and kidney, can be avoided over an entire lifetime. This is encouraging for long term prospects for patients with TSC.

P37. Genotype/phenotype landscape of adult Fabry disease in Republic of Ireland

S James[1], A Sheerin[1], L Grabowsky[1], Z Abidin[1], S Doyle[1], S Senanayake[1], T McVeigh[1], E Treacy[1], G Pastores[1], JJ O'Byrne[1].

[1] The National Centre for Adult Inherited Metabolic Disorders, Mater Misericordiae University Hospital, Dublin.

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

Introduction: Fabry disease is an X-linked inherited disorder due to deficient activity of the enzyme alpha-galactosidase A and progressive lysosomal deposition of globotriaosylceramide in cells.

Aim: To report the genotype/phenotype landscape of the adult Fabry disease cohort attending The National Centre for Adult Inherited Metabolic Disorders (NCIMD).

Method: All Fabry patients (N=70) attending NCIMD until end of May 2019 were included in this analysis. Genotypes and phenotypes were recorded by chart review. Descriptive analyses were performed.

Result: 26 (37.1%) were male (median age 43 [32:54]) and 44 (62.9%) were female (median age 46 [25:61]). The *AGAL* pathogenic variants were missense (52, 74.3%), deletion (9, 12.9%), nonsense (8, 11.4%) and duplication (1, 1.4%). Most missense variants occurred in exon 2 (25%), exon 3 (19.2%), exon 5 (23.1%) and exon 6 (21.2%). 21.2% of missense variants were N215S. 28 patients were on enzyme therapy and 2 were on oral chaperone therapy. The incidence of cardiac (M=18/26; F=18/44; p=0.021), renal (M=14/26; F=18/44; p=0.304), neurological (M=17/26; F=20/44; p=0.107) and hearing (M=14/26; F=19/44; p=0.399) involvement were observed. Within N215S cohort, 2 had hypertrophic cardiomyopathy and 5 with a degree of left ventricular hypertrophy.

Conclusion: Pathogenic variants were observed across the *AGAL* gene in the cohort. Incidence of cardiac involvement in both genders is similar. Females had more frequently observed renal, neurological and hearing involvement. N215S *AGAL* variant is the most common variant which is associated with a predominant cardiac phenotype, thus collaboration between clinical geneticists and cardiovascular physicians are important when establishing diagnosis and management.

P38. 'Long shadow of metabolic entropathies: a Tale of Two Extreme Case'

SL Senanayake[1], S Sadok S[1], GM Pastores[1]

[1] National Adult Centre for Inherited Metabolic Disorders, Mater Misericordiae University Hospital

Inherited genetic disorders of energy utilisation ('entropy') from glucose can have clinical consequences with extreme variability of phenotype. This primarily depends on the location of enzyme defect along the metabolic pathway, i.e. upstream glycolysis or downstream oxidative phosphorylation, thus causing a catabolic bottleneck. Herein, we compare and contrast two extreme clinical cases: one of pyruvate dehydrogenase (PDH) deficiency and another of cytochrome c oxidase (COX) or respiratory chain complex IV deficiency. Through molecular genetic analysis, the first case was confirmed as a homozygous, missense mutation-driven defect in the E2 subunit of PDH which governs entry of glycolytic end product into the citric acid cycle; conversely, the second case demonstrated reduced activity of cytochrome *c* oxidase (COX), the penultimate enzyme complex in the mitochondrial electron transport chain. PDH deficiency is a rare autosomal recessive condition characterised by a constellation of severe neurological symptoms including intellectual disability, seizures and metabolic stroke. On the contrary, complex IV deficiency leads to a phenotype of predominantly generalised myopathy. We coin these syndromes at opposite ends of the bioenergetic pathway 'metabolic enteropathies'. As such, they exemplify two diagnostic baskets that should be high on the differential diagnoses of suspected inherited metabolic disorders (IMDs) of neuromuscular presentation.

P39. Genetic Characterisation of two Copy Number Variants (CNVs) in the *LDLR* Gene causing Familial Hypercholesterolaemia

[1]R Forde, [1]S Savage , [1]A Rakovac, [1]E Rasheed, [1]A Rashid, [1]S Abdelfadil, [1]B Mac Namara, [1]E Keogh, [2]P O'Connor, [3]S Heggarty, [3]P Hart, [1]VEF Crowley

[1] Biochemical Genetics Laboratory, Biochemistry Department, St James's Hopsital, Dublin 8. [2] Dept of Pharmacology & Therapeutics, TCD Health Sciences Building, St James's Hospital, Dublin 8. [3]Northern Ireland Regional Genetics Unit, Belfast City Hospital

Familial hypercholesterolemia (FH) is an autosomal dominant disorder due primarily to mutations in *LDLR, APOB* and *PCSK9*, which causes marked increases in LDL cholesterol levels and predisposes to premature CVD. It has an estimated prevalence of 1 in 250 suggesting approximately 23,000 FH sufferers in the Republic of Ireland. The most cost-effective strategy for identifying FH is genetic cascade screening in kindreds with an identified proband. To date our service has genetically diagnosed 30 disease-associated variants in *LDLR* and *APOB*, including four CNVs in *LDLR* detected using MLPA. The elucidation of mutations which are associated with FH can facilitate a better understanding of the pathology of the disorder, as well as improving genetic diagnostic methods for variant detection. This study reports the characterisation of two CNVs.

A novel exon 6 deletion was identified using a short-range PCR strategy followed by direct sequencing. This variant was then used to validate a long-range PCR assay which subsequently facilitated the identification of an aberrant PCR product caused by a second *LDLR* deletion in exon 15-18.

Over 10% of FH-causing mutations are attributed to complex rearrangements due to the high degree of *Alu* elements within *LDLR i*ntronic sequences. While MLPA is effective at identifying CNVs it is an expensive method to use for cascade screening within large family groups. This project identified the breakpoints in a novel LDLR exon 6 deletion and an aberrant PCR product caused by a deletion of exon 15-18, and both findings will facilitate future cost-effective cascade testing of family members within the respective kindreds.

P40. Characterisation of the pathogenic basis of an early-onset familial mucocutaneous ulcerative condition in Irish families

NE Morgan[1], E Dorris[1], E Cummins[5], F Adeeb[4], C Taylor[5], S Savic[3], O Killeen[6], A Fraser[4], AG Wilson[1]

[1]University College Dublin, Centre for Arthritis Research, Dublin 4, Ireland [2]University Hospital Kerry, Rheumatology, Tralee, Ireland [3]University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom [4]University Hospital Limerick, Rheumatology, Limerick, Ireland [5]University College Dublin, School of Medicine, Dublin, Ireland [6]Our Lady's Children's Hospital Crumlin, Rheumatology, Dublin, Ireland

Bechet's disease (BD) is a heterogeneous multifactorial auto-inflammatory condition characterised by recurrent episodes of oral and genital ulceration, uveitis and skin lesions, with less frequent involvement of the gastrointestinal tract, large blood vessels and central nervous system. Recent studies reported monogenic mucocutaneous ulcerative syndromes with similarities to BD in a number of un-related families caused by mutations in NF-κB pathway genes; RELA, a transcription factor of the NF-κB family, and TNFAIP3, a negative regulator of NF-κB activity and inflammatory cytokine production. The NF-κB pathway is a 'master-regulator' of

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

immune and inflammatory signalling, with the ability to control the expression of genes associated with inflammation, apoptosis and proliferation. Five multi-case Irish families have been identified with a similar illness, primarily involving childhood-onset chronic oral and genital ulcers. Using whole exome sequencing (WES), this study aims to identify the potential disease-causing mutations, and to elucidate their biological effects.

In the largest, a three generation family, WES revealed segregation of a mutation in RELA with the condition. The mutation involves a cytosine deletion causing a His487ThrfsTer7 frameshift resulting in a truncated protein, which is expressed at similar levels as the wild-type in PBMCs. Crucially the mutation interrupts the two C-terminal RELA transactivating domains. Genotyping of this variant in other families revealed the presence of the wild-type allele only, suggesting genetic heterogeneity. Current genetic analysis of the remaining families is expected to reveal novel disease-causing mutations. These discoveries will contribute to our understanding of the disease mechanism and the inflammatory pathway, leading to personalised treatment for patients resulting in earlier disease control.

P41. Hurdles to genetic research in Ireland; GDPR and Health Research Regulation in practice.

Jane Murphy[1], Claire Kirk[1], Terence Prendiville[2], Deirdre Ward[3], Joseph Galvin[4], Sally Ann Lynch[5].

[1]School of Medicine, University College Dublin, Belfield, Dublin 4. [2]Department of Cardiology, Children's Health Ireland at Crumlin, Dublin 12. [3]Centre for Cardiac Risk in the Young, Tallaght University Hospital, Dublin 24. [4]Family Heart Screening Centre, Mater Misericordiae University Hospital, 53-54 Eccles Street, Dublin 7. [5]Department of Clinical Genetics, Children's Health Ireland at Crumlin, Dublin 12.

The General Data Protection Regulation (GDPR) aims to protect EU citizens from privacy and data breaches. The Department of Health in Ireland issued further legislation designated the Health Research Regulation (HRR) pertaining to data processing for the purposes of health research.

We were awarded an international peer-reviewed grant to conduct a translational study on clinical genetics patients. The aims of the project are three-fold: 1. To review cardiac genetic patients and update their variant pathogenicity status using the 2015 ACMG guidelines. 2. To collate phenotypic and penetrance data on these patients over time. 3. To offer extended panel testing to 30 families who were gene-negative on the original four-gene panel.

Due to HRR, the requirement for "explicit consent" to perform a large-scale retrospective genetic test review was highlighted by an ethics committee, despite previous patient consent to genetic testing having been obtained. On consultation with the local Data Protection Officer (DPO), we were advised that explicit consent was not required for parts 1 and 2 of the study (defining them as clinical audit and usual practice, respectively). For part 3, we require explicit consent from participants, issuing our own patient information leaflets/consent forms and arranging consultation with a genetic counsellor prior to enrolling in the study.

Ambiguity over the implementation of the new guidelines was evident throughout the process. This is contributing to stasis in audit and research as all stakeholders are learning how best to interpret the guidelines.

We would encourage researchers to engage with stakeholders to ensure compliance with GDPR.

P42. Diagnostic Yield for genetic testing for Hypertrophic Cardiomyopathy in the Irish Population

C. Carroll[1], T McVeigh[1,2], C Kirk[3], J Murphy[3], A Ward[1], SA Lynch[3,4]

[1.] Department of Clinical Genetics, Our Lady's Hospital, Crumlin.[2.] Royal Marsden NHS Foundation Trust. [3.] Department of Cardiology, Mater Misericordia Hospital.[4.] University College Dublin.

Background: Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease with a worldwide prevalence of 1:500. Genetic etiology is suspected in up to 50% of HCM patients. To gain insight into the diagnostic yield and mutation spectrum of HCM, a retrospective review was performed for 114 consecutive cases with a clinical suspicion of HCM who underwent multigene panel testing at our laboratory between 2014 and 2019.

Method: Data was manually extracted from laboratory reports with respect to indication for testing, number of genes on panel, variants identified and classification at the time of testing.

Results: A total of 114 patients with a diagnosis of HCM had samples submitted for diagnostic testing using a multigene panel of between 16 and 20 genes, depending on the year of testing. 56 patients had no genetic variant identified, 33 patients had a pathogenic or likely pathogenic variant identified and 25 had a variant of uncertain significance identified. One 11 year old patient had a normal result from an 18 gene panel for HCM, but was later diagnosed with Friedrich ataxia. One adult female patient had a normal result from a 19 gene panel but was later diagnosed with Fabry disease.

Conclusion: Clinically actionable 'Pathogenic' or 'Likely pathogenic' variants were identified in 29% of patients with a Clinical diagnosis of Hypertrophic Cardiomyopathy with VUS being identified in 22%. The most common 2 genes in which clinically actionable variants were found were MYH7 (47%) and MYBPC3 (31%).

P43. A 3-year review of Huntington's disease referrals to the Department of Clinical Genetics, CHI at Crumlin.

M Duff[1], E Mooney[2], T Clark[1], C King[1], SA Lynch[3]

[1.]Dept. of Clinical Genetics, CHI at Crumlin. [2.]University College Dublin. [3.]Dept. of Clinical Genetics, CHI at Temple Street

Huntington's disease (HD) is an inherited progressive neurodegenerative condition. In the Republic of Ireland genetic testing for HD is available via two routes. Symptomatic individuals can access testing via a Neurologist. Asymptomatic individuals with a known family history of HD can seek testing via a genetic counselling multi-step process.

Aim: The aim of the audit was to review the activity of the HD specialty clinic.

Methods: Retrospective chart, laboratory and clinical database review for HD referrals received for 2016, 2017 and 2018 was carried out. Parameters examined included: number of referrals, age profile, motivation for testing, results.

Results: Over this 3 year period 93 referrals were received. 80 referrals were for predictive testing and 13 for genetic counselling post testing through neurology. The youngest person was 18 years of age at time of referral. More females requested a referral for predictive testing than males, 48 (60%) and 32 (40%) respectfully. The most common motivation given for predictive testing was with regard to family planning and concerns for children and to

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

help them plan for the future. Of the 30 tests carried out to date, 52% were mutation positive and 42% were mutation negative. The average age of those who proceeded with testing was 37yrs.

Conclusion: These findings reflect data published from the UK with regard to age of presentation and female to male bias. The most common motivation for testing was family planning unlike the UK where the most common reason provided was to reduce uncertainty.

P44. Survival Modelling Incorporating Genetic Profile: application to a TCGA dataset

L Fallah[1], J Hinde[2]

[1.] School of Mathematics and Statistics, University College Dublin. [2.] School of Mathematics, Statistics and Applied Mathematics, National University of Ireland, Galway.

This work is on analysing methods for high-dimensional survival data and applications of them to a TCGA dataset from The Cancer Genome Atlas on ovarian carcinoma. The dataset clinically annotated as "HGS-OvCa" includes both clinical and genomic gene expression profile of patients which was measured with the motivation of increasing the successful treatment strategies in 2011.

Ovarian cancer is one of the leading causes of death in women in recent years with most deaths for patients with advanced-stage, high-grade serous ovarian cancer (HGS-OvCa) as reported in some papers. The standard treatment is aggressive surgery followed by platinum taxane chemotherapy. After therapy, platinum resistant cancer recurs in approximately 25% of patients within six months, and the overall five-year survival probability is 31%.

The Cancer Genome Atlas provided researchers a possibility to study comprehensively genomic and epigenomic abnormalities on clinically annotated HGS-OvCa samples. In this study the mRNA expression, microRNA expression, promoter methylation and DNA copy number in 489 high-grade serous ovarian adenocarcinomas and the DNA sequences of exons from coding genes in 316 of these tumours are measured. In Cancer Genome Atlas projects gene expressions of the samples are measured multiple times on different microarray platforms. We have used the complete-data unified gene expression (a weighted average of the platforms) profile of patients and their associated clinical data, which consists of 269 patients gene profiles with 11864 employed genes, to build a predictive model for patients' survival and interpret how effective the treatment is for the patients in high-risk and low-risk prognosis groups.

UMJ is an open access publication of the Ulster Medical Society (http://www.ums.ac.uk).
The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.