EDITORIAL

The complex genomics of single gene disorders

Using genomic technologies we are beginning to identify some of the mechanisms underlying clinical variability in single gene disorders.

European Journal of Human Genetics (2023) 31:609–610; https://doi.org/10.1038/s41431-023-01386-w

In this issue, Flanagan et al. use a Genome Wide Association Study (GWAS) to identify possible genetic modifiers of phenotype in Duchenne muscular dystrophy (DMD) [1]. The primary determinant of severity is whether the dystrophin gene variant is in frame, with residual Dystrophin (Becker dystrophy), or out of frame, with little/no Dystrophin (Duchenne). Despite this, there is still variability in age of loss of ambulation in DMD. The GWAS implicated variation in 6 genes (ETAA1, PARD6G, GALNTL6, MAN1A1, ADAMTS19, and NCALD) as modifying loss of ambulation in DMD.

It is unclear if children with isolated single suture craniosynostosis should have genomic testing. In a French series, 12.9% of children with single suture craniosynostosis had an identifiable single gene disorder [2]. They confirm the association of SMAD6 variants with metopic synostosis and neurodevelopmental delay. This has clear implications for clinical practice.

Superimposed mosaicism is when an embryo inherits a single variant in a recessive gene, and a post-zygotic second hit occurs in the wild type allele. Asahina et al. provide an example of this in the context of childhood Hailey-Hailey disease [3]. This can account for variability in phenotypes and lower recurrence risk than expected for a recessive disorder. Second variants in recessive genes can be "missed" in clinical exome or genome sequencing. Li et al. report 2 cases in which research analysis of exomes found the second variant in trans, and discuss some reasons why second variants are missed in recessive conditions [4].

Loss-of-function and gain-of-function variants in the same gene can operate by different mechanisms and result in different phenotypes. Amenta et al. report 3 new people with CHAMP1-syndrome and review the literature to demonstrate that loss-of-function is associated with intellectual disability while gain-of-function results in epilepsy [5]. Such observations help inform variant interpretation, diagnosis and clinical counselling.

There remain many undiagnosed rare disease patients. Manzoor et al. report a novel genetic condition associated with bi-allelic DCAF13 variants [6]. The presentation was with a myopathy. Disease onset was in the first 1-2 years of life. Detailed neuromuscular studies such as muscle biopsy were not done. Further clinical characterisation and identification of further families will be required to confirm this as a novel neuromuscular disorder. Undiagnosed patients may still have novel/undiscovered genetic conditions.

Limitations in exome sequencing, such as inability to detect copy number variants can also result in missed diagnoses. Pennings and colleagues analysed exome data from 4800 probands for copy number variants and found a diagnosis in 2% [7]. These included Parkin deletions and dystrophin copy number variants. Where there is a clinical suspicion, specific testing for relevant copy number variants should be considered if they are not covered by local exome pipelines.

There is significant debate around the use of genome sequencing for newborn screening. In this issue, an Australian study finds that only 77% of parents would consider newborn screening using genomic technologies compared to the 99% current utilisation [8]. A majority of healthcare professionals also felt that genome sequencing should not be used in newborn screening. Numerous practical, educational and ethical requirements were identified before newborn genome screening could be implemented in Australia. Van Steijvoort et al. report experiences of Belgian couples after receiving reproductive carrier screening, most were satisfied with the process - this approach may hold lessons for genomic screening in other contexts [9].

Returning results of genome sequencing research projects to participants is at times problematic. Vears et al. produced a checklist of 7 items to define whether and how research genomic sequencing data should be returned to participants including the need for informed consent to receive such results, need for clinical confirmation of identified variant and plans for follow up after disclosure [10].

Genomic analysis of large patient cohorts remains a useful research tool. Riedhammer et al. report exome sequencing of 86 people with congenital anomalies of the kidney and urinary tract (CAKUT) [11]. Identifying a monogenic cause in 7 people, and providing novel phenotypic information. All patients who had a genetic diagnosis had bilateral renal disease. Using UK biobank data, Cornejo-Sanchez et al. identify novel age related hearing loss genes, including PIK3R3 [12]. That we can re-analyse genomic datasets in a research setting is a major strength of such technologies. However, research participants may not fully appreciate the implications of such "immortal" data [13].

Alisdair McNeill[1,2] ✉

[1]*Department of Neuroscience, 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. Flanigan KM, Waldrop MA, Martin PT, Alles R, Dunn DM, Alfano LN, et al. A genome-wide association analysis of loss of ambulation in dystrophinopathy patients suggests multiple candidate modifiers of disease severity. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01329-5.

2. Di Rocco F, Rossi M, Verlut I, Szathmari A, Beuriat PA, Chatron N, et al. Clinical interest of molecular study in cases of isolated midline craniosynostosis. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01295-y.
3. Asahina Y, Tahara U, Aoki S, Nakabayashi K, Tateishi C, Hayashi D, et al. Two sporadic cases of childhood-onset Hailey-Hailey disease with superimposed mosaicism. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01316-w.
4. Li Q, Agrawal R, Schmitz-Abe K, Genetti CA, Fernandes MA, Fryou NL, et al. Reanalysis of clinical exome identifies the second variant in two individuals with recessive disorders. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01291-2.
5. Amenta S, Marangi G, Orteschi D, Frangella S, Gurrieri F, Paccagnella E, et al. CHAMP1-related disorders: pathomechanisms triggered by different genomic alterations define distinct nosological categories. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01305-z.
6. Manzoor H, Zahid H, Emerling CA, Kumar KR, Hussain HMJ, Seo GH, et al. A biallelic variant of DCAF13 implicated in a neuromuscular disorder in humans. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01319-7.
7. Pennings M, Meijer RPP, Gerrits M, Janssen J, Pfundt R, De Leeuw N, et al. Copy number variants from 4800 exomes contribute to ~7% of genetic diagnoses in movement disorders, muscle disorders and neuropathies. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01312-0.
8. White S, Mossfield T, Fleming J, Barlow-Stewart K, Ghedia S, Dickson R, et al. Expanding the Australian Newborn Blood Spot Screening Program using genomic sequencing: do we want it and are we ready? Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01311-1.
9. Van Steijvoort E, Peeters H, Vandecruys H, Verguts J, Peeraer K, Matthijs G, et al. Experiences of nonpregnant couples after receiving reproductive genetic carrier screening results in Belgium. Eur J Hum Genet. 2023, 1–7. https://doi.org/10.1038/s41431-023-01310-2.
10. Vears DF, Hallowell N, Bentzen HB, Ellul B, Nøst TH, Kerasidou A, et al. A practical checklist for return of results from genomic research in the European context. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01328-6.
11. Riedhammer KM, Ćomić J, Tasic V, Putnik J, Abazi-Emini N, Paripovic A, et al. Exome sequencing in individuals with congenital anomalies of the kidney and urinary tract (CAKUT): a single-center experience. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01331-x.
12. Cornejo-Sanchez DM, Li G, Fabiha T, Wang R, Acharya A, Everard JL, et al. Rare-variant association analysis reveals known and new age-related hearing loss genes. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01302-2.
13. Lyle K, Weller S, Horton R, Lucassen A. Immortal data: a qualitative exploration of patients' understandings of genomic data. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01325-9.

AUTHOR CONTRIBUTIONS

AM conceived and wrote this editorial.

FUNDING

No specific funding to declare.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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