EDITORIAL

Advancing genomic medicine: Guidelines, risk scores, and disease discovery

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Cascade testing refers to the situation in which a pathogenic gene variant has been identified in a person, and information is then disseminated within the family to facilitate genetic counseling and testing of interested family members. Common scenarios include cascade testing for cancer risk genes to permit relatives to benefit from screening and testing, or cascade genetic counseling for gene variants that cause neurological conditions to permit predictive genetic testing.

It is widely recognized that there are several barriers to sharing genetic information within families. In this issue of the *European Journal of Human Genetics*, we publish the official European Society of Human Genetics (ESHG) guidelines on cascade genetic testing [1]. These provide practical, consensus-derived suggestions on how to approach this issue in clinical practice. Continuing on the theme of cascade testing, Pang and colleagues describe a novel model of primary and secondary care working together to facilitate cascade screening for familial hypercholesterolemia; this model involves cascade genetic testing undertaken by general practitioners [2].

Genome-wide association studies (GWAS) have identified thousands of genomic loci which modestly increase the risk of a given disease. Combining the strongest predictive SNPs creates what are known as polygenic risk scores (PRS). The use of polygenic risk scores is not yet fully accepted in clinical practice to predict disease risk or target screening. One acknowledged limitation of PRS is that they perform differently in different populations. Carmona et al. publish a repository of polygenic risk scores derived from the Spanish population, available via an easy-to-access online dataset to help interpret PRS in Spanish populations [3]. Tanha et al. report the performance of different breast cancer polygenic risk scores across large datasets derived from the UK and Australia; their findings emphasize the need for population-specific polygenic risk scores for optimal performance [4].

Understanding clinical genotype–phenotype correlations is vital to aid the interpretation of genomic clinical sequencing and provide the best advice to patients and families. Gazzin and colleagues report a large series of *RAF1*-associated Noonan syndrome, identifying genotype correlations for hypertrophic cardiomyopathy and neurodevelopmental disorders [5].

Identifying potentially pathogenic variants in human genome studies can illuminate the developmental role of uncharacterized genes. In this issue, heterozygous variants in *SRRM1* are linked to a neurodevelopmental syndrome; associated functional studies suggest a role for this gene in neural development [6]. Vissing et al. identify homozygous variants in the beta-1,3-N-acetylglucosaminyltransferase 4 gene as the cause of a novel syndrome with brain atrophy and neuromuscular features [7]. A mouse model of this condition replicated the muscle phenotype of the patient, underscoring the value of animal models in understanding human diseases.

Interpreting genomic variants across diverse cohorts remains challenging. In 2002, variants in *RP9* were proposed to be the cause of recognized retinitis pigmentosa phenotypes; in the intervening years, these variants were suggested to be artifactual. In this issue, the original research team exploits updated genomic technologies to confirm that a variant in *RP9* is a bona fide cause of retinitis pigmentosa [8]. Furthermore, while most genomic variants associated with rare diseases are found in the germline, it should be remembered that somatic DNA variants can also cause disease. In this issue, somatic "second hit" DNA variants are demonstrated in vascular malformations in hereditary hemorrhagic telangiectasia [9].

Advances in genomic technology have revolutionized the diagnosis of conditions with a genetic basis, but the importance of appropriate clinical genetic counseling should not be forgotten. Dolling and colleagues report on the ongoing and evolving support needs of parents whose children have received a diagnosis via rapid whole-genome sequencing [10].

Alisdair McNeill[1,2] ✉

[1]*Division of Neuroscience and Neuroscience Institute, The University of Sheffield, Sheffield, UK.* [2]*Sheffield Clinical Genetics Service, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK.*
✉*email: a.mcneill@sheffield.ac.uk*

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The author declares no competing interests.