EDITORIAL

Summer reading in EJHG

European Journal of Human Genetics (2024) 32:885–886; https://doi.org/10.1038/s41431-024-01672-1

A classical clinical genetics rule is that multiple neoplasms are suggestive of a genetic cancer predisposition syndrome. This is true of renal carcinoma. Zhang and colleagues provide a timely review of multiple primary renal neoplasms [1]. In over 60% of cases multiple primary renal neoplasms are synchronous. Von Hippel Lindau disease and Birt-Hogg-Dube syndrome were the most common genetic cancer predisposition syndromes. Of course, not all lesions which occur in people with cancer predisposition syndromes are malignant. For example, around 30% of people with BAP1 tumour predisposition syndrome have benign splenic lesions on imaging [2]. POT1 cancer predisposition syndrome is associated with alterations to telomere length and genomic instability. POT1 is an autosomal dominant condition, with unknown penetrance. In this issue of European Journal of Human Genetics, a broader range of neoplasms associated with POT1 germline variants is reported [3]. A possible association with early onset prostate cancer was noted.

Exome and genome sequencing technologies are complex and require highly skilled staff to manage both the wet lab work and dry lab variant interpretation. Maver and colleagues present the ERN-rare neurological diseases quality assurance framework for next generation sequencing diagnosis of neurological disorders [4]. It is well known that, once identified by sequencing, classifying a variant as pathogenic, or not, can be challenging. Andhika et al. report an approach to improve PAX6 variant classification [5]. PAX6 missense variants are frequently classified as variants of uncertain significance. Ten commonly used pathogenicity prediction tools were evaluated, and thresholds for pathogenicity prediction optimised. Suggestions as to the best performing tools for PAX6 missense variant classification are made. Structural variants, such as deletions and duplications, are a common genomic cause of rare conditions. Most next generation sequencing pipelines are not capable of reliably detecting structural variants. If exome/genome sequencing could detect both structural variants and single nucleotide variants it would improve resource utilisation. Demidov et al. present a diagnostic uplift of 0.4% in unsolved SOLVE-RD participants when adding structural variant calling to exome sequencing [6]. Identifying and classifying splice variants is another challenge in clinical genomics. Zhang et al. use a series of beta-globin gene constructs to identify intron 1 deletions which are likely to cause clinically significant mis-splicing [7]. Such data is valuable for clinical interpretation of splice variants.

In this issue, we publish a range of papers describing the genotypes and phenotypes of rare conditions. Bi-allelic variants in FUZ are reported in additional patients with a syndrome of orofacialdigital syndrome, helping confirm the association [8]. Sajan et al. provide a case series of individuals with neurodevelopmental condition, with or without seizures, in association with GABRA4 variants [9]. Sadly, few genetic neurodevelopmental conditions are treatable. Bi-allelic variants in SLC5A6 are associated with a neurological condition, with potential vitamin treatments [10]. COQ7 pathogenic variants cause a variable disorder, with associated cardiac and neurological involvement, treatable with COQ10 supplements [11]. A prenatal onset of COQ7 disorder was ameliorated by early treatment with COQ10. Layo-Carris and colleagues provide an expansion on the phenotype associated with H3.3 (histone) variants, presenting evidence of possible genotype-phenotype correlations [12]. Noonan syndrome has multiple different genetic associations. In this issue, RAF1 Noonan syndrome is reported to have a severe phenotype - with prominent hypertrophic cardiomyopathy [13]. Dentici et al. report variants in ERF as a novel cause of Noonan syndrome, associated with craniosynostosis [14]. A further patient with a GTDC1 microdeletion is presented; providing further evidence this may be a novel neurodevelopmental condition [15].

Genomics technologies can also be applied in healthcare for common diseases. One application is pharmacogenetics - using genomic variants to predict responses to medications. Massmann et al. provide evidence that genotyping of CYP2C19 can help selection of appropriate anti-platelet therapy [16]. Manson et al. report the Dutch Pharmacogenetics Working Group guideline on pharmacogenetics for anti-epileptic drugs [17]. Pharmacogenomics is a fast developing field, with potential to benefit both people with rare and common medical conditions.

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*

REFERENCES

1. Zhang H, Andreou A, Bhatt R, Whitworth J, Yngvadottir B, Maher ER. Characteristics, aetiology and implications for management of multiple primary renal tumours: a systematic review. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01628-5.
2. Miranda J, Dave P, Kemel Y, Sheikh R, Zong G, Calderon LP, et al. Benign splenic lesions in BAP1-tumor predisposition syndrome: a case series. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01623-w.
3. Baptista Freitas M, Desmyter L, Badoer C, Smits G, Vandernoot I, T'Kint De Roodenbeke D. POT1 tumour predisposition: a broader spectrum of associated malignancies and proposal for additional screening program. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01611-0.
4. Maver A, Lohmann K, Borovečki F, Wolstenholme N, Taylor RL, Spielmann M, et al. Quality assurance for next-generation sequencing diagnostics of rare neurological diseases in the European Reference Network. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01639-2.
5. Andhika NS, Biswas S, Hardcastle C, Green DJ, Ramsden SC, Birney E, et al. Using computational approaches to enhance the interpretation of missense variants in the PAX6 gene. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01638-3.
6. Demidov G, Laurie S, Torella A, Piluso G, Scala M, Morleo M, et al. Structural variant calling and clinical interpretation in 6224 unsolved rare disease exomes. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01637-4.

7. Zhang KY, Joshi H, Marchant RG, Bryen SJ, Dawes R, Yuen M, et al. Refining clinically relevant parameters for mis-splicing risk in shortened introns with donor-to-branchpoint space constraint. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01632-9.
8. Singh S, Nampoothiri S, Narayanan DL, Chaudhry C, Salvankar S, Girisha KM. Biallelic loss of function variants in FUZ result in an orofaciodigital syndrome. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01619-6.
9. Sajan SA, Gradisch R, Vogel FD, Coffey AJ, Salyakina D, Soler D, et al. De novo variants in GABRA4 are associated with a neurological phenotype including developmental delay, behavioral abnormalities and epilepsy. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01600-3.
10. Riley LG, Sabui S, Said HM, Niaz A, Girisha KM, Radhakrishnan P, et al. Genome sequencing enables diagnosis and treatment of SLC5A6 neuropathy. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01641-8.
11. Pettenuzzo I, Carli S, Sánchez-Cuesta A, Isidori F, Montanari F, Grippa M, et al. COQ7 defect causes prenatal onset of mitochondrial CoQ10 deficiency with cardiomyopathy and gastrointestinal obstruction. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01615-w.
12. Layo-Carris DE, Lubin EE, Sangree AK, Clark KJ, Durham EL, Gonzalez EM, et al. Expanded phenotypic spectrum of neurodevelopmental and neurodegenerative disorder Bryant-Li-Bhoj syndrome with 38 additional individuals. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01610-1.
13. Gazzin A, Fornari F, Niceta M, Leoni C, Dentici ML, Carli D, et al. Defining the variant-phenotype correlation in patients affected by Noonan syndrome with the RAF1:c.770C>T p.(Ser257Leu) variant. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01643-6.
14. Dentici ML, Niceta M, Lepri FR, Mancini C, Priolo M, Bonnard AA, et al. Loss-of-function variants in ERF are associated with a Noonan syndrome-like phenotype with or without craniosynostosis. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01642-7.
15. Errichiello E, Lecca M, Vantaggiato C, Motta Z, Zanotta N, Zucca C, et al. Further evidence supporting the role of GTDC1 in glycine metabolism and neurodevelopmental disorders. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01603-0.
16. Massmann A, Christensen KD, Van Heukelom J, Schultz A, Shaukat MHS, Hajek C, et al. Clinical impact of preemptive pharmacogenomic testing on antiplatelet therapy in a real-world setting. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01567-1.
17. Manson LEN, Nijenhuis M, Soree B, De Boer-Veger NJ, Buunk A-M, Houwink EJF, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of CYP2C9, HLA-A and HLA-B with anti-epileptic drugs. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01572-4.

AUTHOR CONTRIBUTIONS

AM conceived, wrote and edited this editorial.

COMPETING INTERESTS

The author declares no competing interests.