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EDITORIAL

Deep phenotyping and population-level data can help resolve genomic variants

Expanded carrier screening involves simultaneously screening for hundreds of recessive conditions. This enables carrier screening across multiple different ancestral groups; rather than screening for recessive disorders prevalent in particular populations. A qualitative interview study of consanguineous couples found that they valued expanded carrier screening—it enabled informed reproductive decision making and they felt they were able to take responsibility for the health of their child [1]. The authors emphasise the information required for fully informed consent to such screening. On the topic of consent to genomic testing, Biasiotto et al. consider the ethical issues around recall by genotype biobank studies and consent issues [2].

As ever, rare conditions are a major focus of EJHG this month. Oppermann et al. define the phenotype associated with CUX1 disease-causing variants [3]. Affected individuals had combinations of intellectual disability, muscular hypotonia and seizures. Some individuals had normal functioning as adults. In CUX1 heterozygous mice, levels of CUX1 transcript and protein were reduced in the brain. Mulligan and Bicknell review the role of nELAVL in neurodevelopmental conditions [4]. Molecular mechanisms and models of phenotypes associated with nELAVL dysfunction are reviewed. The epidemiology of rare conditions remains an open area of study. Reynolds et al. identified all known cases of Pik3ca-related overgrowth syndrome in Piedmont over 25 years to define incidence [5]. Amelogenesis imperfecta is associated with deficient tooth mineralisation. In this issue, novel cases of RELT-associated amelogenisis imperfecta are reported, with identification of novel genetic variants [6]. Bilal et al. report bi-allelic variants in EFCAB7 as a novel cause of non-syndromic polydactyly [7].

BAP1 is a recognised tumour suppressor gene. Autosomal dominant BAP1 tumour predisposition syndrome increases the risk of uveal melanoma, mesothelioma, renal cell carcinoma and non malignant skin tumours. Lifetime tumour risk is 85%. Lalloo et al. propose tumour surveillance guidelines [8]. Imaging surveillance for renal cell carcinoma is one suggestion. Much remains to be learned about cancer predisposition genes. Corso et al. provide strong evidence that BRCA1 increases the risk of metaplastic breast cancer [9].

Nemaline myopathy is defined by rod bodies pathologically and is genetically heterogenous. Classification of potentially causal variants is complex. Reclassification of missense variants reclassified almost 30% from pathogenic to variants of uncertain significance [10]. In addition to classification, identification of the causal gene can be a barrier to genomic diagnosis. Giovenino et al. used skewed x-inactivation to help target sequencing in people with unsolved disorders [11]. By identifying skewed x-inactivation in mothers of boys with neurodevelopmental conditions they focussed exome sequencing analysis to identify the causal variants.

One of the goals of genomic medicine is to facilitate precision medicine. Polygenic risk scores can help identify people at higher risk of certain diseases, to target for preventative treatment. A survey of North American primary care doctors revealed general support of the use of polygenic risk scores to help identify people for enhanced screening measures [12]. Costs and potential for discrimination were listed as barriers. A novel use of polygenic risk score type data is KIT-GENIE [13]. This is a French genetic biobank of kidney transplantation, which will facilitate study of genomic factors that influence transplant success. Boulogne et al. report KidneyNetwork; a database of kidney-expressed genes, to try and improve identification of novel genomic causes of kidney disease [14]. Deep phenotyping is often needed to help interpret genomic variants. For example, cardiac MRI can help distinguish between different genetic forms of cardiomyopathy [15].

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