EDITORIAL

Using exomes better

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Biochemical newborn screening for treatable metabolic disorders is well established. Many countries are now exploring the use of genome sequencing to identify a broader range of genetic conditions. Alongside technical aspects, the views of families are crucial in establishing such screening programs. In a survey of Slovenian mothers, a generally positive and supportive attitude towards genomic newborn screening was identified [1]. Respondents did also recognise negative impacts of genomic diagnoses being established in this way. In this issue, Di Carlo et al. also report parents attitudes towards genome screening research projects involving their healthy children [2]. Parents expected medically actionable results to be returned to them and recognised potential need for treatments and interventions.

Genome wide studies of general populations can help us understand multifactorial disease mechanisms. In Greenlanders, 11 genome wide signals explained 16% of variance in blood lipid levels [3]. This suggested that genetic factors influencing blood lipid levels in Europeans differs from Greenlanders. Norland et al. report an improved method for developing polygenic risk scores for prediction of coronary heart disease [4].

DNA episignatures associated with a range of genomic conditions have been identified in numerous research studies. The performance of episignatures in routine clinical diagnostics is less well established. Husson et al. report a replication study of DNA methylation signatures in 10 different genes [5]. Not all episignatures performed equally well. They conclude that some episignatures are ready for clinical diagnostic use, while others are not sufficiently reliable yet.

Mobile element insertions (MEIs) are an emerging class of gene variant, contributing to human disease. Wijngaard et al. benchmark the performance of bioinformatics tools for detection of MEI, using exome data compared with genome data [6]. Tools which can reliably detect MEIs in exome data were identified. This may help increase diagnostic yield from exome sequencing data. Nonsense variants which undergo manufactured splice rescue are another class of genetic variant that can be difficult to identify and classify clinically. SpliceAI was found to predict this mechanism for under 1% of nonsense variants, these were less likely than other variants to be classified as pathogenic in ClinVar [7].

In this issue, several novel genetic causes of human disease are characterised by exome sequencing. SCN2A is reported to be a novel genetic cause of alternating hemiplegia of childhood [8]. Cahn et al. report a complex rearrangement of TBC1D4 in an individual with severe insulin resistance [9]. Al-Maawali reports additional cases of bi-allelic SV2A variants, replicating its association with a neurodevelopmental condition [10].

Integrating phenotypic information can also improve variant reporting. Lagorce and colleagues present the SOLVE-RD pipeline that integrates phenotypic similarity scores into variant interpretation [11]. This identified a plausible causal variant in 8.8% of cases.

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Paper conceived and written by AM.

COMPETING INTERESTS

The author declares no competing interests.