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Abstracts

19th Meeting of the Irish Society of Human Genetics, Friday 9th September 2016.

Belfast City Hospital

SPOKEN PAPERS:

S01. Deep phenotyping and genomic analysis for Behcet's disease

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Behcet's disease (BD) is a complex, multifactorial rare disease, which is poorly understood. Genetic and environmental factors contribute to BD, but the process of diagnosis is challenging with inconsistent clinical manifestations. A recent survey of individuals living with rare disease(s) in Northern Ireland revealed ~50% of individuals receive ≥1 misdiagnosis with $^{1}/_{20}$ seeing >10 doctors.

Individuals with BD report a range of symptoms, which are variable in onset, severity, and frequency for this systemic vasculitis. Patients describe prolonged journeys to diagnosis with multiple healthcare professionals and medical specialties; there is no BD specialist in Northern Ireland. Using invitations via social media, voluntary groups, and direct contact we are using surveys incorporating micro-narratives, one-to-one semi-structured interviews, and focus groups to collect detailed family histories and stressor information to help characterise recurrent features in patients living with BD and their relatives in Northern Ireland.

BD is most often reported in populations along the Silk Road. The highest prevalence is reported in Turkey at 20-420/100,000, compared 1.5/100,000 individuals in the UK. Mapping through general practitioners revealed a much higher than expected prevalence of 12.6/100,000 in the Northern Ireland population. Clusters were observed in Co. Down and Co. Antrim and plotted with social-demographic information. This high 'UK' prevalence and the identification of several families with multiple members diagnosed makes NI ideal to explore genetic and epigenetic risk factors for BD.

This project involves deep phenotyping and strategies to improve recognition of Behcet's disease, build collaborative partnerships, improve data collection, enhance training, and information sharing.

S02. Capturing Irish Rare Disease activity, a must for improved cross border care and research

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The National Rare Disease Office (NRDO), initiated in June 2015, collates and disseminates Irish rare disease (RD) information. The prevalent nature of RD (1 in 16 of the population, approximately 80% of which has a genetic basis) and the burden to the health care system is under-recognised and a neglected public health issue. Awareness of rare diseases is a challenge, especially for GPs who each care for > 90 RD patients.

The NRDO has made 58 presentations, lectures and publications and received numerous enquiries (58% of contacts from patients/families, 25% from health care professionals and 4% researchers). Mapping Irish RD clinical and research expertise is developing through Orphanet Ireland. Enrolment of clinical expert centres has increased by 50%,but only <10% of the most prevalent RDs are represented. This reflects well-developed services for some conditions, (e.g. vasculitis and ALS), but more disparate services for others (intellectual disability and multisystemic RD). A lack of coding and/or registries makes it difficult to identify rare patients within hospital systems. Numerous cross-border initiatives seek to maximize clinical and research outcomes through collaboration. However, < 1% of Irish RD research and <30% of RD clinical trials are registered on Orphanet. For European recognition and participation, Ireland must make its RD research visible, and 'count' RD patients and activity. Irish patients will be disadvantaged unless we develop systems to prepare for entry to European Reference Networks and become "trial ready". While progress is slow, these are early days and we are optimistic about future developments.

S03. PTEN Hamartoma Tumour Syndrome Screening Audit – Northern Ireland 2016

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Aims: To assess the tumour surveillance advice given to patients in Northern Ireland with confirmed PTEN hamartoma tumour syndrome (HTS).

Methods: We used the surveillance advice laid out by the Pan Thames Cancer Genetics Group in 2014 to benchmark our

patients against. A coding search was carried out on our regional information management system to identify all patients with a confirmed diagnosis. The written/ electronic notes of these patients were reviewed. We adhered to the National PTEN audit inclusion criteria of including patients older than16 years, those with a pathogenic/likely pathogenic PTEN mutation or at 50% risk and those who had received advice between 01/08/10 - 01/08/2015.

Results: 21 patients were identified. All patients had a pathogenic PTEN mutation. 6 children were excluded. 1 adult was excluded due to lack of documented advice. 6 patients had a cancer diagnosis. 9 patients had a positive family history of cancer. Annual breast screening was recommended for 67% of patients which involved mammography in 83% and MRI in 17%. Annual thyroid USS and TFTs were recommended for 54% and 31% of patients respectively. 16% of female patients had gynaecology referrals completed. An annual dermatological review was recommended for 23% of patients. Widely variable colonoscopy and renal USS screening was recommended for 77% and 65% of patients respectively. No cases of Lhermitte-Duclos disease were identified vs 12% in the national UK audit.

Conclusions: There is a need for regional PTEN tumour surveillance guidelines to be produced and implemented through a regional PTEN specialist clinic.

S04. Post-mortem examination of an aggressive case of medullary thyroid carcinoma characterized by catastrophic genomic abnormalities

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Catastrophic genomic alterations can drive unusually aggressive cancer phenotypes. We describe a diagnostically challenging rapidly fatal case of medullary thyroid carcinoma (MTC) occurring in a young, morbidly obese man presenting with diffuse bone marrow involvement and disseminated intravascular coagulation. Whole-exome sequencing and shallow whole-genome sequencing was carried out for the primary tumour and multiple metastases. We identified three germline SNP's within the *RET* proto-oncogene which remained undetected using routine hospital genetic testing procedures. Indeed, one of the variants identified (L769L) has been previously reported in literature to be associated aggressive MTC presentation, yet remains untested for in the routine diagnosis of MTC. Supported by findings from shallow whole genome sequencing, we report for the first time in thyroid cancer, the occurrence of a catastrophic "chromothripsis-like pattern" (CTLP) event, which involved shattering of chromosome 4 leading to complete abrogation of normal chromosomal function, in addition to dramatic wide-spread copy number aberrations (CNA), across both primary tumour and bone marrow samples. We further describe the presence of loss-of-heterozygosity (LOH) in key genes involved in DNA repair mechanism pathways such as *ATM*, which possibly facilitated the CTLP event, in addition to LOH in other disease-associated genes such as *ALK* and *NOTCH1* as key drivers of the aggressive and rapidly fatal clinical course in this patient and unresponsiveness to the standard-of-care targeted agent chosen. Given a possible rapid generation of tumor neo-antigens as a result of the CTLP event, immunotherapy may have been more suitable as a treatment option. Moreover, the presence of disease-associated SNP's within the *RET* proto-oncogene, support their inclusion as part of routine *RET* genetic testing for aggressive MTC cases. These results provide a rationale for application of comprehensive genomic analysis of cancers presenting with unusually aggressive behavior to facilitate more appropriate therapeutic options and diagnoses.

S05. Target 5000: Genetic characterisation of a cohort of inherited retinal degeneration (IRD) patients

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The Target 5000 research project aims to provide genetic testing for the estimated 5,000 people in Ireland who have an inherited retinal condition. Many clinical trials are available for patients with sight loss, however, many such trials require patients to have their causative mutation identified in order to enter the trial. The objective of the study is to genetically characterise patients with inherited retinal degenerations (IRDs) in Ireland and in principle to make clinical trials more accessible to some Irish people suffering from sight loss. The study also seeks to identify previously undiscovered pathological mutations in a panel of known retinopathy genes evaluated utilizing target capture next generation sequencing (NGS).

Thus far in the study, as part of Target 5000 roughly 10% of the Irish IRD population has been sequenced and the results obtained are encouraging. Target 5000 offers not only a chance to discover new causative mutations, but is vital in giving patients access to information regarding the pathogenesis of their disease. Over 50 novel mutations have been discovered, as well as some previously ambiguous phenotypes resolved. More precise matching of genotype with phenotype from this study and similar studies

globally should start to enable clinicians to better formulate accurate future diagnoses and at times prognoses.

S06. Methylation quantitation trait loci and transcriptome analysis of differentially methylated microRNAs in end-stage renal disease

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MicroRNAs are understood to play a functional role within the establishment of epigenetic marks and are in turn under epigenetic control. Emerging evidence suggests microRNAs are vital for both kidney development and renal function. This study aimed to identify differential methylation affecting microRNAs in patients with end-stage renal disease (ESRD).

Methylation status was determined for 485,577 unique CpG sites in 105 individuals with ESRD and 52 donor controls with no evidence of renal disease using the HumanMethylation450K BeadChip array (Illumina). Statistically significant associations ($P<10^{-8}$) were observed between case and control groups for both unique CpG sites within microRNAs and their target genes, identified using miRDB (an online database for microRNA target prediction and functional annotations).

CpG sites (n=11) within top-ranked microRNAs (n=42) alongside 848 CpGs in 198 target genes were evaluated in genotyped renal transplant samples to detect methylation quantitative trait loci (meQTLs) associated with ESRD. Following allelic association PLINK analysis, 116 SNPs were determined from the investigated CpG sites, 12 of which were located in genes previously linked with renal disease or microRNAs.

Blood-derived Ion Total RNA-Seq v2 analysis was performed on10ESRD samples and 29 controls (with no evidence of renal disease)to determine the expression levels of the microRNAs and target genes. Sequencing was completed using the Ion Proton™ (Thermo Fisher Scientific) and the most significant results were*MIR548H4* ($5.79x10^{-6}$) and *WASF3* ($5.59x10^{-9}$) respectively, showing increased expression within the ESRD samples.

This study has identified microRNA-related differential methylation with supporting gene expression data, associated with ESRD.

S07. Genetic overlap between amyotrophic lateral sclerosis and schizophrenia

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Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disease characterized by rapid-onset loss of upper and lower motor neurones, resulting in progressive paralysis and death from respiratory failure. Schizophrenia is a neuropsychiatric disease with positive symptoms, negative symptoms and impairment over a range of cognitive abilities. We have recently shown that schizophrenia occurs more frequently than expected in the pedigrees of ALS patients, suggesting an aetiological relationship between both diseases. Using linkage disequilibrium score regression with summary statistics for GWAS of ALS and schizophrenia comprising over 100,000 unique individuals, we estimated the genetic correlation between ALS and schizophrenia to be 14.3% (95% CI 7.05-21.6; $p = 1\times10^{-4}$). Up to 0.12% of the variance in ALS was explained by schizophrenia polygenic risk scores ($p = 8.4\times10$). We leveraged the apparent pleiotropic relationship between ALS and schizophrenia to identify five potential novel ALS-associated genomic loci at conditional false discovery rate < 0.01. Diagnostic misclassification in the schizophrenia cohort did not contribute significantly to our observations (BUHMBOX $p = 0.94$) and we estimated that 4.86% (2.47-7.13%) of ALS cases would need to be misdiagnosed as schizophrenia to observe our genetic correlation estimate under a true genetic correlation of 0%. Our results indicate that the lifetime risk for comorbid ALS and schizophrenia increases from 1 in 40,000 to 1 in 34,336, which would require an incident cohort of 16,488 ALS patients to observe epidemiologically. Our findings suggest shared underlying biology between ALS and schizophrenia which will direct novel approaches in research and therapeutic development.

S08. Identifying clinically relevant imprinted gDMRs sensitive to a transient loss of DNA methylation in human differentiated cells

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Background: Imprinted genes are autosomal, but only expressed from one parental allele and are often clustered in small groups. They play an important role in the regulation of normal mammalian

development. Differentially methylated regions (DMR) on each allele are important in regulating the genes, with marks being characterised as primary or secondary DMRs, depending on whether they are inherited from the germ cells or arise later, respectively. Imprinting disorders such as Prader-Willi Syndome (PWS) and Beckwith-Weidemann Syndrome (BWS) arise either from uniparental disomy or faulty DNA methylation. We wished to determine 1) which of the loci are most sensitive to loss of methylation 2) to more precisely define the sensitive regions and 3) determine what happens at primary versus secondary imprints. Methods: Stable knockdowns of the maintenance methyltransferase DNMT1 were generated in hTERT-immortalised adult fibroblasts using shRNA. Genome wide methylation levels were assayed using the Illumina 450k BeadChip array and analysed using bioinformatic approaches. Results: We found that 1) the imprinted loci varied extensively in their sensitivity to loss of methylation 2) the extended locus involved in PWS was particularly sensitive 3) that loss of methylation at primary DMR appears to drive gains in methylation at secondary DMR. Conclusion: Our results point to a mechanistic link between primary and secondary DMR which may explain why imprints are difficult to reprogram in somatic tissues.

S09. Disease modelling with mesenchymal stromal cells and induced pluripotent cells uncovers the pathology of familial osteochondritis dissecans: from *ACAN* gene mutation to early onset osteoarthritis

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Osteoarthritis (OA) is a degenerative joint disease that affects millions of people globally with no disease-modifying strategies yet available. Our understanding of the pathology of OA is inadequate and this impedes investigation of efficient diagnosis and treatment. To expand our understanding of the underlying cellular pathology of OA, we studied a monogenic condition, familial osteochondritis dissecans (FOCD), associated with a known mutation in the ACAN gene. Patients with FOCD develop early onset OA with multiple joint involvement.

The objectives of the project were to investigate the cellular pathogenesis of FOCD by studying (a) chondrogenesis of patient-derived bone marrow-mesenchymal stem cells (BM-MSCs) and (b) induced pluripotent stem cells (iPSCs) generated from patient fibroblasts.

Our findings revealed that the mutation resulted in a misfolded or unfolded aggrecan protein, which accumulated in the rough endoplasmic reticulum (rER) during protein production. The consistent accumulation resulted in ER stress throughout chondrogenesis. Moreover, the rER stress caused abnormal or disregulated global extracellular matrix (ECM) production and assembly. Importantly, ECM composition analysis indicated that the patient chondrocytes produced abundant amounts of OA-associated markers.

Using patient-specific stem cell models, we have discovered a cellular pathogenesis of FOCD involving abnormal cell function and defective tissue formation, contributing to the OA phenotype.

S10. Genomic insights into the population structure and history of the Irish Travellers

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Aims: The Irish Travellers are a nomadic population primarily found within Ireland and the UK. Consanguineous unions are common, and as a population they are socially and genetically isolated from the surrounding, "settled" Irish population. Previous low-resolution genetic analyses suggested a common Irish origin between the settled and the Traveller populations. It is not known, however, what is the extent of population structure within the Irish Traveller population, the time of divergence from the general Irish population, and the extent of autozygosity.

Methods: We recruited Irish Travellers from across Ireland and the UK. For inclusion, a participant had to have had at least three grandparents with a surname associated with the Irish Travellers. DNA was extracted from saliva samples, and genotypes were generated using the Illumina OmniExpress SNP genotyping platform. With this data, we investigated population structure using fineStructure, quantified the levels of autozygosity with PLINK, and estimated a time of divergence using a method based on Identity by Descent (IBD) segment sharing.

Results: We merged, cleaned, and analysed data from 42 Irish Travellers, 2232 settled Irish, 2039 British, 143 Roma Gypsies, and 931 individuals from 57 world-wide populations. We confirm an Irish origin for the Irish Travellers, demonstrate evidence for population substructure within the population, confirm high levels of autozygosity consistent with a consanguineous population, and for the first time provide estimates for a date of divergence between the Irish Travellers and settled Irish.

Conclusion: Our findings have implications for disease mapping within Ireland, and they additionally inform on the social history of the Irish Traveller population.

POSTER PRESENTATIONS:

P01. 16p13.11 duplications in a Northern Ireland Cohort

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Copy number variants at 16p13.11 have been described in association with a variety of neurodevelopmental disorders. While deletions of this region are perhaps better described, the clinical significance of the reciprocal duplication is less clearly defined. Phenotypes reported in association with the duplication include developmental delay, speech delay, behavioural difficulties and neurodevelopmental phenotype such as autism, schizophrenia and ADHD. However, the region appears to be subject to variable expressivity and incomplete penetrance.

To date we have detected duplications of 16p13.11 in 5 probands using oligonucleotide array CGH. Of these patients 3 showed duplications within the typical ~1.5Mb duplication region while 2 patients had a larger ~2.8Mb duplication, encompassing all of the above region. The clinical phenotype of these patients will be described. Two of these patients have inherited the duplication from their mothers, one was a de novo finding and the inheritance of the others is currently unknown. One of the maternal duplication carriers are also known to have a phenotype.

Our data provides further clinical information on the phenotypic features of patients with this syndrome and provides more evidence for the pathogenic nature of this duplication.

P02. NI Regional Cancer Genetics Service Patient Satisfaction Questionnaire

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Northern Ireland Regional Genetics Service

Introduction – Patients referred to the NI Regional Cancer Genetics Service for genetic counselling were sent a questionnaire to evaluate patient satisfaction. The questionnaire focused on satisfaction surrounding the referral process, waiting times and communication during and after the appointment.

Method – One hundred patients, whose episode of care was completed between November 2015 and June 2016, were sent an anonymised structured questionnaire by post. Patients were seen by a genetic counsellor for assessment of their family history of cancer, predictive testing and genetic mutation screening

Results – To date (23/06/2016) the questionnaire response rate is 34%. So far 91% have expressed satisfaction with the service that they received. Useful comments and observations have been feedback in the questionnaire to aid service improvement. Data collection will be completed imminently to allow for complete analysis.

Discussion – Useful data has been collected which reinforces the service currently being delivered by genetic counsellors whilst also highlighting areas of service development.

P03. Detection of the 3 primary mitochondrial mutations in Leber's hereditary optic neuropathy with a multiplex allele specific PCR / high resolution melt curve assay

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Leber's Hereditary Optic Neuropathy (LHON) is one of the most commonly inherited optic neuropathies and results in significant visual morbidity among young adults. 95% of LHON patients will present with one of three primary mitochondrial mutations; G3460A, G11778A and T14484C. We describe a novel real time diagnostic test to detect the three common mutations leading to LHON. The test uses a combination of multiplex allele specific PCR (ARMS PCR) in combination with high resolution melt curve analysis to detect the presence of the G3460A, G11778A and T14484C mutations.

PCR primer sets were designed to produce a control PCR product and PCR products only in the presence of the 3460A, 11778A and 14484C mutations in a multiplex single tube format. Products produce discrete well separated melt curves allowing clear detection of the mutations. The test has proved to be robust, cost and time effective with the real time closed tube system taking approximately 1 hour to complete.

This test provides a simple, robust, easy to read output that is both cost and time effective, thus providing an alternative method to individual endpoint PCR – RFLP, PCR followed by Sanger / pyrosequencing and next generation sequencing. It will also allow diagnostic laboratories to detect 95% of LHON causing mutations in a single tube assay allowing diagnostic laboratories to avoid costly NGS assays for the vast majority of LHON patients, thus allowing resources to be focussed on patients with unknown mutations requiring further analysis.

P04. TACE levels in patients at very high risk of Major Adverse Cardiac Events

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Atherosclerotic coronary artery disease (CAD) is a progressive chronic inflammatory condition that can lead to Major Adverse Cardiac Events (MACE) such as heart attacks. Currently there is no definitive test to predict MACE risk. Tumour necrosis factor alpha converting enzyme (TACE), also known as A Disintegrin And Metalloproteinase 17 (ADAM17) is a membrane-anchored protein responsible for the ectodomain shedding of a variety of transmembrane proteins such as cytokines, chemokines, growth factors and their receptors. TACE has been linked to several major acute and chronic inflammatory diseases including atherosclerosis. The aim of this study was to investigate if TACE may be a

valuable predictive biomarker for CAD and MACE risk. TACE levels were measured in the plasma of CAD patients including those with acute coronary syndrome (ACS) and elective patients attending the catheterisation laboratory for coronary angiogram. TACE levels were measured using ELISA and quantitative real time PCR. Levels were compared with control samples collected from apparently healthy individuals and a subset of patients with no CAD as evidenced by coronary angiogram. Other factors that might affect TACE detection were also measured including sample type and storage time. To date 207 consecutive CAD patients and 40 controls have been recruited to the study. Results demonstrate that CAD patients have higher levels of plasma TACE in comparison to controls. TACE protein levels were especially highest in those ACS and elective patients with a previous history of MACE. Results to date indicate that TACE may be a useful marker to predict disease progression and recurrent MACE in CAD patients.

P05. Investigating the role of a single nucleotide polymorphism in NRG1 in predisposition to breast and thyroid cancers

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Introduction: NRG1 (neuregulin1) is a candidate tumour suppressor gene. NRG1 encodes ligands for members of the ERBB family, and has been shown to be silenced by methylation in breast cancer[1]. Breast and thyroid cancers share some genetic loci (e.g. PTEN, STK11), and an increased risk of thyroid cancer has been noted in survivors of breast cancer[2]. A single nucleotide variant (C>G) in NRG1 (rs2439302), has been associated with increased risk of non-medullary thyroid cancer[3]. Aim: Our aim was to investigate the association between rs2439302 in NRG1 and predisposition to thyroid and breast cancers in an Irish population. Methods: A two-arm case-control study was undertaken. Patients with mutations in high-risk cancer susceptibility genes were excluded. Controls included adults with no personal or familial history of breast or thyroid cancers. Male controls were included in thyroid case- control analysis only. DNA was extracted from whole blood/buccal swabs by ethanol precipitation. Genotyping was performed using Taqman-based PCR. Results: 257 patients with thyroid cancer, 518 with breast cancer and 367 unaffected controls were genotyped. Homozygous carriers of the variant were found to have an increased risk of thyroid cancer (OR1.89 (1.21-2.95), p=0.005), but risk for mono-allelic carriers was not significantly increased (OR1.27 (0.87-1.84), p=0.21). The presence of the variant was not associated significantly with breast malignancy for mono-allelic (OR1.31 (0.95-1.8), p=0.095) or biallelic mutation carriers (OR1.15 (0.76-1.73), p=0.51). Conclusion: Homozygous carriers of the G allele were found to be at increased risk of thyroid cancer, but no association was observed between the variant and breast cancer. References:[1]Chua YL1, Ito Y, Pole JC *et al*, The NRG1 gene is frequently silenced by methylation in breast cancers and is a strong candidate for the 8p tumour suppressor gene. Oncogene. 2009;**28(46):**4041-52. [2]Nielsen SM, White MG, Hong S, *et al,* The Breast-Thyroid Cancer Link: A Systematic Review and Meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2016;**25(2):**231-8. [3]Liyanarachchi S, Wojcicka A, Li W, *et al*, Cumulative risk impact of five genetic variants associated with papillary thyroid carcinoma. *Thyroid*. 2013;**23(12):**1532-40.

P06. Expression and modulation of the family of *UGT1A* phase II metabolism genes by liganded Vitamin D receptor (VDR)

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The UGT1A gene family encode (UGT) activity that facilitate the transfer of glucuronic acid to a range of xenogenous and endogenous substrates, the polar end products of which are better suited for elimination through urine and bile. UGT1A genes exhibit an inducible pattern of expression regulated through the activities of such nuclear receptors (NRs) as pregnane X receptor (PXR) farensoid X receptor (FXR) and liver X receptor (LXR) that form a complex interactive network of 'sensors' to facilitate the elimination of potentially harmful metabolites and exogenous toxins. We have previously reported that activation of vitamin D receptor (VDR) through both synthetic agonists and nutritionally derived ligands, can induce the expression of both phase I metabolic (CYP3A) and phase III transporter (ABCA1) genes. Little is known however, as to how activated VDR may impact upon the regulation of phase II genes such as UGT1A1. In this study we demonstrate that ligand-activated VDR can significantly enhance the expression of several members of the UGT1A gene family. With particular respect to UGT1A1, we identify within the proximal promoter region of this gene a functional vitamin D response element (VDRE) also recognized by PXR but distinct from previously established regulatory elements that mediate FXR and LXR signalling. Based upon our data, we propose a model for VDR and circulating levels of vitamin D as maintaining stable expression of phase II and functionally related genes as a means to provide baseline protection against the effects of toxic xeno and endobiotic metabolites.

P07. Investigation of the oral microbiome for candidate markers of depression.

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Depression is a complex disorder with multiple symptoms, including a persistent low mood, anhedonia and cognitive impairments, and is currently the third leading cause of global disability. The underlying pathophysiology of depression is poorly understood but a growing body of evidence supports an important role for the microbiome in the aetiology of depression and other psychiatric disorders. While much interest is currently focused on the role of the microbiome-gut-brain axis in brain physiology and neurochemistry, the importance of the oral microbiome has received little attention. The aim of this study is to characterise the oral microbiome in adults with severe depression versus matched controls with no history of the disease. To achieve this, participants

were asked to complete an online validated mental health survey and to provide a saliva sample. We identified 46 individuals who met the DSM-V criteria for severe depression and 46 age and sex-matched controls with no history of depression. Bacterial DNA was extracted from the saliva samples and 16S rRNA surveys were conducted using next generation sequencing. Differences in the bacterial community composition of the oral microbiota between patients and controls were determined.Metagenomic analyses were conducted using machine learning and computational intelligence algorithms using the 16S RNA data to generate inferred metagenome feature sets. Charting the oral microbiome in depressed patients could therefore provide new insights into the development of the condition, and lead to the identification of novel diagnostic and therapeutic response biomarkers.

P08. Expression and modulation of genes of pharmacokinetic relevance within enteric cells by liganded Vitamin D receptor (VDR)

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The nuclear receptors (NRs) pregnane X receptor (PXR) and constitutive androstane receptor (CAR) modulate transcriptional networks that dictate the bioavailability of many endogenous and exogenous compounds such as steroid hormones and therapeutic drug compounds. Elucidating those factors that invoke PXR/CAR activity has been important for understanding the genetic basis for both metabolic disease and inter-individual variations in drug response. PXR is most closely related to Vitamin D receptor (VDR) for which there is relatively little is known for how this NR may impact upon these same physiological processes.

In this study, we employed enteric cell models and *ex-vivo* based human colon explants to examine how activated VDR may impact upon the expression of genes of a metabolism and transporter function. We find that in relation to PXR and other evaluated NRs, VDR is the most efficient and dominant receptor for induced expression of *CYP2B6*, *CYP3A4/5* and *ABCA1*. We note that upon activation with the synthetic agonist EB1089, VDR will achieve striking and sustained elevated expression of CYP3A4 at mRNA, protein and enzymatic level suggesting the potential for selective metabolic gene targeting through ligand design. In addition, we report members of the *UGT1A* gene family to be novel VDR regulated genes, thus extending the known metabolic effects of vitamin D to also encompass expression of phase II (conjugating) genes. This study intimates that systemic vitamin D status and/or activating VDR ligands may have pharmacokinetic relevance to co-administered drug regimes.

P09. Analysis of Genetic Disease Markers in Ancient Irish Genomes

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Ancient genomes are often typically analysed with regard to ancestry and physical phenotype. Less common is examination and identification of genetic diseases, primarily due to the very low numbers of samples sequenced and poor level of sequencing related to the difficulties in sequencing from ancient DNA.

Here we present the results of analysing 21 ancient Irish genomes. The data were screened for a wide range of pathogenic genotypes and markers. Giving information for the potential effects and prevalence of certain conditions as well as the earliest known confirmation of their presence.

Using records of the remains, we also examined if any displayed phenotypes correlated to identified diseases.

P10. The NLRP3 Inflammasome and related receptors as biomarkers for Atherosclerotic MACE

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Coronary Artery Disease is the largest contributor of CVD, the leading cause of death worldwide. It is caused by atherosclerosis, a build-up of cholesterol in the blood vessels and chronic inflammation. The NLRP3 inflammasome plays a critical role in the secretion of IL-1β, and there is significant evidence that it is involved in the pathogenesis of a number of inflammatory diseases including atherosclerosis. Recent studies demonstrate that particular cell surface receptors namely the scavenger receptor CD36 and the endocannabinoid receptor CB1 are involved in the activation and regulation of the NLRP3 inflammasome and they have also been implicated in the pathogenesis of atherosclerosis. The present study aimed to investigate expression and activation levels of the NLRP3 inflammasome, the CD36 and CB1 receptors in blood samples obtained from patients with atherosclerosis at very high risk of a Major Adverse Cardiac Event (MACE) such as a heart attack. The cell signalling processes involved in NLRP3 inflammasome activation were also investigated in a *THP1 in vitro* model of atherosclerosis. Results to date indicate increased expression of NLRP3 in patients at very high risk of MACE and also demonstrate that THP1 macrophages require both the CD36 and CB1 receptors for optimal NLRP3 expression in response to oxidized LDL. These preliminary findings provide an insight into the mechanism of action of the NLRP3 inflammasome in atherosclerosis and prompt further exploration of this protein complex and its regulatory receptors as potential targets for prognostic and or therapeutic development in the strive towards a more personalised approach to the management of coronary artery disease.

P11. An exploration of *de-novo* mutations underpinning chronic refractory epilepsy

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Approximately 30% of patients with epilepsy are refractory to anti-epileptic drug (AED) treatment and continue to have debilitating seizures that severely impact upon their quality of life. Exome sequencing in encephs etc has illustrated the importance of de-novo variants in the pathogenesis of rare neurological disorders. However, the contribution of *de-novo* mutations to pharmacoresistance in adult epilepsy is uncertain. In this study we investigated whether a trio whole exome sequencing paradigm could be applied to identify genetic causes of chronic, refractory epilepsy.

We selected adult patients (n=5) with onset of seizures after 5 years of age, had failed ≥6 AEDs and were still experiencing >4 disabling seizures per month. Patients were excluded if they had a potentially 'explanatory' lesion on MRI. Parents were exome sequenced to identify *de-novo* mutations and these were assessed bioinformatically for pathogenicity.

We confirmed the presence of coding *de-novo* mutations that were bioinformatically predicted to be functional and damaging in 3/5 patients. One of these occurred in the gene *DNM1L*, which was recently implicated in pharmacoresistant epilepsy (Vanstone *et al*. *EJHG*, 2015;Nov 25). This represents a potential diagnostic yield of 20% however more data is required and more trios are currently being sequenced.

We have demonstrated the potential diagnostic yield of whole exome sequencing in a small number of adult patients with chronic refractory epilepsy. Identifying genetic mutations underpinning this disorder may provide new insight into the underlying biology and offers the potential for therapeutic intervention in the form of precision medicine.

P12. Whole Exome Sequencing to Identify Candidate Mutations for Familial IgA Nephropathy

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IgA nephropathy (IgAN) is the most common form of glomerular nephritis worldwide[1]. Difference in incidences between ethnicities and familial inheritance patterns indicate this is a genetic disorder. An IgAN locus on chromosome 6q22-23 was identified via linkage analysis; however the causal gene remains elusive[2]. We set out to identify mutations underlying familial IgAN using whole exome sequencing.

DNA was collected on 25 (unaffected and affected) individuals across 6 families with IgAN. Families were chosen on the basis of having at least 2 affected members with IgAN. We carried out full exome sequencing on 12 of the affected members from these families. Depending on the pattern of inheritance in a given family, mutations that fitted a dominant, recessive or compound heterozygote model of inheritance were screened for. These variants were then filtered based on being shared between affected individuals within a family, their minor allele frequency, region, function and predicted deleterious nature.

We identified a number of potential candidate mutations in these families and including a mutation in the gene *COL4A5* which was previously described as pathogenic[3]. Mutations in *COL4A5* have previously been found in individuals with Alport syndrome, a disease which is often mistaken for IgAN. We are currently working to confirm these candidate mutations via Sanger sequencing and will be screening for segregation.

References: [1]Bisceglia *et al*. *Am J Hum Genet* 2006;**79(6):**1130-4. [2]Gharavi *et al*., *Nat Genet* 2000;**26:**354-7. [3]Zhou *et al*. *Am J Hum Genet* 1992;**50(6): 1**291-1300.

P13. A computational approach to increase understanding of atherosclerosis

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Atherosclerosis is a chronic inflammatory disorder that is responsible for approximately 71% of incidents of cardiovascular disease. A mathematical model of atherosclerosis has been developed, capturing the cell types and proteins involved in atheroma formation and describing the dynamics of disease progression. This is the first model of this type to be developed using open systems biology standards. We have predicted tertiary protein structures for all the proteins involved in this atherosclerosis model and all of their recorded mutations, using phase 3 sequence data obtained from the 1000 Genomes Project. By comparing the electrostatic potentials of these tertiary structures, we predict how the dynamics of atherosclerosis stratifies across population subgroups.

P14. A feasibility study investigating whether methylation of the oxytocin receptor (OXTR) can serve as a potential biomarker for response to oxytocin administration in women during and after labour.

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The aim of this pilot study was to test the feasibility of carrying out a large scale study using this design to investigate whether methylation of the oxytocin receptor (OXTR) can serve as a potential biomarker for response to oxytocin administration in women during and after labour.

Background: Oxytocin is a nine-amino acid peptide with hormonal and neurotransmitter functions during labour and lactation. We hypothesised that a difference in methylation levels of the oxytocin

receptor (OXTR) gene may impact the woman's ability to become established in labour and her response to oxytocin administration.

Method: Blood samples were taken pre-birth and postnatally from 21 women and subjected to DNA methylation analysis of the OXTR gene by pyrosequencing. Methylation status of CpG sites -924 and -934 upstream from the initiation transcription site (ITS) of the OXTR gene was determined. Expression of the OXTR gene before and after birth was measured using qPCR. Global methylation levels were examined using Luminometric Methylation Assay (LUMA).

Results: We found both hypo and hypermethylation of OXTR promoter at CpG sites -924 and -934 in individual samples, however we observed no profound changes in overall OXTR methylation levels within the patient cohort at these CpG sites. We found a strong correlation between OXTR promoter methylation levels found in whole blood and those found in matched PMBC samples. Global methylation analysis using Luminometric Methylation Assay (LUMA) revealed no significant differences between whole blood and PMBC.

Conclusions: A larger sample is required to determine whether OXTR methylation status is predictive of response to oxytocin administration. Whole blood sampling is a suitable alternative for OXTR methylation analysis in a larger cohort of women undergoing labour.

P15. Investigating microRNAs as Serum Markers of Elevated Blood Pressure

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Background: Cardiovascular disease (CVD) is the leading cause globally of morbidity and mortality. microRNAs (miRNAs) are small, non-coding RNAs which have a fundamental role in the pathology of various diseases including CVD. Circulating serum levels of miRNAs have been proposed as potentially valuable markers of heart failure, stroke, myocardial infarction and arterial hypertension, but the specific miRNAs involved and their function remains unclear. Therefore, this pilot study aims to profile miRNA expression in premature CVD patients to identify which miRNAs correlate best with hypertension.

Methods: The Multiplex Circulating miRNA Assay with Firefly™ Particle Technologies was used to profile 68 miRNAs on a cardiology focus panel in serum samples from 170 premature CVD patients recruited from Altnagelvin Area Hospital and screened for the C677T polymorphism in methylenetetrahydrofolate reductase, a risk factor for hypertension. Samples were collected at baseline and following intervention with riboflavin, a co-factor for MTHFR, which significantly lowers blood pressure specifically in adults with this polymorphism. Statistical analysis was used to correlate miRNA expression with blood pressure, MTHFR genotype and other relevant clinical data.

Results: The assay successfully measured miRNA expression in the sample set. miRNAs which expressed differentially between MTHFR genotype groups were highlighted and the functional significance of these miRNAs was assessed using bioinformatics to identify target genes involved in CVD.

Conclusions: The data provides further evidence that using specific miRNAs as serum markers could aid early prediction of CVD and may lead to better diagnostic modalities and therapeutic regimes.

P16. Investigating the association between genetic and epigenetic variability in the *5-HTT* and *BDNF* genes and depression in young adults.

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Gene-environment interactions, particularly in genes related to regulation of serotonin and neuronal function, have been implicated in the aetiology of depression. Allelic variations in the 5' flanking transcriptional region of the serotonin transporter gene (5-HTTLPR) and higher levels of promoter DNA methylation are associated with depression. Brain derived neurotrophic factor (BDNF) plays an important role in neuronal differentiation and survival, and is also involved in regulation of serotonin. A single nucleotide polymorphism in the BDNF gene, leading to a valine to methionine substitution at codon 66 (Val66Met), and increased methylation of the BDNF promoter have also been associated with depression. The goal of this study is to determine whether length of the 5-HTTLPR, prevalence of the Val66Met polymorphism of the BDNF gene and DNA methylation in both 5-HTT and BDNF promoter regions are associated with depression in the student population. First year students provided a saliva sample for genetic analysis and completed an online mental health survey. Presence and severity of depression was determined from survey responses based on DSM-IV criteria. Length of the 5-HTTLPR was determined by PCR and gel electrophoresis and presence of the SNP at BDNF rs6265 and examined using restriction fragment length polymorphism analysis. Bisulphite-treated DNA was amplified by PCR and pyrosequencing assays used to determine methylation patterns of *BDNF* and *SERT*. Our preliminary findings suggest that genetic and epigenetic variation in the 5HTT and BDNF genes are associated with depression in the student population and may be candidate biological markers to assist in diagnosis.

P17. The potential role of *Propionibacterium acnes* in prostate oncogenesis

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BACKGROUND: Prostate cancer is the most common male cancer in the UK, where it kills approximately 11,000 men annually. There has been growing interest in the role played by the anaerobic bacterium Propionibacterium acnes, an important component if the skin microflora, in the aetiology of the condition via a chronic, asymptomatic infection of the prostate leading to oncogenesis.

METHODS: A quantitative real-time PCR (qRT-PRC) assay for retrospective detection of P. acnes in formalin-fixed paraffin embedded sections from archived prostate samples was developed. An in vitro infection model of prostate infection with P. acnes is being optimised, which should allow us to get insight into the dysregulation P. acnes infection causes in prostate epithelial cells.

RESULTS: A total of 81 biopsy samples, representing one or both prostate lobes, were examined from 53 patients with prostate carcinoma, versus 111 samples from 60 patients whose biopsies were histologically normal, and the assay revealed that 35% of cancerous prostate samples were positive for the presence of P. acnes, compared with only 8% of the disease-free samples ($p<0.001$). Transcriptomic studies of chronically infected epithelial cells revealed a significant dysregulation of genes, previously associated with prostate cancer development, progression and metastasis.

CONCLUSIONS: Our study reveals that P. acnes is significantly associated with cancerous prostate tissue and has a capacity to initiate a host response in vitro, suggesting it may stimulate oncogenesis as a result of a chronic infection. Investigation is needed of the association of different phylogenetic types of P. acnes and their ability to initiate molecular dysregulation resulting in oncogenesis in vitro.

P18. Whole exome and total RNA sequencing reveals candidate drivers in the development of oral squamous cell carcinoma.

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Oral squamous cell carcinoma (OSCC) is one of the top ten most prevalent cancers in the world. Prognosis is poor and quality of life is commonly reduced for patients who survive. OSCC is thought to progress via a premalignant stage called dysplasia. Effective treatment of dysplasia prior to malignant transformation, or the ability to more accurately predict the 10-20% of dysplasias that will progress to OSCC, is an unmet clinical need.

With the aim to better understand the biology of OSCC development, and attempt to identify potential markers of early disease and therapeutic targets, we performed parallel whole exome sequencing and total RNA sequencing on 16 micro-dissected formalin-fixed paraffin embedded dysplasia and their associated OSCC. These are the largest omic analyses on matched patient samples from the oral cavity in non-HPV infected patients where all dysplasias are associated with progression to OSCC, that has been performed to date.

Whole exome analysis revealed that every OSCC and adjacent associated dysplasia sample did have a common clonal ancestor, with many shared potential drivers of progression, but that there is also considerable genomic heterogeneity between associated pre-invasive and invasive disease, as seen in a previous study[1]. RNAseq analysis revealed differences in the immune cell signatures present at different disease stages, distinguished early events in pathogenesis from later events and identified several novel coding and non-coding candidates with potential involvement in oral dysplasia development and malignant transformation. These findings merit further investigation in a larger retrospective longitudinal study of patients with oral dysplasia.

[1]Wood HM, Conway C, Daly C, *et al*. The clonal relationships between pre-cancer and cancer revealed by ultra-deep sequencing. *J Pathol* 2015; **237:**296-306.

P19. Evaluation of Potential Mitochondrial Therapies using a Novel Complex I Assay

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Many disorders involving tissues, which have significant energy requirements, involve mitochondrial dysfunction often due to mutations affecting the mitochondrial genome. Some such mutations can involve genes coding for subunits of complex I of the electron transport chain leading to a complex I deficiency in disorders such as Leber Hereditary Optic Neuropathy (LHON) amongst others. Mitochondrial dysfunction leads to a lack of energy production and ultimately the death of the cell. In disorders such as LHON, retinal ganglion cells (RGCs) are affected, leading to retinal dysfunction. These observations have prompted interest in exploring innovative therapeutics to modulate mitochondrial disorders involving complex I deficiency. The Farrar laboratory has explored candidate gene therapies for complex I deficiency using Ndi1, a yeast gene which is a complex I homologue.

In order to test the efficacy of candidate therapies, we have developed a robust, empirical assay of mitochondrial function. Previous assays measured the level of NADH oxidation in a sample, both before and after rotenone as a measure of complex I activity. To optimally distinguish between the activity of complex I and the potential therapeutic, the assay was modified with the addition of a second inhibitor which allowed specific measurement of the therapeutic, such as Ndi1. Given that this is an in vitro assay, it enables large-scale screening of potential therapeutics and ensures only those that show strong evidence of efficacy are then tested in vivo. In combination with other quantitative assays such as Reactive Oxygen Species (ROS) generation this allows detailed evaluation of the health of mitochondria within a sample.

P20. A Study of Genes that Function in the Centrosome for Involvement in the Aetiology of Schizophrenia and Associated Cognitive Deficits.

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Schizophrenia is an adult-onset mental illness with that impacts cognitive function. The largest GWAS has revealed 108 loci associated with schizophrenia risk but how variation affects genes and impacts brain function to increase risk is largely unknown.

The centrosome is the microtubule organising centre of the cell and seeds the growth of the primary cilium. The disproportionate number of brain disorders associated with centrosomal genes suggests the organelle underlies normal brain and cognitive development. Schizophrenia is neurodevelopmental and cognitive deficits are a core element of the disorder. We hypothesise that some of the newly identified risk genes for schizophrenia will function in the centrosome and variants in these genes will be associated with cognitive deficits.

Cross-referencing genes with centrosomal functions with genes from schizophrenia GWAS, identified six candidate genes; SDCCAG8, MAD1L1, GIGYF2, MPHOSPH9, PRKD1 and MAPK3. The effect of risk SNPs on cognition was examined using an Irish dataset of psychosis cases and controls (n=1,236) using linear regression. Among the associations identified, the SDCCAG8 risk SNP was shown to affect attribution style, a measure of social cognition (P=0.001). The MAD1L1 risk SNP was associated with poorer performance on episodic memory tasks (P=0.003).

A suitable replication dataset was not available for social cognition measures. We attempted replication for episodic memory results in UK and German samples but results were non-significant. Overall, we have identified a number of schizophrenia risk genes that function in the centrosome but further larger datasets are required to establish a role for these genes in cognition.

P21. Analysis of Candidate Schizophrenia Risk Gene *CHD7* and Associated Interacting Genes Suggests a Role in Cognition for Novel Network of Genes.

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Epigenetic mechanisms are an important heritable and dynamic means of regulating various genomic functions, including gene expression to orchestrate brain development. These processes when perturbed are thought to contribute to schizophrenia (SZ). A core feature of SZ is cognitive dysfunction. GWAS have identified 108 genomic loci associated with SZ risk, containing 350 genes. My aim was to identify genes that have epigenetic functions which map to loci associated with SZ, and to test the associated SNPs for association with cognitive deficits. Risk SNPs in 8 genes: *BCL11B, CHD7, EP300, EPC2, GATAD2A, KDM3B, RERE* and *SATB2* were analysed using an Irish dataset of psychosis cases and controls (n=1235) who had completed tests across 5 cognitive domains. Five of the eight variants had significant associations with at least one cognitive task. Strongest associations were for *CHD7* (rs6984242) for IQ (p=0.001) and episodic memory (p=0.007). These results did not replicate in independent samples. We link rs6984242 to *CHD7* via a long range expression quantitative trait loci (eQTL) and *CHD7* has not been previously reported as a candidate risk gene for SZ. To further explore its novel association with SZ, we identified a set of 45 interacting genes and used SNPs across these genes to develop a polygenic risk score for SZ, independent of *CHD7* itself. This score was tested for association with cognitive function. Significant associations($p<0.05$) were found with 3 measures of IQ, 2 measures of episodic memory and 1 measure of working memory, suggesting a role for this gene network in cognition.

P22. Folate-sensitive differentially methylated regions: are we trying to predict the unpredictable?

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The relevance of nutrition and other environmental influences on epigenetic modifications including DNA methylation is a topic of considerable interest. Folate One Carbon Metabolism (FOCM) is the principal supplier of the methyl groups required for DNA methylation, giving folate status a strong biological plausibility of having an impact on an individual's and an offspring's DNA methylation profile at both the mitotic and meiotic level.

We sought to identify DNA methylation sites in the human genome that are sensitive to folate status i.e., Folate-sensitive Differentially Methylated Regions (FS-DMR) using a folic acid intervention trial in pregnant women known as FASSTT (Folic Acid Supplementation in the Second and Third Trimesters). To minimize the amount of DNA methylation 'noise' due to non-folate related factors such as other environmental stimuli and individual genetic variation, we

compared the DNA methylation profile of the same individual pre- and post- intervention to identify putative FS-DMR. We selected six healthy pregnant women, three from the folic acid intervention arm and three from the placebo arm of the trial. We performed MeDIP (Methylated DNA Immunoprecipitation) on all 12 samples and hybridized to a Roche Nimblegen Delux 2.1M promoter array. While we observed DNA methylation changes pre- and post- folic acid intervention in each individual, *the actual DNA methylation sites were not consistent across all three individuals*. Of course, it is possible that a more in-depth Next Generation Sequencing approach might yield our elusive FS-DMRs. However, the published literature to date does not appear to support such a promise.

P23. A Novel Approach to Promoter Identification – Development of a Ganglion Cell-specific Promoter for AAV-mediated Gene Therapy

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The loss of retinal ganglion cells (RGCs) is a hallmark of a number of retinopathies. There are a number of gene therapies being developed that have shown efficacy in preserving RGCs when administered using an AAV vector. Localising expression of any therapeutic to the target cell type (ganglion cell layer, GCL) would represent a significant optimisation of the approach. The packaging capacity of AAV (4.7kb) imposes a limit on the size of promoters and genes relevant for AAV-mediated gene delivery. Few GCL-specific promoter sequences have been defined of a size suitable for use in AAV-guided gene expression.

Exploring this, a panel of genes was chosen with GCL-limited expression profiles. A pipeline program was developed that analysed regions upstream of these genes for sequence conservation across placental mammals (as a proxy for putative promoter function), weighted by enriched GCL expression levels. Adopting this strategy, ganglion cell promoter 1 (GCP1), demonstrating the key features outlined above, was identified. To test its function, GCP1 (2.2kb in size) was engineered into an AAV2 virus expressing EGFP.

Here we demonstrate the effectiveness of GCP1 in localising EGFP expression to the GCL when administered via intravitreal injection. Furthermore, absence of EGFP expression was demonstrated when targeted towards photoreceptors via subretinal injection, verifying GCP1 tissue-specificity. Expression of AAV2.GCP1-EGFP was compared to expression from a non-specific promoter construct, AAV2.CMV-EGFP. GCP1-EGFP was shown to provide equivalent expression to CMV-EGFP in the GCL. GCP1 thus offers a tissue-specific promoter option, suitable for deployment within AAV vectors without compromising functionality.

P24. Targeting hypoxic prostate tumours using the novel hypoxia-activated prodrug OCT1002 inhibits expression of genes associated with malignant progression.

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Purpose: Hypoxia is a common hallmark of the tumour microenvironment. Recently we have shown the anti-androgen bicalutamide induces profound hypoxia in prostate tumours in vivo. This resulted in the promotion of epithelial to mesenchymal transition. Here we target tumour hypoxia using a novel unidirectional hypoxia-activated prodrug OCT1002 to enhance the anti-tumour effect of bicalutamide.

Experimental Design: The effect of OCT1002 treatment on LNCaP-luc cells was measured in normoxia and hypoxia *in vitro*. *In vivo*, tumour growth and lung metastases were measured in mice treated with bicalutamide, OCT1002 or a combination. Dorsal skin fold chambers were used to image tumour vasculature *in vivo*. Longitudinal genetic changes in tumours were analysed using PCR.

Results: Reduction of OCT1002 to its active form (OCT1001) decreased LNCaP-luc cell viability. In LNCaP-luc spheroids, OCT1002 caused increased apoptosis and decreased clonogenicity. *In vivo*, treatment with OCT1002 alone or with bicalutamide, showed significantly greater tumour growth control and reduced lung metastases compared to controls. Re-establishment of the tumour vasculature following bicalutamide-induced vascular collapse is inhibited by OCT1002. Significantly, the up-regulation of *RUNX2* and its targets caused by bicalutamide alone were also blocked by OCT1002.

Conclusions: OCT1002 selectively targets hypoxic tumour cells and enhances the anti-tumour efficacy of bicalutamide. Furthermore, bicalutamide causes changing genetic profiles during treatment, with development of a more malignant genotype; OCT1002 can block this effect. This study indicates that more attention should be attached to understanding genetic changes that may occur during treatment. Early targeting of hypoxic cells with OCT1002 can provide a means of inhibiting prostate tumour growth and malignant progression.

P25. Regulation of miR-200c and miR-141 by methylation in prostate cancer

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Background: In prostate cancer (PCa), abnormal expression of several microRNAs (miRNAs) has been previously reported.

Increasing evidence shows that aberrant epigenetic regulation is a contributing factor to their altered expression in cancer. In this study we investigate whether expression of miR-200c and miR-141 in PCa is related to the DNA methylation status of their promoter.

Methods: PCR analysis of miR-200c and miR-141, and CpG methylation analysis of their common promoter, was performed in PCa cell-lines and in FFPE prostate biopsy specimens. The functionality of miR-200c and miR-141 expression in prostate cancer cells was assessed by a series of in vitro bioassays.

Results: miR-200c and miR-141 expression correlates inversely with the methylation status of the miR-200c/miR-141 promoter in PCa cells. In PC3 cells, miR-200c and miR-141 expression is elevated by treatment with the demethylating agents suggesting their expression is linked to methylation. Expression of miR-200c and miR-141 in prostate biopsy tissue was inversely correlated with methylation in CpG sites closest to the miR-200c/miR-141 loci. Over-expression of miR-200c in PC3 cells inhibited growth and clonogenic potential, as well as inducing apoptosis. Expression of the genes DNMT3A and TET1/TET3 were down-regulated by miR-200c and miR-141 respectively. Finally, treatment with the soy isoflavone genistein caused demethylation of the promoter CpG sites closest to the miR-200c/miR-141 loci resulting in increased miR-200c expression.

Conclusions: Our findings provide evidence that miR-200c and miR-141 are under epigenetic regulation in PCa cells. Profiling their expression and methylation status may have potential in the improved diagnosis and prognosis of PCa.

P26. Folic acid supplementation in late gestation and the effects on DNA methylation in the offspring

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Increasingly accurate surveys of human health throughout the life course has led experts to propose that stresses on the child while still in the mother's womb can affect the individual's health much later in life. Such long-term effects on health are thought to be mediated by a semi-permanent trace on the genes of the affected person called an epigenetic mark. Epigenetic mechanisms, such as DNA methylation, are dynamic during pregnancy whereby epigenetic marks are seeded which persist throughout the lifetime of the developing child. It has been suggested that these patterns may be altered by the mother's diet, particularly folate – a key component in the DNA methylation cycle. Currently, mothers are universally recommended to supplement their diet with 400μg folic acid/day as a preventative measure against neural tube defects in the offspring prior to and during the first trimester. However, there remains no clinical recommendation as to whether mothers should continue supplementation during the final two trimesters and the potentially heritable effects on DNA methylation. Observational studies have suggested that folate-rich maternal diets are associated with changes in DNA methylation of the child during this period of gestation. We present here the results of a randomised control trial (FASSTT study) examining the effects of folic acid supplementation in late gestation (week 12 onwards) on DNA methylation of several gene classes in offspring cord blood samples. We report small but significant sex-specific differences between the two intervention groups. These preliminary results indicate that folic acid supplementation throughout pregnancy may exert significant effects on cord blood DNA methylation.

P27. Whole exome sequencing for the identification of variants associated with new-onset diabetes after transplantation

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Introduction: New-onset diabetes after transplantation (NODAT) is a common complication of kidney transplantation which increases risk of subsequent graft failure, cardiovascular complications and death. NODAT is defined as the new requirement for oral hypoglycaemic agents or insulin as a result of hyperglycaemia after renal transplant. The first genome wide association study (GWAS) for NODAT was published by our group in 2014; seven of the eight top-ranked, common SNPs are implicated in β-cell apoptosis.

Methods: To further understand the genetic architecture of the NODAT phenotype we used whole exome sequencing for 134renal transplant recipients from a Northern Ireland renal transplant cohort. We sequenced 53 individuals with NODAT (cases)and 81 transplant recipients without NODAT (controls). Library preparation was performed using the Ion TargetSeq™ Exome Kit with samples sequenced on an Ion Torrent Proton sequencer. TheIon OneTouch 2 for emulsion PCR and Ion Enrichment System were used. Association analysis was performed using PLINK Version 1.9 to identify variants associated with NODAT (with age and weight at transplant included in the regression model).

Results: Following appropriate quality control, initial analysis identified 6 variants nominally associated with NODAT (P_{trend}<1x10^{-5})using the test for trend. The top two hitsrs2305765 (P_{trend}=2.50x10^{-6}; P_{LR}=1.0x10^{-4} OR:0.07(95% CI:0.02-0.26)) andrs8110964 (P_{trend}=4.47x10^{-6}; P_{LR}=1.4x10^{-4} OR:0.04 (95% CI:0.01-0.20))were in linkage disequilibrium (r^2=0.86) in the *MYO9B* gene. Variants in this gene have previously been associated with autoimmune diseases including type 1 diabetes. We propose *MYO9B* as a candidate gene for NODAT predisposition in immunosuppressed renal transplant recipients.

P28. Provision of a genetic testing service for five rare diseases in the Irish Traveller population: 'The story so far'

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The Irish Traveller community has a high incidence of autosomal recessive (AR) disorders due to consanguinity. The Division of Molecular Genetics at the DCG offers genetic testing, primarily to members of this community, for five specific pathogenic mutations found in five AR disorders. The pathogenic mutations are detected by bi-directional Sanger sequencing and the service includes:

Gene	Disorder/ Disease	Phenotype
LARS (leucyl-tRNA synthetase)	Infantile Liver Failure Syndrome 1 (ILFS1)	Infantile hepatopathy with failure to thrive (FTT) and developmental delay.
MCM4 (minichromosome maintenance 4)	Natural Killer Cell & Glucocorticoid Deficiency with DNA Repair Defect (NKGCD)	FTT, adrenocorticotropin hormone (ACTH) resistance, familial glucocorticoid deficiency (FGD), mosaic Fanconi anaemia and recurrent infections due to NK cell deficiency.
STRA6 (stimulated by retinoic acid 6 gene)	Autosomal recessive isolated colobomatous microanopthalmia (MCOPS9)	Microphthalmia, anophthalmia, coloboma. Specific *STRA6* mutation can also cause the Matthew-Wood syndrome [anophthalmia/ severe microphthalmia, with pulmonary hypoplasia/ aplasia]
LEPRE1 (Leucine- and proline-enriched proteoglycan 1) *syn. PH31*(prolyl-3-hydroxylase-1)	Type VIII Osteogenesis Imperfecta,	Variable phenoptype of bone fragility, susceptibility to fracture, short stature, bowing of the long bones and can be perinatally lethal.
ATP8B1 (ATPase, Class I, Type 8B, Member1)	Progressive Familial Intrahepatic Cholestasis type 1 (PFIC1) *syn.* Byler disease	Hepatic and systemic accumulation of bile acids, hepatic fibrosis, end-stage liver disease and growth retardation.

This study will detail (1) the service offered to users, (2) an audit of the test requests received over the last two years, (3) the challenges encountered in offering this unique service and (4) some interesting family pedigrees.

P29 The role of miR-210 in Prostate Cancer tumour development

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Background: Hypoxia in prostate tumours has been linked with promotion of disease progression and metastasis. miR-210 is a microRNA which is apparently affected by hypoxia, but this relationship has not been extensively studied in a prostate cancer setting. Therefore, in this study, we investigate the link between hypoxia and miR-210 in prostate cancer cells.

Methods: We have used 2D and 3D cell prostate cell models of hypoxia to investigate the functionality of miR-210. Expression levels of miR-210 have been measured by qPCR and functional bioassays used to examine its effect on prostate cell behaviour. Target genes have been identified and bioinformatic analysis has been employed to investigate a clinical significance for miR-210 in prostate cancer.

Results: miR-210 is induced by hypoxia in prostate cancer cell-lines. Over-expression of miR-210 impacts upon target genes, including SP1 and TPD52, which in turns affects cell proliferation. Data-mining of online repositories of clinical data and bioinformatic analysis of miR-210 cellular networks reveal that miR-210 plays a key role in a number of important cell processes, the dysregulation of which can lead to development of prostate cancer.

Conclusions: We propose that miR-210 could be an important microRNA in the pathogenesis of prostate cancer and has potential as a biomarker in this disease.