EDITORIAL

No April fools in clinical genomics

European Journal of Human Genetics (2022) 30:389–390;
https://doi.org/10.1038/s41431-022-01084-z

Patient and family support groups have long been a feature of medical care. This month, Bertonazzi and colleagues report a systematic review of the effectiveness and impact of patient support groups for BRCA1 and BRCA2 variant carriers [1]. The qualitative synthesis identified that these support groups may help with decisions around risk-reducing treatments. These groups also helped provide emotional support and helped reduce feelings of isolation. What is the need for such support groups in terms of numbers of potential participants? Woodward and colleagues report a 30-year experience of cancer gene predisposition testing [2]. On average, for a range of cancer genes, they found that for each positive index case, 3.05 further cascade tests in unaffected relatives were generated. Cancer Genetics services have a clear potential to produce a large pool of people with variants in cancer predisposition genes who may need ongoing support. Some malignancies do not have a single gene in which a large proportion of causal variants are found. For example, in multiple myeloma at least 23 risk loci, with low individual penetrance, have been identified. Even when combined into a polygenic risk score, these loci only explain a fraction of the disease risk [3]. For most loci identified in Genome-Wide Association Studies, the mechanisms of disease susceptibility are unclear. A study of the 2p23.2 ER-negative breast cancer susceptibility locus identifies potential candidate genes [4]. Genotype-phenotype correlations can also help in clinical practice, Moualed and colleagues describe the effect of NF2 pathogenic variants on tumour progression [5].

In both rare diseases and cancer, correct interpretation of genetic variants is vital to safe practice. Mur and colleagues provide evidence against pathogenicity of the *POLD1* p.V295M variant [6]. *POLD1* variants in the exonuclease domain are the most frequent *POLD1* variants associated with cancer. In this study, a missense variant near the exonuclease domain was conclusively shown not to affect exonuclease activity. This has implications for variant interpretation. In vitro assays have long been used to provide evidence for genetic variant pathogenicity in research practice. Some of these are now being translated in clinical care. Assays of DNA methylation being one such example. Wang and colleagues report a blood DNA methylation signature for *ZNF711*, which is associated with non-syndromal X-linked intellectual disability [7]. Given the lack of a distinctive clinical phenotype, a distinct DNA methylation pattern helps support the classification of *ZNF711* as a distinct clinical entity.

Deciding whether or not to have a genetic test can be complicated. Ahmed reports on the use of a decision support aid for beta-thalassaemia testing [8]. It was felt by participants to be appropriate and to help with certain aspects of decision-making. It was noted that it could not help with broader issues such as feelings of stigma. Decision-making in prenatal genetic testing is an especially complicated scenario. In the month's EJHG a retrospective study of 90 pregnancies suggests that singleton exome sequencing can be diagnostically useful in such scenarios [9].

Exome sequencing remains a useful tool for variant identification, expanding our knowledge of pathogenic variants and phenotype associations. Bi-allelic variants in *SLC5A6* were previously associated with a multi-system disorder; in this issue a role for these variants in motor neuropathies is defined [10]. Previously, the role of *LMOD2* in dilated cardiomyopathy was unclear, with evidence from a single patient. Via exome sequencing, Yuen et al identify a further sibship with homozygous *LMOD2* variants providing further evidence for its role in cardiomyopathy [11]. Wade and colleagues identify deletion of the last 2 exons of *FGF10* as a novel molecular genetic cause of lacrimo-auriculo-dental-digital syndrome [12]. Such reports help in clinical classification of variants and counselling families.

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

REFERENCES

1. Bertonazzi B, Turchetti D, Godino L. Outcomes of support groups for carriers of BRCA 1/2 pathogenic variants and their relatives: a systematic review. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01044-7
2. Woodward ER, Green K, Burghel GJ, Bulman M, Clancy T, Lalloo F, et al. 30 year experience of index case identification and outcomes of cascade testing in high-risk breast and colorectal cancer predisposition genes. Eur J Hum Genet. 2021. https://doi.org/10.1038/s41431-021-01011-8
3. Canzian F, Piredda C, Macauda A, Zawirska D, Andersen NF, Nagler A, et al. A polygenic risk score for multiple myeloma risk prediction. Eur J Hum Genet. 2021. https://doi.org/10.1038/s41431-021-00986-8
4. Mendoza-Fandiño G, Lyra PCM Jr., Nepomuceno TC, Harro CM, Woods NT, Li X, et al. Two distinct mechanisms underlie estrogen-receptor-negative breast cancer susceptibility at the 2p23.2 locus. Eur J Hum Genet. 2021. https://doi.org/10.1038/s41431-021-01005-6
5. Moualed D, Wong J, Thomas O, Heal C, Saqib R, Choi C, et al. Prevalence and natural history of schwannomas in neurofibromatosis type 2 (NF2): the influence of pathogenic variants. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-021-01029-y
6. Mur P, Magraner-Pardo L, García-Mulero S, Díez-Villanueva A, Del Valle J, Ezquerro E, et al. Solving the enigma of POLD1 p.V295M as a potential cause of increased cancer risk. Eur J Hum Genet. 2021. https://doi.org/10.1038/s41431-021-00926-6
7. Wang J, Foroutan A, Richardson E, Skinner SA, Reilly J, Kerkhof J, et al. Clinical findings and a DNA methylation signature in kindreds with alterations in ZNF711. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-021-01018-1
8. Ahmed S, Jafri H, Faran M, Ahmed WN, Rashid Y, Ehsan Y, et al. Cascade screening for beta-thalassaemia in Pakistan: relatives' experiences of a decision support intervention in routine practice. Eur J Hum Genet. 2021. https://doi.org/10.1038/s41431-021-00974-y
9. Smogavec M, Gerykova Bujalkova M, Lehner R, Neesen J, Behunova J, Yerlikaya-Schatten G, et al. Singleton exome sequencing of 90 fetuses with ultrasound anomalies revealing novel disease-causing variants and genotype-phenotype correlations. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-021-01012-7

10. Holling T, Nampoothiri S, Tarhan B, Schneeberger PE, Vinayan KP, Yesodharan D, et al. Novel biallelic variants expand the SLC5A6-related phenotypic spectrum. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-021-01033-2
11. Yuen M, Worgan L, Iwanski J, Pappas CT, Joshi H, Churko JM, et al. Neonatal-lethal dilated cardiomyopathy due to a homozygous LMOD2 donor splice-site variant. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01043-8
12. Wade EM, Parthasarathy P, Mi J, Morgan T, Wollnik B, Robertson SP, et al. Deletion of the last two exons of FGF10 in a family with LADD syndrome and pulmonary acinar hypoplasia. Eur J Hum Genet. 2021. https://doi.org/10.1038/s41431-021-00902-0

AUTHOR CONTRIBUTIONS

AM conceived and wrote the article.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Alisdair McNeill.