EDITORIAL

Solving medical mysteries with genomics

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In this month's issue of the European Journal of Human Genetics, genomic technologies solve some medical mysteries. Traverso and colleagues identify heterozygous loss of function variants in DAG1 as the cause of undiagnosed, isolated hyperCKaemia [1]. Previously bi-allelic DAG1 variants were found in severe myopathy cases and muscle-eye-brain disease. This paper adds a further gene that can cause both dominant and recessive diseases. Gustavson syndrome was first reported in 1993, being associated with X-linked intellectual disability and early death. Genome sequencing identified in-frame deletions in RBMX as the cause, with skewed X-inactivation in female carriers [2]. The mechanism proposed to be disruption of RNA polymerase II transcription. A team from the University of Antwerp report a paper describing the identification of the gene for the MRX20 family [3]. Exome sequencing identified a loss of function variant in DLG3; a known intellectual disability gene. RNA sequencing on patient derived lymphoid cells identified pathways dysregulated by DLG3 loss of function. Bradley et al. report novel endocrine phenotypes associated with SIN3A variants [4]. Exome and genome sequencing identified further patients with TCEAL1 variants [5]. Adult patients had novel phenotypes including hyperphagia and endocrinopathies.

Of course, identification of a sequence variant in a gene does not prove causality for a given medical condition. Episignatures have emerged as a valuable "functional" assay to aid variant classification. In this issue, a diagnostic episignature (using the illumina EPIC array) for Koolen-de Vries syndrome is reported [6]. This may have diagnostic utility for variants of uncertain significance.

Some genes have parent of origin effects. In this issue a novel case of Wilm's tumour (nephroblastoma) with a paternally inherited TRIM28 variant raises important issues for clinical counselling [7].

Genomic technologies have the ability to diagnose the cause of a person's medical condition and also provide information about their future health. For example, receiving additional findings from non-invasive prenatal testing is reported as being associated with psychological distress [8]. Tiller and colleagues report on the Australian publics' perspective on genetic discrimination when seeking life insurance [9]. The Australian public overwhelmingly reported that genetic discrimination by insurers should not be allowed. Most participants in the paper supported legislation to prevent genetic discrimination by insurers. Creation of large genomic datasets is vital for both research and certain aspects of genomic medicine. Clearly, information governance is critical to secure genome sequencing datasets. A study of members of the Australian public identified that data security was the major concern about such datasets - with a desire for control over whom could access an individual's genomic data [10]. Large genomics datasets help identify genomic markers that predict response to medications, including potential adverse effects. Beunk and colleagues describe a Dutch guideline for gene-drug interactions and antipsychotic medications [11]. The UK biobank is used by Langlois et al. to explore the link between CYP2A6 structural variants and lung or ovarian malignancy [12]. Such studies would not be possible without participants donating their DNA and data. Mize and Evans describe a novel, tissue based method for assigning SNP effects in heritable traits to genes [13].

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AUTHOR CONTRIBUTIONS

AM conceived and wrote this article.

COMPETING INTERESTS

The authors declare no competing interests.