EDITORIAL

A new system for variant classification?

European Journal of Human Genetics (2022) 30:137–138; https://doi.org/10.1038/s41431-021-01032-3

Identifying causal genetic variants using next-generation sequencing technologies at the individual level improves healthcare, and at the population level increases our understanding of disease mechanisms. The crucial step is the ability to accurately identify those genetic variants which are causing a given disease or phenotype. In this issue, Houge and colleagues propose an "ABC" classification system to complement existing protocols [1]. A is a functional classification: is the variant predicted to alter protein function? B is a clinical classification: e.g. does the phenotype fit the gene? C is then selection of a comment to classify the variant. More efficient identification of copy number variants from genome sequencing data will also increase the accuracy of variant detection. A study in this month's EJHG suggests that combining variant callers improves copy number variant detection and may offer better breakpoint resolution than comparative genomic hybridisation [2].

In this issue, accurate variant interpretation and exome sequencing enables the reporting of novel disease phenotypes. A child with bi-allelic SOX4 variants and neurodevelopmental delay is described [3]. This is yet another example of a gene that has both heterozygous and bi-allelic variant phenotypes. Premature ovarian insufficiency (menopause before age 40) occurs in 1:100 women. The aetiology is not fully understood. Here, Tucker and colleagues use exome sequencing to identify variants in HROB and REC8 [4]. This implicates alterations to meiosis as a pathological mechanism. TP63 variants are a recognised cause of ectodermal abnormalities. Schmidt et al. describe a unique family with the striking phenotype of a split tongue and a dominantly inherited variant in the translation initiation codon [5]. Studying genetic variants in underrepresented populations is crucial, to reduce healthcare inequalities and also aid variant interpretation. A study of genetic variants causing Alkaptonuria in Russia helps expand our knowledge of pathogenic variants in this disease [6].

Of course exome sequencing can identify variants not only in genes relevant to the patient's presentation, but also in genes that might cause medical conditions such as cancer many years in the future (secondary findings). Van der Shoot and colleagues' work demonstrates that such secondary (or unsolicited) findings are rare on exome sequencing (0.58% of patients) [7]. Many of these were, however, medically actionable and disclosed to participants. Interestingly, not all of these genes were in the "ACMG-59" list of actionable secondary findings. This suggests that the list of genes for which secondary findings should be reported might need to expand. Sharing information on genetic variants within families has long been recognised as problematic. Having a genetic counsellor directly discuss genetic risk with at risk relatives was investigated in a randomised controlled trial for inherited heart disease [8]. It had no effect on increasing uptake of genetic testing. Deciding whether or not to have a genetic test is challenging for lay people. King et al describe the development of a decision aid to assist with choices around testing for carriage of recessive disease variants [9]. Similarly, Yeates et al. explore the decision making process in couples have preimplantation genetic diagnosis for inherited heart conditions [10].

Traditionally genetic testing took many months to complete. Advances in sequencing platforms and variant interpretation pipelines have now led to exome sequencing being used to diagnose acutely unwell children. Stark and Ellard review the state of the art and argue that rapid genome/exome sequencing should be the standard of care for acutely unwell children [11]. We assume that acutely unwell children will have a "serious" genetic disease, here Felicity Boardman and Corinna Clarke explore differing definitions of "serious" [12].

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AUTHOR CONTRIBUTIONS

AM conceived and wrote this editorial.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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