EDITORIAL

2023 in the European Journal of Human Genetics

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Let us open 2024 with a review of what was published in the European Journal of Human Genetics in the calendar year 2023. Our impact factor remained stable at 5.2, while the citescore of European Journal of Human Genetics rose to 9.1 and the journal is ranked 11th in the category of Clinical Genetics.

January 2023 opened the year with a range of clinically useful papers. Van der Sanden et al examined the role of genome sequencing as a first line test for neurodevelopmental disorders [1]. They found a limited diagnostic uplift from genome sequencing compared to exome sequencing, but that genome sequencing was better able to identify copy number variants. Genome sequencing can also detect short tandem repeats (which exome sequencing struggles to), Rafehi and colleagues report an unexpected diagnosis of myotonic dystrophy type 1 using this technology [2]. Identifying a genetic cause for a persons illness is a technical challenge; asking them to share the information with relatives is a clinical one. Young et al report a systematic review of interventions to encourage BRCA variant carriers to share information with their relatives [3].

With the increasing profusion and complexity of genomics tests, clinical guidelines are needed more than ever. In February 2023, Mavraki et al report guidance for diagnosis of mitochondrial disease [4]. The key principle being a shift from "biopsy first" toward genome sequencing of blood or urine derived DNA. An increasing number of rare genetic conditions are "treatable". Short stature associated with PRMT7 variants may respond to growth hormone [5]. Genome sequencing is the available first line genome test in the UK National Health Service; but Hocking et al provide further evidence that the increased cost does not perhaps result in an increased diagnostic yield [6]. Using genomic testing in post-natal settings is well established, but its use prenatally is controversial. In structurally normal foetus's, exome sequencing identified pathogenic variants in under 1% of cases and also secondary findings in 2 cases [7]. Part of the issues with interpreting genome variants is understanding their clinical effect. Interestingly, pathogenic variants causing epilepsy are found in the general population and associated with neurological and psychiatric conditions [8].

Genomic testing is being evaluated for use in population screening programs. A review by Alarcón Garavito et al identified factors critical to success of such endeavours [9]. Exome and genome sequencing remain critical to diagnosis of rare disease, and identification of novel genomic causes. In March 2023, Luppe et al reported mono- and bi-allelic variants in STX1A as causing a novel neurodevelopmental disorder [10]. Genome sequencing identified that copy number variants of FGF14 underlie a condition of early onset nystagmus and variable ataxia [11] while ARHGAP35 was identified as causing a range of anterior chamber malformations [12].

In April 2023, REST variants were identified as the cause of Jones syndrome (a dominant syndrome characterised by gingival fibromatosis and hearing loss) [13]. An affected father, and 2 children, underwent exome sequencing. A loss of function REST variant segregated. There may be genotype-phenotype correlations; some REST variants causing Jones syndrome and others isolated hearing loss. LARS2 variants provide a further example of phenotypic variability - being reported here to cause isolated ovarian insufficiency without hearing loss [14]. CHEK2 bi-allelic variants were described as a novel condition with chromosome instability; with phenotypic variability in the form of cancer predisposition in heterozygous carriers [15].

The May 2023 edition reminded us that technological innovations drive improvements in diagnosis in clinical genetics. In 2 families with a clinical diagnosis of duchenne muscular dystrophy no causal variant was found with conventional testing [16]. Long read sequencing identified large inversions in the dystrophin gene. This pipeline could be used in clinical practice. Dixon et al report the use of nanopore sequencing to describe the heterogeneity of structural variants in breast cancer susceptibility genes [17]. Rayani et al compared a range of in silico tools to aid with diagnosis of splice site variants in cardiogenetic disease [18]. Francis and colleagues report that saliva samples can have greater diagnostic yield for detection of mosaic copy number variants than blood [19]. Innovation does not always have to be expensive!

The June 2023 issue focussed on papers describing novel disease genes or disease-gene associations. Isolated midline craniosynotsosis is not typically felt to be "genetic". Di Rocco et al provide evidence of an association with a number of genes and this phenotype, especially SMAD6 [20]. DCAF13 bi-allelic variants were identified as a novel cause of a neuromuscular disorder [21]. When novel disease-gene associations are identified, follow up papers are vital to define the clinical features and inform management. For example, Amenta et al identify genotype-phenotype correlations in CHAMP1 variant carriers [22]. Single gene variants may be associated with a range of rare disease presentations; however the role of genetic modifiers is vital. Flanigan et al report a genome wide association study that identifies putative genomic loci modifying age of loss of ambulation in Duchenne muscular dystrophy [23].

Diagnosing and managing rare disease requires specialist expertise. Often this is best done in centralised clinics. The benefits are the accrual of experience and knowledge. For example, Bowen and colleagues provide an insight into care of monogenic forms of Ehlers-Danlos syndrome [24]. Specialist skills are increasingly needed for variant identification. Mobile element insertions cannot be detected with standard clinical pipelines; Garret et al identify 2 cases in exome data that might explain the clinical presentation [25]. Deep understanding of unusual phenotypes is also crucial for rare disease diagnosis. Singh et al demonstrate the variable auditory features of POU4F3 associated deafness [26]. In addition, functional validation is important for clinical diagnosis. Vaché et al confirm HOMER2 as a deafness gene using RNA analysis and a zebrafish model [27].

Throughout 2023 EJHG published several novel disease-gene associations. Hedberg-Oldfors report RNH1 deficiency as a novel cause of a neurodevelopmental condition [28]. With a phenotype of infection induced regression. Desroziers et al describe hypomorphic variants in SFTB in pulmonary fibrosis [29]. EFCAB7 variants were reported in a novel cause of polydactyly (Bilal et al. [30]). Ronchi and colleagues described a neonatal phenotype of COX18 variants [31]. AGPAT3 was described as a novel cause of intellectual disability and retinitis pigmentosa [32].

On the laboratory side of things, genomic reanalysis and DNA methylation studies emerged as key developments. Li and colleagues report that reanalysis of exome data for a the missing second variant in recessive genes can aid diagnosis [33]. Reanalysis of exome data 5-years after initial reporting resulted in an 18% diagnostic uplift (Bartolomaeus et al. [34]). DNA episignatures are well established to define variant pathogenicity for an increasing range of genes. Oexle report epigenetic effects of mosaic variants and hypomorphic variants [35]. EJHG reported emerging DNA methylation signatures for HNRNPU variants [36] and Renpenning syndrome [37].

Our journal could not function without the hard work of our section editors and editorial board. It is fitting to ask them for their highlight papers from 2023.

Dr Magdalena Mroczek selected: "Skewed X-chromosome inactivation in unsolved neurodevelopmental disease cases can guide re-evaluation for X-linked genes" [38].

"The authors present a series of examples of how the reanalysis of exome sequencing data after XCI skewing testing may target a diagnosis to the X-linked genes in a cohort of NDD with an intellectual disability, autism spectrum disorders and complex syndromic cases with facial dysmorphism. In a cohort of 92 affected females, and 189 mothers of affected males undiagnosed, the authors were able to solve 25% (7/28 cases) of extremely unbalanced (> 90%) XCI skewing. These seven variants were missed because the variant was not consistent with X-linked segregation, the variant was a structural rearrangement or the gene was not associated with NDD at the time of the first ES analysis. XCI testing was shown to be a cost-effective and efficient method for re-analysis of exome data."

Dr Angela Peron selected "Episignatures in practice: independent evaluation of published episignatures for the molecular diagnostics of ten neurodevelopmental disorders, by Thomas Husson et al." [39].

"Episignatures have become one of the most popular areas of research in the last five years, and an increasing number of episignatures have been recently discovered. Most data were generated by the first group who discovered this new technique, and an unbiased evaluation was needed. This study provides this independent evaluation, with appropriate methods and interesting results that are extremely useful for clinical practice."

Dr Orsetta Zuffardi selected Oxele et al. [35]:

"The authors were able to increase the sensitivity of the episignature-classifiers by 30%, giving novel insights. Indeed, they demonstrate that both hypomorphic variants and mosaics can lead to minimal alterations of genome methylation which are associated with relatively mild phenotypes or late-onset focal diseases such as late-onset focal dystonia. The finding by the re-trained classifiers of episignature's alteration in persons with no or late-onset (mean = 26 years) dystonia, highlights the possibility that at least for KMT2B, even moderate deficiency has a causative role in a set of patients, with effects also depending on polygenic inheritance. Oexle et al data confirm that DNA methylation analysis is indispensable to increase the diagnostic performance of unresolved cases and predict VUS pathogenicity."

Dr Reuben Pengelly chose "I am not a number!" Opinions and preferences of people with intellectual disability about genetic healthcare [40].

"This paper highlights ID patient views on their care, particularly important now large cohort studies are the norm in medical genomics, making it more necessary that we return to patient views of what they need."

Prof Angus Clarke also highlighted the above paper as being of special value.

Dr Patrick Benusiglio chose "Clinical case study meets population cohort: identification of a BRCA1 pathogenic founder variant in Orcadians" by Kerr et al. [41].

"The authors identified a founder pathogenic variant in BRCA1 among people of Orcadian ancestry (Orkney, Northern Isles of Scotland, UK), using complementary approaches. This study is an example to follow for those exploring founder variants associated with common diseases."

Prof Claire Morgan selected "Knowledge, attitudes and decision regret: a longitudinal survey study of participants offered genome sequencing in the 100,000 Genomes Project" [42], commenting:

"I have chosen the above article because in the early stages of the project, it was heralded as "pioneering", and a "flagship project" to raise the profile of genomics and "transform the NHS". Patient confidentiality and anonymity appeared to be the primary concern of participants during initial recruitment. It is interesting that now, just over 10 years' time this article explores the psychological impact of the 100,000 genome project participants, highlighting that some individuals had a high level of regret in participating, concluding the need to identify patients' level of understanding and expectations around genomic sequencing given how mainstream genome sequencing is becoming."

Alisdair McNeill[1,2] ✉
[1]Division of Neuroscience and Neuroscience Institute, The University of Sheffield, Sheffield, UK. [2]Sheffield Clinical Genetics Service, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK.
✉email: a.mcneill@sheffield.ac.uk

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The author declares no competing interests.