Clinical Genetics Society Conference 2025

Crowne Plaza Royal Victoria Sheffield

11th March 2025

Welcome and Introduction

On behalf of CGS Council and Conference organising committee, we are very pleased to welcome you to the 2025 Clinical Genetics Society meeting in the vibrant city of Sheffield, thank you for coming.

We warmly welcome new members of the Society, especially our new Specialist Registrars and our medical student essay prize winners who are joining us for the first time.

The CGS is the key professional society for UK Clinical Geneticists, we provide a network across England and the devolved nations. As a summary of what we do and have been working on this year - we promote high professional standards, linking with lead clinician groups and Genomics England, develop sub-speciality groups, work with the Genomics Education Programme and the Royal Colleges. We have a fantastic workforce group which works with the Royal College of Physicians to provide intelligence on current status and predicted trends, these results are on our website. We promote research collaborations though national and international studies. We are closely linked with our European counterparts, especially the Dutch Clinical Genetics Society with whom we hold joint scientific meetings promoting collaborative research in science, clinical practice and genetic counselling every other year.

We hope you enjoy the scientific programme, which includes invited speakers who will update us on some of the key developments in our field. We thank all the authors for their contributions and look forward to hearing about their exciting work which covers many topics in genetics and genomic medicine. The quality of the research and presentations has been outstanding in recent years which bodes well for the future of Clinical Genetics.

We welcome and thank the Carter Lecturer, Professor Sarah Smithson, and all our session chairs. We would like to thank the Conference Organising Team who have worked with us over the last year. Our thanks also go to CGS executive and Council members, the essay prize markers, abstract assessors and Robin Winter Prize scorers. We look forward to seeing you during the course of the meeting and at the Yorkshire-themed dinner.

Professor Diana Baralle
CGS President

Dr Suresh Somarathi
CGS Conference Organiser

Conference organising committee:

Professor Meena Balasubramanian (Local Host)
Professor Mohnish Suri
Dr Ian Ellis
Dr Emily Woods
Dr Emily Cottrell
Dr Sarah Wilson

Robin Winter prize scorers:

Dr Angela Brady
Dr Kate Chandler
Dr Joanna Jarvis
Dr Helen Stewart

Medical Student prize scorers:

Dr Melody Redman (Lead)
Dr Ionna Tsigkouli
Dr Sarah Wilson
Dr Mairead Hegarty
Dr Sunayna Best
Dr Hannah Massey
Dr Helen Livesey

Title : *Horizon scanning: how will advances in genomics shape patient care over the next 10 years?*

Winner: Alasdair Purves (link to essay below)

Medical Students: Essay Prize - Clinical Genetics Society

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Conference Programme 11th March 2025

(Approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 6 category 1 (external) CPD credit(s)).

09.30 - 10:00 **Registration**

Invited speakers (Emerging technologies for genomic variant identification)

Chairs*: Prof Diana Baralle and Prof Meena Balasubramanian*

10:00 - 10:18 **Overview of the various technologies**

Dr Greg Elgar - Director of Sequencing, Genomics England, UK

10:18 - 10:36 **Leveraging additional diagnoses in mitochondrial disease from the application of new and emerging technologies**

Prof Rob Taylor - Professor of Mitochondrial Pathology, Newcastle University, Consultant Clinical Scientist and Head of the NHS Highly Specialised Mitochondrial Laboratory, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

10:36 - 10:54 **Use of long-read technologies in craniosynostosis: Lessons learnt**

Prof Andrew Wilkie - Nuffield Professor of Pathology, University of Oxford and Honorary Consultant in Clinical Genetics, Oxford University Hospitals, UK

Robin Winter Prize presentations

Chairs: *Dr Mary O'Driscoll and Dr Ian Ellis*

10:54 - 11:03 **Lynch Syndrome diagnostic testing pathways in endometrial cancers: a nationwide English registry-based study**

Dr Catherine Huntley – Clinical Research Fellow, Institute of Cancer Research, UK

11:03 - 11:12 **Human synonymous codon variation is constrained within multivalent coding regions**

Dr Rhys Dore - Academic Clinical Fellow in Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, UK

11:12 - 11:21 **A case series highlighting the need for a clinical scoring system in solving variants of uncertain significance**

Dr Vijayalakshmi Ramakumaran - Higher Specialist Trainee in Clinical Genetics, University Hospitals of Leicester, UK

11:21 - 11:30 **Improving the diagnostic yield of skeletal dysplasia through targeted systematic re-analysis of known disease genes**

Dr Megan Baxter - Skeletal Dysplasia Clinical Fellow, Guy's and St Thomas' Hospital, UK

11:30 - 11:50 **Coffee break**

Selected Abstracts

Chairs*: Prof Kate Tatton-Brown and Dr Emily Woods*

11:50 - 11:59 **Using cancer phenotype sex-specificity to enable unbiased penetrance estimation of SMARCA4 pathogenic variants for small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)**

Prof Clare Turnbull - Professor of Translational Cancer Genetics, Institute of Cancer Research, UK

11:59 - 12:08 **NanoporE Enhances Diagnosis in rarE Disease (NEEDED study)**

Dr Hannah Titheradge - Consultant in Clinical Genetics, Birmingham Women's and Children's NHS Foundation Trust, UK

12:08 - 12:17 **Cleft genetics: a new Clinical Excellence Network and national service evaluation**

Dr Emily Anderson - Consultant in Clinical Genetics, Liverpool Women's Hospital, UK

12:17 - 12:26 **Quantifying evidence for phenotypic specificity (PP4) for syndromic phenotypes:Large-scale integration of rare germline FH variants**

Miss Sophie Allen – Student, The Institute of Cancer Research, UK

12:26 - 12:35 **DECIPHER – Sharing rare disease patient data and providing variant interpretation tools to empower rare disease diagnosis and research**

Dr Julia Foreman - DECIPHER Project Leader, EMBL-EBI, UK

12:35 - 12:44 **Should Silent Cis carriers be silenced?**

Dr Neeta Lakhani - Consultant in Clinical Genetics, University Hospitals of Leicester NHS Trust, UK

12:44 - 12:53 **TBCK-related encephalopathy associated with early-onset osteoporosis**

Dr Ayse Kavasoglu - Specialty Doctor, UHBW NHS Foundation Trust, UK

12:53 - 13:02 **Sudden Infant Death Syndrome and Sudden Unexplained Death in Childhood as an indication for Whole Genome Sequencing through the R441 panel**
Dr Julie Vogt - Consultant Clinical Geneticist, South West Thames Centre for Genomics, St George's University Hospitals NHS Foundation Trust, UK

13:02 - 13:11 **Maximising patient benefit in the new era of genomic medicine: the importance of diagnosis registration for variant identification**
Dr Samuel Liebert - Research Assistant, North West Thames Regional Genetics Service, UK

13:11 - 13:20 **A homozygous variant in ARHGAP39 is associated with lethal cerebellar vermis hypoplasia in a consanguineous Saudi family**
Dr Sulman Basit - Assistant Professor, Taibah University, Saudi Arabia

13:20 - 14:20 **CGS AGM and Lunch**

Invited speakers (Model systems for genomic variant interpretation)
Chairs: *Prof Mohnish Suri and Prof Andrew Wilkie*

14:20 - 14:38 **Advancing Understanding and Therapeutics: Insights from Disease Model Systems**
Prof Meena Balasubramanian - Professor of Medical Genetics, University of Sheffield and Honorary Consultant Clinical Geneticist and Clinical Director of Research, Sheffield Children's NHS Foundation Trust, UK

14:38 - 14:56 **Using Human Pluripotent Stem Cells for Disease Modelling**
Prof Sue Kimber - Professor of Stem Cells and Development, University of Manchester and Director of the MRC/EPSRC Centre for Doctoral Training in Regenerative Medicine, UK

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14:56 - 15:14 **The MRC NMGN Congenital Anomalies Cluster: modelling variants of uncertain significance in mice**
Prof Steve Twigg - Associate Professor of developmental genetics, University of Oxford

Robin Winter Prize presentations
Chairs: *Dr Nicola Foulds and Dr Sarah Bowdin*

15:14 - 15:23 **A pilot virtual triage meeting for Paediatric clinical genetics**
Dr Rachel Coles - Clinical Genetics Registrar, London - Northwick Park, UK

15:23 - 15:32 **Increasing CAG length in the huntingtin gene is associated with smaller global and subcortical brain volumes in individuals that have normal and intermediate alleles**

Dr Harriet Cullen - ST6 Clinical Genetics, King's College London and Guy's and St Thomas' NHS Foundation Trust, UK

15:32 - 15:41 **Non-invasive prenatal testing can detect maternally and paternally inherited variants in the KCNJ11 and ABCC8 genes: An opportunity for targeted treatment in utero**

Dr Pamela Bowman - Academic Clinical Lecturer, University of Exeter Medical School, UK

15:41 - 15:50 **An Update on the Generation Study**

Dr Katrina Stone - Clinical Genetics SpR, Great Ormond Street Hospital, UK

15:50 - 15:59 **Neonatal Central Apnoea presenting feature of an underlying genetic condition**

Dr Titiksha Masand - Clinical Genetics SpR, Leicester Royal Infirmary, UK

15:59 - 16:08 **Cardiac involvement in MYO6: what should we advise patients?**

Dr Jaynee Chauhan - Specialty registrar, Liverpool Centre for Genomic Medicine, UK

16:08 - 16:30 **Afternoon tea**

16.30 - 17.30 **CGS Lecture**

Prof Sarah Smithson, University Hospitals Bristol NHS Foundation Trust, UK
Chair: *Prof Diana Baralle*

17.30 - 17.45 **RW prize, medical student essay prize & other presentations**

Chairs: *Prof Diana Barelle and Dr Suresh Somarathi*

Close

19:00 - onwards **Welcome drinks and conference dinner**

Invited speakers

Dr Greg Elgar
Director of Sequencing Genomics England, UK

Greg has over 40 years' experience in molecular biology, including 30 years in Genomics at Principal Investigator level, establishing, co-ordinating and managing multi-disciplinary teams and pipelines. He has contributed to over 150 peer-reviewed publications and has played lead roles in several international genome sequencing projects. He completed his PhD with Sydney Brenner in Cambridge, and his academic career includes positions at the Wellcome Trust Genome Campus, QMUL, the MRC National Institute for Medical Research and the Crick Institute, leading research groups and running sequencing facilities. In January 2018, Greg joined Genomics England as Director of Sequencing, co-ordinating programmes across diverse omics platforms. Over the past 5 years his R&D lab has assessed and developed sequencing technologies with the aim of clinical implementation in both Cancer and Rare Disease. He also coordinates epigenetic, transcriptomic, proteomic and metabolomic programmes of research in Rare Disease.

Prof Rob Taylor
Professor of Mitochondrial Pathology, Newcastle University, Consultant Clinical Scientist and Head of the NHS Highly Specialised Mitochondrial Laboratory, Newcastle upon Tyne Hospitals NHS Foundation Trust,

Rob Taylor is Professor of Mitochondrial Pathology at Newcastle University, Consultant Clinical Scientist and Head of the NHS Highly Specialised Mitochondrial Laboratory at Newcastle upon Tyne Hospitals NHS Foundation Trust. He is Scientific Director of the North East and Yorkshire Genomic Laboratory Hub, co-chairs the NHS England Rare Disease Test Evaluation Working Group and is Chair of the Association for Clinical Genomic Science.

His research focuses on mitochondrial gene discovery and delineating disease mechanisms, translating genomic innovation and discovery into clinical practice through improved diagnosis and clinical management. His laboratory collaborates extensively both nationally and internationally, leading studies to identify ~40 disease genes associated with a range of mitochondrial and neurological disease phenotypes and contributing to >550 peer-reviewed scientific papers.

Prof Andrew Wilkie
Nuffield Professor of Pathology, University of Oxford and Honorary Consultant in Clinical Genetics, Oxford University Hospitals, UK

Andrew Wilkie is Honorary Consultant in Clinical Genetics at the Oxford University Hospitals and Nuffield Professor of Pathology at the University of Oxford. Working closely with plastic surgeons, his clinical research aims to identify the molecular genetic basis of craniofacial malformations, particularly craniosynostosis. Over the past 30 years his group identified many new disease-associated genes, providing information to establish the scientific underpinning of genetic testing within the NHS. Work on Apert syndrome led to fundamental discoveries concerning the mechanisms of mutation associated with paternal age effects.

Prof Meena Balasubramanian
Professor of Medical Genetics, University of Sheffield and Honorary Consultant Clinical Geneticist and Clinical Director of Research, Sheffield Children's NHS Foundation Trust, UK

Meena Balasubramanian is an academic clinical geneticist. In genomic medicine, she has several studies focused on genotype-phenotype correlation in newly identified genes including Osteogenesis Imperfecta (OI). She has led several projects focused on genetics of rare bone disorders and research projects focussed on identifying novel genomic approaches to rare bone disorders and exploring newer targets for therapy for these conditions. She has established her own lab on zebrafish disease models and published over 135 principal-author publications and textbooks including a recent molecular medicine series. She has also edited and written several patient information leaflets on rare genetic disorders for Unique (www.rarechromo.org) and Brittle Bone Society.Meena's group has published the largest clinical cohorts for the following RNDD genes: HNRNPU, ASXL3, SIN3A, IQSEC2, YWHAG, ZMYND11 and written the expert literature reviews (Genereview/ Orphanet/ NORD guides) for ASXL3, HNRNPU & SIN3A. Her other roles include Clinical Director of Research at Sheffield Children's Hospital; Secretary for Clinical Genetics Society and she serves on the 'Medical Advisory Board' for Brittle Bone Society, HNRNP Family Foundation and Chair of the 'Early Phase Safety Review Committee' for delivery of first in human gene therapies at Sheffield Children's Hospital.

Prof Sue Kimber
Professor of Stem Cells and Development, University of Manchester and Director of the MRC/EPSRC Centre for Doctoral Training in Regenerative Medicine, UK

Sue Kimber is Professor of Stem Cells and Development at the University of Manchester, UK, Director of the MRC/EPSRC Centre for Doctoral Training in Regenerative Medicine and was Co-Director of the North West Embryonic Stem Cell Centre (NWESCC).

Following training in the University of Cambridge, she has over 30 years experience in cell and developmental biology and 16 years experience in regenerative medicine, disease modelling and tissue engineering with >170 publications. Her lab has derived nearly 50 human induced pluripotent stem cell (hiPSC) lines both from healthy individuals and those with disease conditions caused by mutations affecting the skeleton, kidney, nervous system and vasculature. They have developed and applied different 2D and 3D protocols to human embryonic stem cell and hiPSC, differentiating them to these tissues for understanding human development and for modelling genetic, often rare, diseases with a view to finding new drug targets. She has participated in two UKRI UK Regenerative Medicine Platform hubs ('Stem Cell Niche' and 'Safety of Stem Cells') and has supervised over 60 PhD students, as well as post docs and fellows. In 2019 she was awarded a Suffrage Science Award for her tissue engineering research by the Royal Society. Relevant external activities include Co-Chair of 2023 meeting of European chapter of TERMIS; Founder and Co-Chair of Mercia Stem Cell Alliance to promote stem cell biology in the NW and Midland and several UKRI and research charity as well as European grant committees.

Steve Twigg
Associate Professor of developmental genetics, University of Oxford

Steve Twigg is a basic scientist working on craniofacial genetics at the MRC Weatherall Institute of Molecular Medicine, University of Oxford where he is Associate Professor of developmental genetics. He has a degree in Applied Biology from the University of Bath and a DPhil from the University of Oxford. He has been a member of the Clinical Genetics Group at Oxford since 1996 studying craniofacial development, with a focus on craniosynostosis and understanding pathogenic mechanisms. He is co-lead of the MRC National Mouse Genetics Network Congenital Anomalies Cluster.

Clinical Genetics Society Lecture

Professor Sarah Smithson DM FRCP FRCPCH
Consultant in Clinical Genetics at University Hospitals Bristol and Honorary Professor at the University of Bristol.

Sarah Smithson is a Consultant in Clinical Genetics at University Hospitals Bristol and an Honorary Professor at the University of Bristol. Her background is in hospital paediatric medicine and clinical genetics, training as a registrar in Oxford and senior registrar at Great Ormond Street Hospital in London. Her Doctoral research in Oxford focused on clinical and genetic aspects of Apert syndrome. Her research interests include clinical dysmorphology and the genetic mechanisms that impair development, especially in the skeleton. As part of her full time NHS role, Sarah has with colleagues, developed a skeletal dysplasia service for the South-West region and established in Bristol a supra-regional service for Osteogenesis Imperfecta. Additionally, she has been involved with the Royal College of Physicians as Chair of the Special Advisory Committee, the UK Skeletal Dysplasia Group as Genetic Representative, and the 100 000 Genome Project as Clinical Director of the West of England Genomic Medicine Centre. Within the Clinical Genetics Society, she has worked on Council as an elected member, National Governance Lead, Academic Vice-President and more recently as President, completing her term of office in 2024.

Invited speaker abstracts

Use of long-read technologies in craniosynostosis: lessons learnt

Yang Pei,[1] Dagmara Korona,[1] Eduardo Calpena,[1] Jill M. Brown,[2] Ron Schwessinger,[2] Lucy Platts,[3] Simon J. McGowan,[4] Tazeen Ashraf,[5,6] Siddarth Banka,[7,8] Jill Clayton-Smith,[8] Francesca Forzano,[6] Jane A. Hurst,[5] Wendy D. Jones,[5] Ajoy Sarkar,[9] Astrid Weber,[10] Richard J. Gibbons,[2] Stephen R. F. Twigg,[1,8] **Andrew O. M. Wilkie**[1,8]

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2 *MRC Molecular Haematology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK;*
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4 *Centre for Computational Biology, MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK;*
5 *North East Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street Hospital, London, UK;*
6 *Clinical Genetics Department, Guy's & St Thomas' NHS Foundation Trust, Guy's Hospital, London;*
7 *Division of Evolution, Infection and Genomics, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK;*
8 *Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University NHS Foundation Trust, Health Innovation Manchester, Manchester, UK;*
9 *Clinical Genetics Service, Nottingham University Hospitals NHS Foundation Trust, City Hospital, Nottingham, UK;*
10 *Department of Clinical Genetics, Liverpool Women's NHS Foundation Trust, Liverpool, UK*

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ABSTRACT

When routine genetic tests (now including whole genome sequencing [WGS]) fail to identify a genetic cause, the possibility remains that a structural/copy number variant (SV/CNV) may have been missed. With this in mind, we investigated 20 unsolved patients with craniosynostosis, most of whom had previously had negative short-read (Illumina) WGS and array testing. Although we found that the error rate of ONT nanopore CNV callers (Sniffles/Sniffles 2) available at the time of the study was too high for de novo SV/CNV calling, we had greater success using Bionano optical genome mapping (OGM) and I will focus on the latter technology in my talk. Aside from solving a long-standing diagnostic mystery in a family with Saethre-Chotzen syndrome (4.3 Mb inversion of 7p21.2-p21.1), OGM proved very powerful at disambiguating SV/CNV in four patients who harboured multiple duplication/triplication events, each of which was compatible with multiple structural interpretations (respectively 4, 3, 3 and 12 different types), that could not be distinguished from the short-read data alone. In three of these four cases, the duplications were of "linked interspersed" type making the interpretation even more challenging. A key concept is that successful analysis of these events requires a technology *able to span the entire duplicated segment(s) on single molecules*. Bionano OGM served this purpose well for duplications in the 30-350 kb size range, but could not reliably span distances >600 kb. I will also present the use of predictive topologically-associating domain (TAD) analysis to assess the potential consequences of different rearrangement types. Apart from illustrating some key general principles for the analysis of such SV/CNV, this work identified a novel cause of Pierre-Robin sequence and craniosynostosis (partial duplication of the *HOXC* gene cluster on chromosome 12q13.13) and implicates *KCNJ2* as a likely causal gene for the HTC3 locus on chromosome 17q24.3.

Using human pluripotent stem cells for disease modelling

Susen J Kimber

School of Biological Science Cell Matrix Biology and Regenerative Medicine, School of Biological Sciences, University of Manchester.

Human pluripotent stem cells (hPSCs) have been identified by researcher and pharma as useful tools for generating models of rare and not so rare diseases, particularly monogenic disease originating during fetal development. They can be expanded almost indefinitely and have potential to form virtually any body cell type. The advent of complex differentiation protocols to generate organoids and other 3D assemblies of cells has further increased interest and modelling validity. In our lab we have generated models for kidney, skeletal and neural tissues allowing us to investigate how development is altered in often rare conditions caused by monogenic mutations. Our aim is to identify the early changes in fetal tissue development and aberrant pathways, and so pinpoint target genes that can form the basis of drug repositioning or discovery. Timely use of such drugs would be hypothesised to prevent or reverse developmental changes. We have identified such pathways in several disparate diseases. I will illustrate this by reference to the dysregulated morphology, signalling pathways and transporter profile seen in HPSC-mini kidney (organoids) with a heterozygous HNF1B mutation causing kidney disease. Matrilin 3 mutations cause a Chondrodysplasia (Multiple Epiphyseal Dysplasia; MED) and we have shown that this disrupts cellular and extracellular chondrocyte /cartilage phenotype at different levels. Two D and 3 D protocols to generate cortical neurons have also been used to investigate conditions affecting intellectual ability including Kabuki syndrome and are starting to generate novel mechanistic data.

Oral presentations

(1) Lynch Syndrome diagnostic testing pathways in endometrial cancers: a nationwide English registry-based study

C. Huntley[1,2], L. Loong[1,2], J. Pethick[2], F.E. McRonald[2], F. Santaniello[2,16], B. Shand[2], O. Tulloch[2], S. Goel[2,16], M. Lüchtenborg[2,17], S. Allen[1,2], B. Torr[1], K. Snape[3], A. George[1,4], F. Lalloo[5], G. Norbury[6], D.M. Eccles[15], M. Tischkowitz[7], A. Antoniou[8], P. Pharoah[9], A. Shaw[10], E.J.A. Morris[11], J. Burn[12], K. Monahan[13,14], S. Hardy[2], C. Turnbull[1,2]

1 *Division of Genetics and Epidemiology, The Institute of Cancer Research, Sutton, UK*
2 *National Disease Registration Service, NHS England, London, UK*
3 *Department of Clinical Genetics, St George's University Hospitals NHS Foundation Trust, London, UK*
4 *The Royal Marsden NHS Foundation Trust, London, UK*
5 *Clinical Genetics Service, Manchester Centre for Genomic Medicine, Manchester University Hospitals NHS Foundation Trust, Manchester, UK*
6 *South East Genomic Laboratory Hub, Guy's and St Thomas' Hospitals NHS Trust, London, UK.*
7 *Department of Medical Genetics, Cambridge Biomedical Research Centre, National Institute for Health Research, University of Cambridge, Cambridge, United Kingdom*
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9 *Department of Computational Biomedicine, Cedars-Sinai Medical Center, Los Angeles, California*
10 *Guy's and St Thomas' NHS Foundation Trust, London, UK*
11 *Applied Health Research Unit, Big Data Institute, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom*
12 *Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK*
13 *The Lynch Syndrome and Family Cancer Clinic, St Mark's Hospital and Academic Institute, Harrow, London, UK*
14 *Imperial College London, London, UK*
15 *Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton, Southampton, UK*
16 *Health Data Insight, Cambridge, UK*
17 *Cancer Epidemiology and Cancer Services Research, Centre for Cancer, Society & Public Health, Comprehensive Cancer Centre, King's College London, London, UK*

Background

An estimated 3% of endometrial cancers (ECs) are caused by Lynch syndrome (LS). LS carriers can be identified via a pathway of tumour testing followed by germline mismatch repair (MMR) gene testing. We aimed to describe the national patterns of LS testing in all ECs diagnosed in 2019.

Methods

This was a national, population-based, observational study. We used comprehensive data collections of functional, germline, and MMR tests available via the English National Cancer Registration Dataset, held by the National Disease Registration Service (NDRS). We examined the proportion of ECs tested, time to testing, and results obtained. We additionally explored demographic, social, and geographic factors influencing testing initiation.

Results

7,928 patients were diagnosed with EC in 2019. 17.8% (1408/7928) had a recorded immunohistochemistry

(IHC) or microsatellite instability (MSI) test. 43.1% (149/356) of those with MLH1 protein IHC loss or MSI had a recorded MLH1 promoter hypermethylation test. 25% (26/104) of those eligible for germline testing following tumour testing triage had a germline MMR test recorded. The median time to germline MMR testing from EC diagnosis was 315 days (IQR 222-486).

Interpretation

Recorded LS testing patterns varied by region. We found evidence of patient attrition, delays, and missed opportunities to diagnose LS. In 2020, the National Institute of Health and Care Excellence issued guidance on universal reflex testing. This analysis constitutes a baseline against which the impact of this guidance may be measured.

(2) Human synonymous codon variation is constrained within multivalent coding regions

R. Dore[1], J. Ule[1,2]

[1] *UK Dementia Research Institute at King's College London, The Wohl, 5 Cutcombe Road, London, SE5 9RX, UK*
[2] *The Francis Crick Institute, 1 Midland Rd, London, NW1 1AT, UK*

Cellular homeostasis hinges on precise protein dosage control, particularly for proteins harbouring disordered low complexity domains (LCDs). We recently reported a new regulatory mechanism termed 'interstasis', facilitating mutual dosage regulation of LCD-containing proteins. Interstasis leverages multivalent CDS regions encoding LCDs, which stems from the repetitive amino acid arrangement, similarity of codons for biophysically akin amino acids, and conserved synonymous codon biases. Specific RNA-binding proteins bind to multivalent RNA regions and orchestrate the interstasis through feedback regulation of mRNAs encoding LCD-containing proteins.

Exploring the impact of RNA multivalency on human genetic variation in coding regions, we analysed common polymorphisms from dbSNP. They found that the more multivalent a CDS region is, the greater the relative synonymous constraint - i.e. the less variation is tolerated in synonymous relative to non-synonymous mutations. Moreover, in cases such as arginine that contains 6 possible codons, human synonymous variation tends to maintain high RNA multivalency by mimicking the codons of other nearby amino acids.

Additionally, we probed the role of CDS multivalency in cancer-related genetic variation using Cosmic data. Multivalent regions exhibited increased relative synonymous variation in Cosmic as compared to dbSNP, and we identified transcripts with particularly high rates of multivalence-disrupting synonymous variants as candidates for further study.

Our findings underscore the importance of synonymous constraint patterns linked to RNA multivalency in LCDs. This opens new opportunities for future investigations to explore the contribution of these constraints for the interstasis-mediated dosage control of LCD-containing proteins.

(3) A case series highlighting the need for a clinical scoring system in solving variants of uncertain significance

V Salem Ramakumaran, T Masand, N Lakhani E Craft P Vasudevan

Department of Clinical Genetics, LNR Genomics Medicine Service, University Hospitals of Leicester, NHS Trust, United Kingdom

Variant(s) of uncertain significance (VUS) are a common challenge in Clinical Genetics practice. A collaborative effort involving the Clinical team, Genetics Scientists, and corroborative evidence utilising several databases, support tools and functional evidence is often required to reach a conclusion. In many cases where clinically the variant is considered highly relevant, despite additional variant related and computational evidence the criteria for upgrading the variant falls short. This is also compounded by skewed representation of ethnicity specific variant information in the current databases.

We present a cohort of 8 cases to explore the utility of clinical judgment and expertise of clinical skills in resolving these variants or considering them as relevant, where evidence would be insufficient to meet guideline thresholds for reclassification. In two cases, reverse phenotyping was consistent with the variant associated condition, and episignature evidence resulted in classifying the variants as likely pathogenic. In one of the cases clinical relevance of the variants based on literature and clinical course was considered strong, however a classification of likely pathogenicity could only be reached following in silico modelling evidence. In three other cases with the variants remain classified as uncertain, either due to the atypical nature of the clinical presentation or the lack of clinical specificity.

We emphasize the need for consideration of a clinical scoring system to be incorporated into the variant interpretation guidelines to address these specific clinical scenarios for clinical benefit and actionability.

(4) Improving the diagnostic yield of skeletal dysplasia through targeted systematic re-analysis of known disease genes

M.F Baxter[1]

Musculoskeletal GECIP Group

[1] *Guy's and St. Thomas' NHS Foundation Trust, London*

Background:
Identifying the underlying genetic cause of a patient's rare disease is critical to provide appropriate counselling and access to novel treatments. Currently a prolonged diagnostic odyssey exists and often the underlying cause is never identified. Collectively 1 in 5000 individuals are affected by a skeletal dysplasia for which there are 552 known disease genes published in The Nosology of genetic skeletal disorders:2023 revision. More than 900 individuals with skeletal dysplasia were recruited for the 100000 Genomes Project however at present only 27.3% (256/937) of the cases are listed as solved.

Methods:
Utilising a targeted approach, systematic re-analysis of all genes present in Skeletal Nosology was completed for individuals enrolled in the 100000 Genomes Project with an overarching diagnosis of skeletal dysplasia, currently listed as unsolved. Analysis was completed in R, assessing both SNV and/or structural variants, respective of the disease genes inheritance pattern.

Results:
Strong candidate variants in known disease genes were found for more than 3% of the currently listed as unsolved skeletal dysplasia cases. This included variants that for a myriad of reasons were not originally tiered at a level to be identified on original analysis including recent novel disease genes, splice site variants, and structural variants.

Conclusion:
This project significantly improved the diagnostic yield of unsolved skeletal dysplasia cases and highlighted the diverse landscape of molecular mechanisms that underly skeletal dysplasia. It also demonstrated the potential for continued re-analysis of available data and the need for similar approaches to be utilised across other rare disease domains.

(5) Using cancer phenotype sex-specificity to enable unbiased penetrance estimation of SMARCA4 pathogenic variants for small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)

I Wade[1], L Witkowski[2,3], A Ahmed[2], C F Rowlands[1], S Banerjee[4], JG Pressey5, T P McVeigh[4], M D.Tischkowitz6, W D Foulkes[2,3], **C Turnbull[1,4]**

1. *Institute of Cancer Research, London, UK*
2. *Cancer Research Program and the SCCOHT/SMARCA4 Registry and Biobank, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada*
3. *Department of Human Genetics, McGill University, Montreal, Quebec, Canada*
4. *Royal Marsden NHS Foundation Trust, London, UK*
5. *Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA*
6. *Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK*

Background: Small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT) is an extremely rare, highly lethal cancer (mean age of onset, 24 years). In approximately half of cases studies a germline pathogenic variant (GPV) in *SMARCA4* has been identified. Very early bilateral oophorectomy (in their teens/twenties) is recommended for unaffected female relatives with a *SMARCA4* GPV. However, existing penetrance estimates of *SMARCA4* GPVs for SCCOHT have been sizeably influenced by ascertainment bias.

Methods: Leveraging the early-onset, sex-specific, high morbidity of SCCOHT, we hypothesised that the penetrance for SCCOHT could be quantified from the deficit in *SMARCA4* GPVs in females compared to males in UK Biobank, for which recruitment was restricted to those age 40-69.

Results: We observed *SMARCA4* GPVs in 8/210,182 (0.0038%) female and 18/179,210 (0.0100%) male participants in UK Biobank (p = 0.028), representing a male:female odds ratio of 2.64 (95%CI 1.15-6.07), implying a lifetime penetrance of 62% for SCCOHT. This supported the observation of high rates of paternal inheritance and/or familial disease observed in probands in the international *SCCOHT-SMARCA4* Registry.

A deficit of GPVs in females was also demonstrated for *BRCA1* (20%) and *TP53* (48%), providing a measure for these genes of penetrance for early-onset female-specific disease the associated mortality/morbidity of which precluded enrolment into UK Biobank.

Conclusions: Our methodology provides a (reasonably) unbiased estimate for penetrance of *SMARCA4* GPVs. These data are of high clinical value in supporting the difficult recommendation of very early bilateral oophorectomy for at-risk females.

(6) NanoporE Enhances Diagnosis in rarE Disease (NEEDED study)

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Background/Objectives: Currently patients in England with monogenic developmental disorders will undergo NHS genetic testing including microarray and Whole Genome Sequencing (WGS) using short-read sequencing technology, with additional relevant genetic tests, such as methylation studies. For suspected monogenic cancer disorders a gene panel is used only. This means that a significant proportion of patients remain undiagnosed. We aim to evaluate the utility of Nanopore long-read sequencing (LRS) as a tool to increase the diagnostic rate of suspected monogenic rare disorders.

Methods: We identified 25 individuals highly likely to have a monogenic disorder, who have no molecular genetic diagnosis, and have reached the ceiling of investigation within the NHS genomic medicine service. They were recruited as trios and quads (affected patient(s), and their parents) to Understanding the Genomic Basis for Human Disease. Trio (or quad) WGS is performed using the Oxford Nanopore Promethion P24 instrument. We are using a range of existing software packages to study participants' genomes for potentially disease-causing variants including, sequence, copy number, methylation variants, and tandem repeats.

Results: We have identified the underlying molecular aetiology for 3 patients and their families so far including a diagnosis of Coffin Siris syndrome, Familial Adenomatous Polyposis and Roifman syndrome. We will discuss the bioinformatic pipeline and downstream analysis tools utilised as well as the feasibility of implementation of Nanopore sequencing into NHS diagnostic testing pathways.

Conclusion: Nanopore LRS has increased the diagnostic rate for patients with likely monogenic disorders in families who have reached the ceiling for investigation in the NHS.

(7) Cleft genetics: a new Clinical Excellence Network and national service evaluation

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Cleft lip and/or palate is a common congenital anomaly, affecting approximately 1 in 700 babies in the UK. However, there is currently a lack of consensus to support clinicians and families when deciding whether to offer genetic testing for these individuals.

With the aim of bringing together healthcare professionals and researchers to deliver high quality service, education and research nationally, we established the Cleft Genetics Clinical Excellence Network (CEN) in 2023.

The CEN has already completed a national service evaluation, to benchmark current cleft genetics provision across the UK. This project has confirmed anecdotal information that practice varies widely between centres.

The CEN has hosted three meetings, including one face to face, to further the discussion around the indications for genetic testing for patients with a cleft, particularly in the prenatal setting and for isolated, non-syndromic cases.

In addition, the CEN has worked closely with cleft charities, patient groups and the RCPCH to provide expertise regarding cleft genetics.

The CEN is aligned with other cleft CENs (e.g. surgeons, orthodontists). This allows for discussion and collaboration with cleft teams. Furthermore, the Cleft Genetics CEN has provided insight for the new cleft service specification, with specific reference to the role of the Clinical Geneticist within the cleft team.

In summary, the Cleft Genetics CEN is a new network that aims to standardise and improve cleft genetics services for patients across the UK, by developing evidence-based consensus guidelines and encouraging further research. We present the CEN and the results of the service evaluation.
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(8) Quantifying evidence for phenotypic specificity (PP4) for syndromic phenotypes: Large-scale integration of rare germline FH variants

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Background: For ACMG/AMP variant classification there is often uncertainty and inconsistency in evidence weighting for very rare variant (VRV) observations in highly specific (and less specific) phenotypes, for example of *FH* variants in HLRCC versus unselected renal cancer.

Methods: We collated germline testing data from four diagnostic laboratories (3 UK, 1 USA (Ambry)) for 387 affected probands who would meet the eligibility criteria for R365 (HLRCC-phenotype), and for 1,780 patients with renal cancer who underwent *FH* testing as part of a renal panel. We defined a VRV as a variant with an allele frequency of <0.000015 (calculated MTAF), i.e. plausibly pathogenic. We compared the frequency of VRVs in each phenotypic cohort against a total of 562,295 controls to calculate pan-gene likelihood ratios (PG-VRV-LR), and performed spatial clustering analysis to identify enriched regions of very rare missense variants within the gene.

Results: For HLRCC, the PG-VRV-LR was estimated to be 2,669.4 (95% CI: 1,843.4-3,881.2, LLR 10.77) for truncating variants and 214.7 (185.0-246.9, LLR 7.33) for missense variants. For renal cancer, the PG-VRV-LR

was 95.5 (48.9-183.0, LLR 6.23) for truncating variants and 5.8 (3.5-9.3, LLR 2.39) for missense variants. Clustering analysis of very rare missense variant enrichment in HLRCC cases revealed three 'hotspot' regions wherein the domain-specific LR increased to 1226.9.

Interpretation: These data provide quantitative measures which may be applicable in clinical variant classification for very rare variants in *FH*. This methodology is potentially applicable in other diseases to quantify the specificity of the relationship between phenotype, gene, and variant type.

(9) DECIPHER – Sharing rare disease patient data and providing variant interpretation tools to empower rare disease diagnosis and research

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Accurate variant classification and clinical interpretation is essential for the robust timely diagnosis of patients with rare genetic disorders. DECIPHER (https://deciphergenomics.org) is a global platform which enables the sharing of phenotype-linked candidate diagnostic variants and provides interpretation interfaces. It sits at the boundary between rare-disease research and the clinical community to ensure that the most up-to-date data and tools are readily accessible to the clinical and research communities. These are optimally presented within DECIPHER's interpretation interfaces to improve clinical care and to empower rare disease research.

DECIPHER currently hosts ~50,000 open-access records containing >64,000 variants and >200,000 phenotypes. DECIPHER facilitates more refined within-consortium sharing of >86,000 patient records within seven groups, including the NHS Consortium, which links all UK NHS genomic medicine services and GLHs.

DECIPHER variant classification interfaces summarize and contextualize genotypic and phenotypic data, including a protein browser, which allows users to visualize their patient's variant on a 2D protein view and on an experimental or AlphaFold predicted 3D protein structure. Gene/disease information and mechanism of disease is also provided. Variant annotation interfaces present information, such as gnomAD allele frequencies, functional annotations (e.g. MAVE data), pathogenicity prediction scores (e.g. AlphaMissense, CADD) and case/cohort data. Variant pathogenicity classification using ACMG/ClinGen technical standards for CNVs and ACMG/AMP/ACGS guidelines for sequence variants is supported. For sequence variants, predictions for applying ACMG/AMP criteria are available with details of the evidence for each prediction.
Since its inception DECIPHER has facilitated over 3,700 publications; a testament to the importance of match-making in rare disease.

(10) Should Silent Cis carriers be silenced?

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Background:
Silent cis carriers of Spinal Muscular Atrophy (SMA) present a critical yet often overlooked aspect of the disease landscape. With the increased frequency of SMA carriers in our region, understanding the implications of silent cis carriers becomes imperative. Silent carriers, while phenotypically normal, harbor pathogenic heterozygous SMA alleles, which are not identified using current first line testing techniques. This poses significant implications for reproductive options and genetic counselling.

Methods:
The estimated prevalence in our cohort is more than twice the reported prevalence of 4%. The chance of false negative parental carrier status results due to first line testing will result in erroneously concluding that the affected individual has a de novo variants and inaccurate recurrence estimation for the family. This raises ethical and emotional considerations regarding reproductive decision-making.

Results:
Furthermore, the haplotyping of silent carriers are crucial adjunct to carrier testing, for accurate risk assessment and genetic counselling. Through this we can predict the likelihood of disease transmission and guide personalized reproductive strategies.

Conclusion:
Here we present a case series of families with silent cis carrier status and how the family journey, though extended, significantly changes their reproductive outcomes.

(11) TBCK-related encephalopathy associated with early-onset osteoporosis

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TBCK-related syndrome is a rare autosomal recessive disorder characterised by infantile hypotonia, developmental delay, distinctive facial features, seizures and cortical atrophy. Recent reports of this complex phenotype suggest multisystem involvement including osteopenia and pathological fractures in some patients.

We present a 10 year old girl who was referred in infancy to investigate her dysmorphic features, slow developmental progress, obstructive apnoea, seizures and feeding difficulties which required gastrostomy. The key clinical findings included bi-temporal narrowing, open mouth with apparent macroglossia, tented upper lip, sparse hair, pectus excavatum, joint laxity, cutis laxa, profound hypotonia, diminished reflexes and sensorineural hearing loss. Later she developed femoral, tibial and vertebral fractures in the absence of significant trauma. Her development is delayed in all domains and speech is absent.

Her brain MRI scans show widespread delayed myelination and loss of cerebral volume. Past negative genetic analyses include karyotype, array-CGH, spinal muscular atrophy, chromosome 11 and 15 methylation, *SNRPN*, *MEF2C*, gene panels for epilepsy, cutis laxa and osteogenesis imperfecta. Although primary analysis within the 100,000 Genomes Project was also negative, the Diagnostic Discovery arm has recently identified compound heterozygous pathogenic variants in *TBCK*, encoding TBC1 domain-containing kinase.

We summarise the current literature on this emerging phenotype and illustrate treatment of recurrent fractures with bisphosphonate in our patient.

(12) Sudden Infant Death Syndrome and Sudden Unexplained Death in Childhood as an indication for Whole Genome Sequencing through the R441 panel

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Sudden Infant Death Syndrome (SIDS) and Sudden Unexplained Death in Childhood (SUDC) affects around 200 infants and 40 children annually in England. Although these deaths remain unexplained after extensive investigation including full post-mortem, monogenetic causes have been implicated in around 10% of cases providing families with important information. SIDS/SUDC as an indication for whole genome sequencing (WGS) R441 panel is comprised of cardiac, epilepsy and inborn errors of metabolism disease genes and was approved for inclusion in the National Genomic Test Directory in England in April 2023. Challenges to implementing the R441 service have included deploying diagnostic WGS in a novel setting, involvement of multiple specialties, complexities in the clinical pathway and regional differences in practice and resources.

On review of the R441 genomic testing service in England, approximately 17% of eligible families have undergone WGS to date. Of the fifty-eight cases reported nationally with the primary clinical indication as R441 two cases tested positive, seven were inconclusive and forty-nine were negative.

The R441 panel is a powerful tool providing a broad disease-based genomic testing approach for identifying monogenetic causes of SIDS/SUDC which may be relevant to the wider family. This testing strategy facilitates the first national collation of clinical and genotypic data across SIDS/SUDC patients. England is the first country internationally to offer routine diagnostic WGS following SIDS/SUDC. This will assist with advances in analysis and data interpretation, interfaces with active research environments, unravelling new genetic causes and mechanisms for SIDS/SUDC, as well as informing public health.

(13) Maximising patient benefit in the new era of genomic medicine: the importance of diagnosis registration for variant identification

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In the current era of genomic medicine, genomic testing is widely available for individuals and families with clinical diagnoses of rare disease and cancer. As more diagnoses are confirmed through genomic testing, there is a growing need for clinical genetics services to be able to identify their patients on a disease, variant or phenotypic level. This strongly ties into the ability of services to accurately identify patients eligible to participate in research or share new clinical guidance strategies for individuals with specific conditions. Unfortunately, inadequate time and underutilisation of specialised databases prevent the efficient identification of patients or specific variants, and an effective solution is urgently required.

To address this challenge, we established a working group in the Northwest Thames Regional Genetics Service to develop a sustainable diagnosis registration system for individuals with rare disease and a genomic diagnosis. We chose to adopt the DECIPHER (*D*atabas*E*_of_genomi*C*_variation_and_*P*henotype_in_*H*umans_using_ *E*nsembl_*R*esources- https://www.deciphergenomics.org/) international database to input rich variant and phenotypic information from our patients seen within the last 12 years.

Over 2 years, we have successfully registered over 2200 patients, establishing a cohort that can be filtered on a gene, variant and phenotypic level to a intricate degree. This has included National rare disease/ cancer registries and studies, allowing us to identify which of our patients in the service meet complex criteria in a matter of seconds through a single multi-filtered search. This has subsequently led to increased research engagement and recruitment at a local level, pioneering the way for other genetic services to follow.

(14) A homozygous variant in ARHGAP39 is associated with lethal cerebellar vermis hypoplasia in a consanguineous Saudi family

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Cerebellar vermis hypoplasia refers to a varying degree of incomplete development of the cerebellum and vermis. A Saudi family with four affected individuals with cerebellar vermis hypoplasia, facial dysmorphology, visual impairment, skeletal, and cardiac abnormalities was ascertained in this study. Three out of four patients could not survive longer and had died in early infancy. Genetic analysis of the youngest affected was performed by genome-wide homozygosity mapping coupled with whole exome sequencing (WES), followed by Sanger validation. Genome-wide genotyping analysis mapped the phenotype to chromosome 8q24.3. Using an autosomal recessive model, considering deleterious variants with minor allele frequency of less than 0.001 in WES data, a homozygous missense variant (NM_025251.2; ARHGAP39; c.1301G>T; p.Cys434Phe) was selected as a potential candidate for the phenotype. The variant (c.1301G>T) in the ARHGAP39 is in the region of homozygosity on chromosome 8q24.3. ARHGAP39 is a Rho GTPase-activating protein 39 and has been known to regulate apoptosis, cell migration, neurogenesis, and cerebral and hippocampal dendritic spine morphology. Mice homozygous for arhgap39 knockouts have shown premature embryonic lethality. Our findings present the first ever human phenotype associated with ARHGAP39 alteration
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(15) A pilot virtual triage meeting for Paediatric clinical genetics

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Great Ormond Street Hospital for Children

Mainstreaming genetic testing has benefits, however there is a need for support and guidance of Paediatricians/Neonatologists. Long waits for genetic clinics and results mean appropriate testing at point of referral is important.

A novel weekly virtual meeting for Paediatricians/Neonatologists was designed and piloted as a service improvement project. The meeting created a forum for clinicians to discuss cases with consultant geneticists and has been running for 5 months.

The meeting provides virtual triage, addressing whether referral is indicated, urgency, genetic and non-genetic testing to initiate and information to provide with the referral.

24 advice meetings, discussing 38 patients were held from 03/07-26/11. The meeting was rated as effective (using a survey and Likert scales) by mainstream clinicians attending. Most clinicians (n = 24) either strongly agreed or agreed that they would attend the meeting again, and that they found the discussion helpful. Attendance improved clinician's confidence in the patient's management plan. Benefits noted included 'enhanced learning' and 'improved patient care'. A barrier was difficulty attending due to other commitments. Data showed at least one aspect of management was altered by the meeting in all cases.

Our results indicate this pilot virtual meeting has been beneficial to both patients and clinicians. We plan to implement a further 3 months and re-evaluate, and also to survey clinical genetics consultants. Data analysis from our electronic patient records is ongoing to assess whether the meeting reduces time from referral to diagnosis or impacts carbon footprint.

(16) Increasing CAG length in the huntingtin gene is associated with smaller global and subcortical brain volumes in individuals that have normal and intermediate alleles

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Huntington's disease is an adult-onset neurodegenerative disease caused by an expanded CAG trinucleotide repeat in the Huntingtin gene (*HTT*). Individuals with pathological alleles typically demonstrate neuroimaging changes several decades prior to clinical diagnosis with atrophy in the striatum being particularly marked. A few studies have suggested intermediate allele carriers may have associated neuroimaging and neurocognitive phenotypes however little is known about the clinical relevance of expansion variability outside the pathological range.

Short tandem repeat expansions can now be accurately quantified from whole genome sequencing (WGS). This project integrates MRI and WGS from UK Biobank to investigate whether variability in the *HTT* CAG expansion length is associated with measurable differences in subcortical and global brain volumes for individuals with alleles in the normal and intermediate range.

Our cohort comprises 36100 unrelated individuals (33781 normal alleles, 2319 intermediate alleles). *HTT* CAG repeat length was quantified using ExpansionHunter and UK Biobank MRI image-derived phenotypes were used to estimate the relevant brain volumes. We investigate the relationship between *HTT* CAG repeat length and both subcortical and global brain volumes using a linear regression model with appropriate covariates.

Increasing CAG repeat length was significantly associated with reduced brain volume in the nucleus accumbens, thalamus, hippocampus, total subcortical grey matter and total grey and white matter. These associations were largely driven by older individuals in our cohort. This work provides the first evidence in a population cohort for an association between *HTT* CAG repeat length and altered brain volume for individuals with normal and intermediate alleles.

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(17) Non-invasive prenatal testing can detect maternally and paternally inherited variants in the KCNJ11 and ABCC8 genes: An opportunity for targeted treatment in utero

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INTRODUCTION

Activating variants in *KCNJ11* and *ABCC8* cause low birth weight, neonatal diabetes (NDM) and neurodevelopmental disorders. NIPT could bring clinical benefit for affected families because confirming foetal genotype can inform postnatal surveillance and enable early identification and appropriate treatment of diabetes. For maternally inherited variants, there is an opportunity to utilise placental transfer of glibenclamide to improve foetal growth and neurodevelopment by providing targeted treatment *in utero.*

AIM

To assess the feasibility of NIPT for NDM caused by maternally and paternally inherited variants in *KCNJ11* and *ABCC8.*

METHODS

A droplet digital polymerase chain reaction assay was used to detect the presence of a familial variant in the cell-free circulating DNA (cfDNA) extracted from maternal plasma samples taken between 12-35 weeks' gestation of at-risk pregnancies.

RESULTS

Nine at-risk pregnancies were identified from 5 families. Assays could be designed for 4 of the 5 different *KCNJ11/ABCC8* variants, enabling NIPT for 8/9 pregnancies. Testing of cfDNA from 7 pregnancies was undertaken which confirmed that 4/7 offspring had inherited the familial variant (3 maternal and 1 paternal) and were at high-risk of NDM. For maternally inherited variants, results were confirmed using a cord blood sample. Testing is ongoing for the one remaining pregnancy.

CONCLUSIONS

Our data support the feasibility of NIPT to determine foetal genotype in NDM-related pregnancies, for maternally and paternally inherited *ABCC8* and *KCNJ11* variants. Further research will explore pregnancy management and clinical outcomes, including the effects of *in utero* sulphonylurea treatment on growth and neurodevelopment in those with maternally inherited variants.

(18) An Update on the Generation Study

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The Generation Study (GS) is an NHS-embedded research study being delivered by Genomics England. The GS aims to explore the feasibility, acceptability and impact of genomic newborn screening (gNBS). The GS was developed over a two year period during which extensive stakeholder engagement contributed to the co-design of the study. The goal is to recruit 100,000 newborns.

The GS began recruiting participants in March 2024. Parental consent is recorded during pregnancy and a sample is taken after birth. Participants' genomes are sequenced using short read sequencing technology. gNBS is carried out via a custom built bioinformatic pipeline. Newborns are screened for more than 200 rare genetic conditions. All conditions have a treatment or intervention available through the NHS in England which is likely to improve outcomes for the affected individual. 'Condition suspected' results are returned to the family by an NHS paediatrician with relevant subspecialty expertise who will facilitate confirmatory testing and ongoing care within the NHS.

An interim update will be provided on the Generation Study. This will cover recruitment including numbers and locations of recruiting maternity units and overall recruitment and sampling numbers. The talk will also cover insights on how the bioinformatic pipeline has been functioning to identify condition suspected results and the impact on seconded NHS clinical scientists. An interim update on results will cover the proportion of condition suspected results and focus on the return of these results, the outcomes of confirmatory testing and early experience handling these results.

(19) Neonatal Central Apnoea presenting feature of an underlying genetic condition

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Case 1: Term baby born to non-consanguineous parents, presented with persistent hypoventilation and hypercapnia requiring non-invasive ventilation. Septic screens, echocardiogram, cranial ultrasound and MRI head were normal. Initial plan for central hypoventilation panel, however examination noted thumb abduction and micrognathia and syndromic cause was suspected. R14: homozygous pathogenic MADD frameshift variant.

Case 2: 1 month-old with central apnoea requiring ventilation, ventriculomegaly, and short bones antenatally. Family history of consanguinity. MRI head: subdural haemorrhages. Examination: subtle hand skeletal features and squint. R14: Homozygous KIAA0753 variant consistent with KIAA0753-related ciliopathy. MRI head re-review: probably vermian hypoplasia, Molar-tooth sign, corpus callosum thinning suggestive of Joubert syndrome.

Cases 1&2 highlight subtle dysmorphic features detected by Clinical Genetics can aid diagnosis.

Case 3: Preterm with recurrent apnoeas requiring ventilation, hypospadias, bilateral undescended testes, laryngomalacia, hypogammaglobinaemia, mixed hearing loss. MRI head: suggestive of tubulinopathy. ArrayCGH: Mosaic ring 18 chromosome with loss of information on 18pa and 18q, including TCF4.

Case 4: Prolonged significant apnoeas from early infancy. Myelomeningocoele detected in postnatal period (surgically repaired), Arnold Chiari-2 malformation (resolved post-surgery). Although, Neural-tube defects (NTD) are associated with central apnoeas, this was particularly severe and alternative diagnoses were considered. Despite comprehensive genetic testing, no genetic cause was identified. Apnoeas secondary to NTD. This case highlights the importance of distinguishing between genetic and non-genetic (secondary to brain malformation) apnoeas for best use of genetic resources and investigations.

(20) Cardiac involvement in MYO6: what should we advise patients?

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MYO6 variants are a known cause of inherited deafness, but prevalence has not been estimated.

Mohiddin et. al. reported one large pedigree where some individuals with *MYO6* c.737A>G p.His246Arg had hypertrophic cardiomyopathy (HCM), QT prolongation and/or deafness. Detailed genomic testing for cardiac phenotypes was not undertaken. This report, along with mouse model data, potentially implicated *MYO6* in prolonged QT syndrome and HCM.

England-wide R67 deafness testing is undertaken in Manchester and London. Through this, 38 probands were identified with *MYO6*-related deafness and sufficient clinical data regarding cardiac phenotype.

Results:
1. Pedigrees were consistent with multi-generational autosomal dominant inheritance of deafness
2. No aggregation of cardiac problems was apparent in extended family pedigrees
3. No individual with *MYO6*-related deafness had known cardiac involvement
4. Laboratory reports varied in whether recommendations about cardiac evaluation were made

This is the largest series of patients with *MYO6* variants reported to date. The absence of any identified cardiac problems in this cohort suggests *MYO6* variants associated with deafness do not confer a substantial risk of cardiac pathology and that no additional screening is warranted.

Evidence from cardiac cohorts is also not supportive of *MYO6* variants predisposing to HCM or other heart pathology, suggesting there is no true clinicopathological association This is reflected in its 'red' PanelApp classification for HCM. Further evaluation in additional cohorts, those with deafness and those with cardiac pathology, could be beneficial.

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Meeting Feedback

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