EDITORIAL

The value of exomes across the ages

European Journal of Human Genetics (2023) 31:129–130; https://doi.org/10.1038/s41431-023-01281-4

In this issue, Mavraki et al. present an updated set of UK guidelines for genetic diagnosis of mitochondrial disease [1]. Primary mitochondrial disease is a diverse group of neurometabolic disorders characterised by impaired oxidative phosphorylation. It may affect isolated or multiple organ systems and is associated with significant morbidity and mortality. Mitochondrial disorders are challenging to diagnose due to clinical and genetic heterogeneity. Next-generation sequencing technologies have facilitated the diagnosis of many cases by increasing sensitivity compared to targeted common pathogenic mtDNA variant testing. There are two main alternative approaches/strategies for genetic testing of patients with suspected mitochondrial disease: targeted testing and whole genome sequencing. mtDNA testing is typically undertaken early in the diagnostic pathway via analysis of blood and/or urine DNA, but muscle biopsy may be required for certain genetic diagnoses. Nuclear gene testing in a proband with suspected mitochondrial disease may be appropriate. This testing may be single gene based, gene panel based, or gene-agnostic WGS/WES, and may be appropriate as a first-line test or as an additional test for other referrals with a strong clinical suspicion. Testing of asymptomatic children with a family history of mtDNA-related mitochondrial disease is particularly challenging and routine practice in the UK is not to test these children.

Carriers of pathogenic variants in BRCA1 have a six-fold increase in breast cancer risk and a 30-fold increase in ovarian cancer risk, but penetrance is incomplete and age at cancer diagnosis varies. Studies to identify modifier genes have been ongoing since the early 2000's, largely through the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). VNTRs may plausibly account for some of the missing genetic risk, but a genome-wide investigation has been hampered by technical difficulties. Ding et al identified eight VNTRs associated with risk of developing breast cancer in women carrying the 185delAG BRCA1 PV, and another four VNTRs associated with risk of developing invasive breast cancer [2].

Daum et al. aimed to determine the incremental yield of exome sequencing (ES) in the prenatal setting [3]. From February 2017 to April 2022, 1526 fetuses were subjected to ES; 482 of them were structurally normal (31.6%). Four fetuses (4/482; 0.8%) had P/LP variants indicating a moderate to severe disease in ATP7B, NR2E3, SPRED1 and FGFR3, causing Wilson disease, Enhanced S-cone syndrome, Legius and Muenke syndromes, respectively. In a linked editorial, Boardman and Horn comment on the complex ethical and social issues of prenatal ES [4].

In the postnatal setting, reverse phenotyping of developmental disorders diagnosed via ES provides valuable clinical information [5]. Wong et al describe the developmental profile of CDKL5 syndrome [6]. The study of 350 people with a CDKL5 variant helps define age of acquisition of milestones and potential genotype-phenotype correlations. Cantu syndrome is characterised by hypertrichosis, osteochondrodysplasia and cardiomegaly. Gao et al. describe a patient with Cantu syndrome who presented initially with lymphoedema, formally diagnosed after ES, functional studies and reverse phenotyping [7]. Very few people with PRMT7 associated syndrome have been reported in the literature. Rodari et al. report in this issue a potential response to Growth hormone in PRMT7 variant carriers [8]. A novel case series of people with KDM5C variants identifies a mosaic individual, 13 novel variants and confirms disturbed sleep as an important clinical feature [9].

ES is an established clinical test for the diagnosis of rare genetic disorders. The American College of Medical Genetics recommends reporting pathogenic variants for 56 genes as secondary findings (SF), but the European Society of Human Genetics advocates for a cautious approach. Despite the ongoing debate of scientific societies, several studies have shown that SFs are highly accepted among participants of ES studies. Although factors such as non-European ancestry, professional providing consent and anticipatory regret may influence the decision, actual acceptance rates may vary in clinical situations. In a clinical setting in a tertiary hospital in Spain, 90% of patients with rare disorders opted to receive SFs, although differences among studies made direct comparisons difficult [10]. The study highlights the difficulty of conveying the implications of receiving SFs and the difficulty of engaging the patient in the discussion. 27 pathogenic or likely pathogenic variants were identified in 27 individuals, with an SF prevalence of 3.6%. The most common disorders were long QT syndrome, arrythmogenic cardiomyopathy, hereditary breast and ovarian cancer and Lynch syndrome.

Hocking et al. report the value of genome sequencing with panel based analysis in Scotland [11]. Although genome sequencing is now well established in research, evaluation of its advantages and disadvantages in the context of routine care is required to inform healthcare funding decisions. In Scotland, the NHS offers clinical ES for specified disease gene indications. This paper reviews the diagnostic yield of genome sequencing in the NHS Scotland setting, and discusses the economic evaluation of genome sequencing. 394 eligible probands consented with 605 co-recruited family members, of which 258 (66%) were recruited with family members. Sixty-nine relatives (11% of the co-recruited family members) had the same rare condition as the proband. In 72/264 families, a new diagnosis was made that fully explained the phenotype. In 320 families, a further 16 diagnoses were made that fully explained the phenotype, and in 286 families, the molecular basis of the phenotype remains unidentified. SGP successfully performed clinical genome sequencing for a diverse group of rare phenotype patients using the 100,000 Genomes Project data analysis pipeline, obtaining new diagnoses for 23% of cases where previous genetic testing had previously failed to identify a cause.

Genomic tests can have value in common diseases. Monogenic conditions can cause or predispose to stroke, but they have been difficult to diagnose because of still incomplete knowledge on how monogenic mechanisms are related to disease. Massively parallel sequencing methods have led to the discovery of more and more gene-disease associations. Ilinca et al. identified 168 new stroke-genes and 72 new stroke-genes that were associated with vascular

malformations, metabolic phenotypes, and stroke severity [12]. Three genes previously considered suitable for clinical screening were now only recommended for research, whereas 10 other stroke-genes were strengthened and now fulfill the criteria for clinical testing. Smuk et al. report novel phenotypic insights from genome sequencing of epilepsy genes [13] and Boonsimma et al. treatment implications from exome testing in epilepsy [14].

Does genome sequencing have any value in archaeology? This paper by Jackson et al. suggests so [15]. Two adult male individuals buried in a Medieval graveyard at Ballyhanna, near the town of Ballyshannon in Co. Donegal, Ireland, displayed multiple bony tumours suggestive of multiple osteochondromas, a rare, autosomal dominant bone condition. An unbiased genome-wide approach involving shotgun sequencing and ancient DNA protocols to identify likely causative mutations in EXT1. Only one mutation in each individual had the level of support required by the American College of Medical Genetics guidelines to classify them as pathogenic. To date, only a few historical samples have been used to identify causal Mendelian lesions, and none have been studied with a genome-wide approach, suggesting that this technique might be of value in future research in this setting.

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

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AUTHOR CONTRIBUTIONS

AM wrote and proof read this paper.

FUNDING

There are no financial or other competing interests.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Alisdair McNeill.

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