EDITORIAL

Genes=disease (?)

European Journal of Human Genetics (2023) 31:255–256; https://doi.org/10.1038/s41431-023-01314-y

If you want to understand why people are concerned about genetic selection via preimplantation genetic testing, an entertaining place to start is the 1997 film Gattaca. If you want to read the latest about current controversial issues read the letters in this issue of the European Journal of Human Genetics by Tellier et al. [1] and Forzano et al. [2].

The use of genomic testing to screen for disease at the population level is becoming more widely accepted. Alarcón Garavito et al. review the issues around implementation of population level genomic screening [3]. They found that the lack of genomic education and literacy, the need for significant upskilling of the healthcare workforce, the significant costs of enacting system-wide change, and the perceived lack of government and policy-making support for genomics were barriers to implementation of genomic medicine. Six articles identified barriers to successful genomic medicine implementation, including a lack of integration between EHR and genomics data, the need for evidence-based reimbursement, and parents' emotional, psychological and time costs. A key suggestion to implement genomic medicine is the need for ongoing education of healthcare staff in issues relating to genomic medicine.

Studying populations also helps us understand genomic causes of multi-factorial disease and physical traits. Chen et al. studied genomic factors contributing to male pattern baldness [4]. They identified 4 sufficiently powered GWAS which had replicated hundreds of male pattern baldness-associated SNPs, available for prediction modelling. These studies involve 205,327 UKBB male participants, and are followed by an independent replication study in 31,112 men. Despite sophisticated modelling involving dozens of SNPs….age was still found to be the strongest predictor of male pattern baldness! Mortensen et al. report the first phase of the FarGen study [5]. The Faroe Islands are among the most isolated populations in the North Atlantic, and their low genetic diversity and small effective population size may have led to substantial genetic drift and loss of genetic diversity, and an enrichment of some pathogenic variants and complete loss of others. The results show that the Faroese population is genetically rather homogenous, with almost no geographical structure and distinct from the general European population. Lipedema is a condition occurring mainly in women, characterised by the bilateral enlargement of the lower limbs. It is heritable, but the genetic basis remains unclear. Klimentidis et al. studied the UK biobank to identify genetic causes [6]; they define lipedema as having a relatively high leg fat percentage along with a relatively small waist circumference. Their GWAS identified 18 loci across the genome, 2 of which were replicated in an independent population. These increase our understanding of the causation of lipidemia. de los Campos et al. present a method to use Bayesian variable selection models to predict complex traits in biobank participants [7]. Glessner presents a novel method for using copy number variations in GWAS [8].

Several articles in this month's issue focus on the core mission of Clinical Genetics: finding disease causing genes to help patients. Luppe et al. help introduce STX1A as an epilepsy gene [9]. All individuals with ultra rare variants in STX1A had intellectual disability, neonatal hypotonia and motor delay. Some individuals had epilepsy, but others had a neurodevelopmental disorder with primarily intellectual disability and autistic behaviour. Epilepsy occurs in individuals with missense variants in STX1A that are predicted to disturb the interaction of STX1A with STXBP1. Reis report ARHGAP35 as a novel cause of ocular phenotypes [10]. This study presents the first evidence implicating ARHGAP35 in human developmental ocular phenotypes. The micro-ophthalmia related phenotypes observed in three families are consistent with those reported in the mouse model. In combination with the mouse model, this study supports a role for ARHGAP35 in vertebrate ocular development. The C-terminal clustering of the identified alleles indicates a possible common mechanism for ocular disease. Ceroni confirm that FGF14 is a causal gene for isolated early onset nystagmus [11]. Anorectal malformations (ARMs) are common birth defects, and typically require surgery within the first two years of life. Deloge utilised exome sequencing in a large cohort of individuals with ARMs [12]. They identified previously under recognised genetic associations. Deruelle examines the effect of the COVID pandemic on peoples' willingness to have a genetic test [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. Tellier LCAM, Treff NR, Hsu SDH, Lello L, Widen E. Scientific refutation of ESHG statement on embryo selection. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01237-0.
2. Forzano F, Antonova O, Clarke A, de Wert G, Hentze S, Jamshidi Y, et al. Reply to Letter by Tellier et al., 'Scientific refutation of ESHG statement on embryo selection'. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01241-4.
3. Alarcón Garavito GA, Moniz T, Déom N, Redin F, Pichini A, Vindrola-Padros C. The implementation of large-scale genomic screening or diagnostic programmes: a rapid evidence review. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01259-8.
4. Chen Y, Hysi P, Maj C, Heilmann-Heimbach S, Spector TD, Liu F, et al. Genetic prediction of male pattern baldness based on large independent datasets. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01201-y.
5. Mortensen Ó, Thomsen E, Lydersen LN, Apol KD, Weihe P, Steig BÁ, et al. FarGen: Elucidating the distribution of coding variants in the isolated population of the Faroe Islands. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01227-2.
6. Klimentidis YC, Chen Z, Gonzalez-Garay ML, Grigoriadis D, Sackey E, Pittman A, et al. Genome-wide association study of a lipedema phenotype among women in the UK Biobank identifies multiple genetic risk factors. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01231-6.

7. de Los Campos G, Grueneberg A, Funkhouser S, Pérez-Rodríguez P, Samaddar A. Fine mapping and accurate prediction of complex traits using Bayesian Variable Selection models applied to biobank-size data. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01135-5.
8. Glessner JT, Li J, Liu Y, Khan M, Chang X, Sleiman PMA, et al. ParseCNV2: efficient sequencing tool for copy number variation genome-wide association studies. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01222-7.
9. Luppe J, Sticht H, Lecoquierre F, Goldenberg A, Gorman KM, Molloy B, et al. Heterozygous and homozygous variants in STX1A cause a neurodevelopmental disorder with or without epilepsy. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01269-6.
10. Reis LM, Chassaing N, Bardakjian T, Thompson S, Schneider A, Semina EV. ARHGAP35 is a novel factor disrupted in human developmental eye phenotypes. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01246-z.
11. Ceroni F, Osborne D, Clokie S, Bax DA, Cassidy EJ, Dunn MJ, et al. Analysis of Fibroblast Growth Factor 14 (FGF14) structural variants reveals the genetic basis of the early onset nystagmus locus NYS4 and variable ataxia. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01197-5.
12. Belanger Deloge R, Zhao X, Luna PN, Shaw CA, Rosenfeld JA, Scott DA. High molecular diagnostic yields and novel phenotypic expansions involving syndromic anorectal malformations. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01255-y.
13. Deruelle T, Kalouguina V, Trein P, Wagner J. Is there a "pandemic effect" on individuals' willingness to take genetic tests? Eur J Hum Genet. 2022, 1-3. https://doi.org/10.1038/s41431-022-01223-6.

AUTHOR CONTRIBUTIONS

AM conceived and wrote this article.

FUNDING

No specific funding.

COMPETING INTERESTS

The author declares no competing interests.