EDITORIAL

New year, new insights in genomic medicine

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Happy New Year from The European Journal of Human Genetics!

The EJHG enters 2026 with a continued focus on novel gene discoveries and emerging insights that are shaping genomic medicine, from rare disease mechanisms to clinical implementation.

Understanding neurodevelopmental disorders requires both the identification of new genes and careful delineation of clinical phenotypes. Luo et al. describe WSB2 as a novel neurodevelopmental disease gene, supported by shared clinical features among affected individuals and functional evidence from animal models [1]. Morison et al. further demonstrate that language and speech impairment are core features of KIF1A-associated neurological disorder; most individuals in their cohort had delayed first words and language impairment, and all had dysarthria [2]. Their findings highlight the importance of early speech and language interventions in clinical management. Although PBX1 is primarily associated with congenital anomalies of the kidney and urinary tract (CAKUT), in this issue, Iwai et al. also report cases with de novo missense PBX1 variants, expanding the clinical spectrum to distinctive skeletal features and developmental delay without CAKUT features [3].

Structural variation continues to challenge traditional assumptions about penetrance, inheritance, and phenotypic predictability. Van De Vondel et al. identify a heterozygous 9q34 deletion involving SPTAN1 as the cause of childhood-onset distal myopathy, demonstrating variable penetrance within a single family [4]. Many copy number variants (CNVs) linked to neurodevelopmental disability are known to exhibit incomplete penetrance. However, Goh et al. report that re-evaluation using a clinically relevant definition revises previous estimates, which were once thought to range from 10–40%, with many now recalculated at 1–10% [5]. Illustrating this complexity, pericentric inversions, where a chromosome segment including the centromere is reversed, can generate recombinant chromosomes during meiosis, leading to deletions or duplications and highly variable phenotypes. Wen et al. describe a mosaic pericentric inversion of chromosome 18 in a three-generation family, resulting in a spectrum of outcomes ranging from minimal features to holoprosencephaly [6].

Epigenetics is not only descriptive; it also offers potential as a diagnostic biomarker. In this issue, Silva et al. show that DNA methylation episignatures associated with MEF2C-related neurodevelopmental disorders share features with other genetic neurodevelopmental conditions, providing insight into disease biology [7]. Similarly, Van der Laan et al. demonstrate that Smith-Magenis syndrome (SMS) and Potocki-Lupski syndrome (PTLS), mirror genomic disorders caused by deletions and duplications of 17p11.2, respectively, exhibit strikingly reciprocal DNA methylation patterns (hypomethylation in SMS and hypermethylation in PTLS), highlighting their potential as diagnostic biomarkers [8].

Advances in genomic technologies continue to transform diagnostics. Smits et al. report that ultrarapid nanopore long-read sequencing (LR-GS) in 26 critically ill infants achieved a 42% diagnostic yield with an average turnaround of 5.3 days, versus 18.4 days for standard testing [9]. Beyond rapid sequencing, expanding analysis to regulatory and non-coding regions also enhances diagnostic yield. Wedd et al. uncover rare 5′-UTR variants in PKD1 as a cause of Autosomal Dominant Polycystic Kidney Disease in patients missed by conventional coding-region testing, highlighting therapeutic implications [10]. Complementing these genomic advances, this issue presents updated guidelines for microsatellite instability (MSI), providing standardised approaches for mismatch repair deficiency testing with direct implications for Lynch syndrome diagnosis and cancer therapy [11].

Certainly, the success of genomic medicine ultimately depends on patient-centred care. In this issue, Ciucă et al. show genetic counselling for familial colorectal cancer improves patient empowerment and psychological outcomes, supporting its value for both affected and at-risk individuals [12]. Similarly, Balfour et al. report that rare disease–specific patient passports enhance communication, care coordination, and patient confidence. In their pilot evaluation, over 70% of users reported easier communication with unfamiliar healthcare teams, nearly two-thirds felt more confident expressing their needs [13].

Pharmacogenomics enables tailored therapy and improves safety. The Dutch Pharmacogenetics Working Group (DPWG) provides practical dosing recommendations for thiopurines based on TPMT and NUDT15 genotypes, reducing toxicity in intermediate and poor metabolisers [14]. While pharmacogenomics is reshaping precision medicine, global regulatory frameworks remain variable. This issue also reviews global policy for high-risk drug reactions, indicating growing momentum toward harmonised pharmacogenomics implementation [15].

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AUTHOR CONTRIBUTIONS

SSZ wrote this editorial.

COMPETING INTERESTS

The author declares no competing interests.