EDITORIAL

Unusual genomic variants require unusual analyses

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Many rare disease patients remain without a genomic diagnosis after exome or genome sequencing. Mobile elements are a variant class that is usually not reported in clinical reporting pipelines. During retrotransposition, mobile elements duplicate their targeted region while inserting, this can duplicate or delete genes. It is estimated that around 0.3% of all human genetic diseases are due to de novo mobile element insertions. Garret et al. use a package called MELT to identify mobile element insertions in exome sequencing data [1]. Only 2 additional diagnoses were made using this, confirming the relatively low contribution of mobile elements to genetic disease pathogenesis.

Other novel variant classes can also prove difficult to detect on clinical exome sequencing. Vaché et al. report a non-stop variant in HOMER2 in autosomal dominant deafness. The genomic variant turned a stop codon into a tryptophan [2]. This predicted elongation was confirmed using RNA studies. A zebrafish model of the HOMER2 variant demonstrated altered acoustic startle response, supportive of pathogenicity. The presence of unusual variant classes must be considered in clinical exome and genome reporting. In hearing loss, the correct ascertainment of affected family members can also limit identification of causal genes. In this issue, deep auditory phenotyping was performed in a large family, which assisted in the identification of a POU4F3 pathogenic variant [3]. This study also emphasised the heterogeneity in age of onset and severity of hearing loss associated with this gene. Deep intronic variants are also elusive on exome sequencing. Bozsik et al. used genome sequencing to find a novel variant in APC in an intron [4].

The most common reason for a negative genomic test result is that the causal gene was not sequenced or reported on the panel. In 225 patients with dilated cardiomyopathy and a negative 48-gene panel, an expanded 299-gene panel was found to increase the rate of diagnosis [5]. However, the use of this larger panel was associated with an increased rate of VUS detection, but not of detection of causal variants.

Atrial fibrillation is perhaps one of the most common cardiac conditions in the general population. Until recently it was not felt that genomic testing was of value in this population. Chalazan et al. focussed on people with early onset atrial fibrillation (<60 years old) and no clear environmental risk factors [6]. Utilising exome sequencing they identified a pathogenic or likely pathogenic variant in 3%. Variants were found in genes previously linked to atrial fibrillation and also in cardiomyopathy genes.

Short tandem repeats (STRs) can be difficult to map to the reference genome using short read sequencing. Long read sequencing has enabled the mapping of many previously unlocalised STRs. Hadar et al. use the T2T reference genome to map all known STRs, demonstrating that the T2T reference genome doubles the number of known STRs compared to previous short read reference genomes [7]. They present their findings in a database known as STRavinsky.

Amino terminal acetylation is an important protein modification. Multiple genes regulate the process. Variants in NAA10 and NAA15 have been associated with neurodevelopmental disorders, but the phenotypes are incompletely defined. In keeping with the X-linked condition, males with NAA10 had a much more severe cardiac phenotype [8]. It was observed that cognitive function was generally higher in males with frameshift NAA10 variants than missense NAA10 variants. Developmental delay and intellectual disability was generally more severe in people with NAA15 variants. There was no facial dysmorphism to separate NAA10 and NAA15 patients. Ocular manifestations were more common in people with NAA10 than NAA15 variants.

Variants in several members of the RHO GTPase superfamily have been implicated in human neurodevelopmental diseases. Priolo et al. report 2 novel variants in RAC1 associated neurodevelopmental disorder [9]. Extensive cell biology studies were undertaken to demonstrate a gain-of-function mechanism. Clinical findings are compared with 8 previously reported cases to describe facial dysmorphism, neurodevelopmental features and a high incidence of congenital heart disease.

Morison et al. deep phenotype speech, language and communication in CDK13 disorder. Childhood apraxia of speech was common [10]. Most required a communication aid in early childhood. Speech production was found to be the most significantly impaired with relative preservation of social motivation. They emphasise the importance of detailed analysis/diagnosis of communication in children with neurodevelopmental conditions rather than just a blanket diagnosis of speech delay.

Large study cohorts are required to produce statistically significant and robust findings. By definition, this is challenging in rare diseases. Bowen et al. report findings from 180 people affected by vascular Ehlers-Danlos syndrome [11]. They demonstrate that outcomes are improved by early diagnosis allowing appropriate management.

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ADDITIONAL INFORMATION
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