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Beyond the Single Gene: Rethinking Diagnosis in Rare Pediatric Disorders through Integrative Genomics

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Introduction

In pediatric medicine, the most powerful stories often arise not from common conditions, but from the outliers—the children whose clinical constellations challenge what we think we know about inheritance, phenotype, and disease mechanisms. The report in this issue of *Pediatrics* describes one such case: a 6-year-old boy presenting with multiple osteochondromas, short stature, and dysmorphic features, in whom next-generation sequencing revealed a single heterozygous pathogenic variant in *SMARCAL1*, the gene classically associated with Schimke immuno-osseous dysplasia (SIOD). Though SIOD is canonically an autosomal recessive multisystem disorder, the identification of only one pathogenic allele—paired with a compatible but incomplete phenotype—raises an important question: how do we define and interpret "disease" in the genomic era?

The Boundaries of Mendelian Thinking

Since the early descriptions of SIOD more than half a century ago, the condition has served as a paradigm of pleiotropy: short stature, skeletal dysplasia, cellular immunodeficiency, and steroid-resistant nephropathy unified by loss-of-function variants in *SMARCAL1*, a chromatin-remodeling gene essential for genomic stability. Yet, as genetic technologies have expanded, the limits of classic Mendelian models have become increasingly apparent. Up to 50% of clinically diagnosed SIOD cases lack identifiable biallelic *SMARCAL1* variants, suggesting hidden layers of complexity—noncoding variants, copy-number changes, epigenetic silencing, or modifier loci that modulate expression and penetrance [1–3].

In this child, the discovery of a single pathogenic *SMARCAL1* variant exemplifies that diagnostic gray zone. The variant (c.1933C>T, p. Arg645Cys) is well recognized in association with severe, early-onset SIOD when biallelic. Its presence in a heterozygous state, however, invites a nuanced discussion: might certain alleles exert dominant-negative or dosage-sensitive effects? Could partial haploinsufficiency or context-dependent epigenetic regulation explain a milder phenotype? The case challenges us to move beyond binary categorizations of "affected" versus "carrier," acknowledging that gene–environment and gene–gene interactions may blur these distinctions.

Clinical Reasoning Meets Genomic Uncertainty

For the practicing pediatrician, such scenarios are increasingly common. The availability of targeted panels, exome, and genome sequencing has outpaced our ability to interpret the biological meaning of every variant uncovered. Diagnostic reports that read "heterozygous pathogenic variant in an autosomal recessive condition" demand a careful synthesis of molecular, radiologic, and clinical data rather than a reflexive dismissal as "carrier only."

In the case presented, the authors illustrate exemplary clinical reasoning: thorough phenotyping, multidisciplinary evaluation, and recognition that the coexistence of multiple osteochondromas and dysmorphic features cannot be fully explained by hereditary multiple exostoses (EXT1/EXT2-related). Their interpretation—an atypical or partial *SMARCAL1*-related phenotype—balances caution with curiosity. Importantly, it avoids overdiagnosis while emphasizing the need for extended analyses such as copy-number variant detection, MLPA, or long-read sequencing to uncover potential second-allele changes.

This reflective approach embodies the evolving philosophy of genomic pediatrics: diagnosis as an iterative process, not a fixed endpoint. Each molecular finding is a hypothesis to be refined by longitudinal observation, family studies, and, when feasible, functional assays.

From Phenotype to Endotype

Beyond its immediate clinical implications, the case also underscores the importance of redefining disease categories through *endotyping*—the integration of molecular pathways, functional data, and clinical patterns. In conditions like SIOD, where genotype-phenotype correlation is weak, clustering patients by shared molecular signatures rather than traditional labels could reveal new therapeutic avenues [4].

For example, *SMARCAL1* encodes a replication-stress response factor involved in chromatin remodeling, DNA repair, and immune homeostasis. Its dysfunction links skeletal growth, renal filtration, and immune resilience through converging mechanisms of genomic instability [5,6]. Recognizing such cross-system biology reframes SIOD not only as a skeletal dysplasia or immunodeficiency, but as a "genome maintenance disorder," part of a larger family of replication-stress syndromes that may share pathophysiologic nodes amenable to future targeted interventions.

Equity and the Global Diagnostic Gap

While the mechanistic discussion is compelling, this case also reflects broader inequities in rare disease diagnosis, particularly in low- and middle-income settings. Limited access to advanced molecular testing, scarcity of reference laboratories, and cost constraints often delay or preclude definitive diagnosis [7]. Even when sequencing is available, variant interpretation depends heavily on population databases that underrepresent Latin American and other diverse ancestries, leading to persistent uncertainty about variant pathogenicity. Addressing this inequity requires not only technological investment but also collaborative data sharing, regional genomic initiatives, and clinician training to interpret findings within each population's genetic landscape.

Why This Case Matters

Every rare disease case report offers more than a single story—it expands the boundaries of what is possible in human biology. This child's presentation reminds clinicians that multiple osteochondromas, often attributed to hereditary exostosis, may herald broader syndromic or multisystemic disease. It demonstrates how modern genomics can refine, but also complicate, the diagnostic journey. And it highlights the essential role of pediatricians as both clinicians and interpreters of uncertainty—balancing evidence, probability, and empathy in the service of their patients.

Ultimately, the lesson extends beyond SIOD. In the era of precision medicine, our task is not merely to *find the gene* but to *understand the genome in context*. That requires integration—of clinical acumen with molecular insight, of rare disease expertise with population diversity, and of curiosity with humility. Only by embracing that complexity can pediatrics fulfill its promise: translating the code of rare disorders into better care for every child.

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