EDITORIAL

Genomics elucidates both common and rare disease aetiology

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Welcome to the final issue of European Journal of Human Genetics for 2021. We close the year with a range of interesting and informative papers. Birth defects (congenital anomalies) affect many thousands of neonates every year; yet the aetiology of many of them remains unresolved. Schreiner et al review what is known about the genomic basis of congenital diaphragmatic hernia (CDH) [1]. Around 10% of cases of CDH are associated with a copy number variant. Implicated pathways include NRF2 and vitamin A homeostasis. In contrast to common malformations, the genetic basis of rare disease continues to be elucidated with more and more causal genes identified annually [2–4]. Guo and colleagues identify variants in SLIRP as a novel cause of mitochondrial disease [5]. In this issue, variants in IMPDH2 are associated with dystonia in a large family [6]; IMPDH2 acts in the dopamine synthesis pathway previously implicated in the aetiology of dystonia. Of course, even with modern technology there remain patients for whom a molecular genetic diagnosis remains elusive. Pham et al demonstrate that variants in DLK4 are not responsible for Silver-Russell-Syndrome [7].

Kawasaki disease is a paediatric vasculitis with a risk of coronary artery involvement. In this month's EJHG Hoggart et al identify a potential genetic risk factor for coronary artery involvement in Kawasaki disease [8]. For many genetic diseases, little is known about population epidemiology. In a study of malignant hyperthermia gene variants in Iceland, it was estimated that 1/1450 Icelanders carry an actionable variant in a malignant hyperthermia gene [9]. Keratoconus (defined as non-inflammatory corneal ectasia) is of uncertain aetiology. Fransen et al identify a shared genetic link between keratoconus and the connective tissue disease Ehlers-Danlos syndrome [10]. Male factor infertility is frequently of unknown aetiology. Arafat and colleagues identify variants in *GCNA* in association with low sperm count and impared sperm motility [11].

Not all (rare) disease is monogenic (that is explained by variants in a single gene). In an Indian study, 14 families with clinical phenotypes associated with causal variants in more than one mendelian disease gene are reported [12]. The clinical consequences were described as blended phenotypes, a mild phenotype from gene A being obscured by a severe phenotype from gene B or 2 distinct phenotypes in the same patient. Undoubtedly such multilocus variation has the potential to contribute to phenotype variability in genetic diseases. Sharing information on pathogenic gene variants is crucial to help clinical reporting. The updated LOVD3 platform provides one mechanism for doing so [13].

All genomics research must be ethically approved and adhere to conditions set by the relevant committees. But do research ethics committees have sufficient understanding to review and grant permission for ethically robust genomics research? A study of Australian research ethics committees highlights a potential need for extra training for committee members [14].

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AUTHOR CONTRIBUTIONS

Alisdair mcneill conceptualised and wrote this article.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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