EDITORIAL

Advances in genomic medicine: from diagnosis to patient perspectives

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The European Journal of Human Genetics features studies on rare conditions, advances in diagnostic approaches, the evolving roles within genomic medicine and patients' perspectives in this issue.

Long-read sequencing (LRS) is transforming the diagnosis of rare and complex genetic disorders, uncovering pathogenic variants that traditional methods often miss. Soriano-Sexto et al. identify six pathogenic variants for inherited metabolic diseases through LRS. They show that targeted sequencing combined with functional assays can reveal hidden causes and expand mechanistic understanding [1]. Congenital adrenal hyperplasia (CAH) is predominantly associated with the *CYP21A2* variants. However, diagnosis can be challenging due to homology with its pseudogene *CYP21A1P* as well as limitations of traditional diagnostic methods. Lildballe et al. provide a faster, scalable and more precise diagnostic method for *CYP21A2*-associated CAH. Using adaptive sampling LRS and the custom tool NanoCAH, they clarify structural variants and confirm 94% of CAH patients without parental testing [2]. In this issue, Ahn et al. also demonstrate the value of LRS in improving diagnostic accuracy for rare ataxias. They report that SCA36 accounts for a substantial proportion of previously undiagnosed cases and is the most prevalent rare spinocerebellar ataxia in South Korea, once common SCAs are excluded [3].

Further illustrating the value of advanced genomic approaches in rare disease diagnosis, Albuainain et al. report two siblings diagnosed with cardiofacioneurodevelopmental syndrome (CFNDS) using RNA sequencing (RNA-seq) after conventional DNA tests failed. This rare condition is caused by *CCDC32* variants and associated with microcephaly, facial malformations, developmental delay, cerebellar hypoplasia and cardiac anomalies. Their study expands the phenotypic spectrum and highlights the complementary power of RNA-seq to detect complex variants [4]. This issue also presents studies highlighting the importance of looking beyond conventional assumptions in variant interpretation. Bird et al. identify a novel mechanism for familial hypercholesterolaemia, showing that 5'UTR variants in *LDLR* can create upstream start codons that truncate the protein [5]. Similarly, Horowitz-Cederboim et al. demonstrate that a synonymous *SGCA* variant, previously considered benign, can disrupt splicing and lead to severe cardiac complications in Limb-girdle muscular dystrophy type R3 (LGMDR3), expanding the clinical spectrum of the disease [6].

The EJHG continues to expand our knowledge of novel genetic discoveries. *RSF1* is highlighted as a novel candidate gene for a syndromic neurodevelopmental disorder, with variants disrupting chromatin remodelling crucial for brain development. Jost et al. present eleven unrelated individuals with intellectual disability, autism, or developmental delay, supporting the key role of *RSF1* in gene expression during cortical development [7]. Extending genetic insights to complex traits, Mitchell et al. uncover a genetic link between acne and schizophrenia by combining large-scale GWAS analyses and population data. Their findings may explain why acne is more common in people with schizophrenia [8].

Alongside efforts to improve safety and risk monitoring in clinical genetics, strengthening genomic services also requires a well-defined workforce to deliver them. Lambert et al. demonstrate how targeted interventions can reduce errors in clinical genetics, mapping high-risk steps across the patient journey and proposing practical tools for monitoring and mitigating adverse events [9]. Complementing this system perspective, Lake et al. examine the evolving role of genetic practitioners (GenPs) within NHS genomic services. While GenPs contribute valuable expertise across different stages, the study highlights the variability in their roles and limited career progression pathways, particularly towards genetic counselling [10]. Clarifying these roles will be important for building a sustainable workforce to support the continued expansion of genomic medicine.

Beyond systems and workforce considerations, the needs of patients and families remain central to the delivery of genomic services. Godino et al. underscore the importance of effective communication in genetic risk disclosure. Healthcare-mediated and family-centred approaches that balance clarity, reliability and sensitivity are important for patients [11]. These approaches are likely to support more effective cascade testing within families. Willis et al. also highlight the perspectives of older adults on returning medically actionable genetic test results. Although many people aged over 70 appreciate the limited actionable options for themselves, they desire to know the risks that could affect their younger relatives [12]. Recognising patient preferences is therefore essential for shaping the genomic services.

Improving health literacy is essential for informed healthcare decisions, particularly for young people with intellectual disabilities, who often face challenges in genetics education. Hansen et al. further highlight this gap, emphasising their expectations and the need to train teachers in person-centred and respectful approaches to prepare these young people for informed decision making [13].

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COMPETING INTERESTS

The author declares no competing interests.