Pediatric genetics: rare is common

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One of the most promising applications of genomic diagnostics has been to pediatric genetics. Early-onset and/or extreme disease manifestations are more likely to be monogenic. However, genetic heterogeneity, phenocopies, rarity, and a large fraction of disease due to de novo variants made traditional strategies like linkage analysis or association studies challenging to apply to many pediatric diseases until the era of affordable genomic analysis: first chromosome microarrays, then exome/genome sequencing, and now sometimes transcriptomics. Increasingly the questions are not if we can identify the genetic basis for disease in children, but how fast and how cost-effectively can this be done?

We are gratified to see the reports in this special issue of *Cold Spring Harbor Molecular Case Studies* reflecting the breadth of uses for genomic sequencing in children. Most of the case reports in this issue use molecular data to both identify mutations underlying conditions in single patients and fill out the phenotypic characteristics for rare childhood disorders. As we are all learning with each new condition identified, there is usually not a simple, genotype–phenotype relationship.

Splicing variants are increasingly identified as causes of disease. Although hundreds of cases of neonatal respiratory distress syndrome have been linked to mutations in *ABCA3*, Oltvai et al. have the first report of a cryptic, exonic splicing variant in the gene as one of the compound heterozygous alleles seen in their patient. Koboldt et al. describe novel intronic variants in *ATP7B* leading to exon skipping in Wilson disease, whereas Ichikawa et al. report a novel pathogenic noncanonical splicing variant in *AK2* in a patient with reticular dysgenesis. In all of these cases, DNA sequencing alone was insufficient to definitely identify the variant responsible for the phenotype; additional molecular samples and analyses were required.

Additional analyses are important in cryptic cases where there is no obvious diagnosis, such as that reported by Sjaarda et al. Use of quantitative transcriptome analysis allowed them to detect a duplication on Chromosome 19 leading to a range of neurodevelopmental phenotypes in a family. Newer methodologies such as that reported by Ng et al. are helping to untangle complex cytogenetic cases, precisely identifying breakpoints and deleted genes in a case of 9p– syndrome as well as the complex background variation throughout the genome, which may be relevant for determining the therapeutic course.

In fact, genomic data are leading us to alter taxonomy for some pediatric conditions. AbuBakr et al. reexamine contributions of mutations in the *MAP3K7* gene in two overlapping disorders: cardiospondylocarpofacial syndrome (CSCFS) and frontometaphyseal dysplasia 2 (FMD2). Also in this issue, Xu et al. use the case study of a patient with mutations in *RAB3GAP2* to expand the genotypic and phenotypic boundaries of Martsolf syndrome, suggesting that hypogonadotropic hypogonadism be established as a key part of the syndrome's description. As in other rare genetic conditions, the use of unbiased genomic

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analysis to identify more patients has led us to redefine the boundaries between conditions and to appreciate the broader phenotypic spectrum of conditions than when we clinically diagnosed disorders based on cardinal clinical features.

Mosaic variant is proving to be more common, yet is more complicated to accurately access with routine depth of sequencing for most genomic analyses, and Miller et al. provide a useful summary of their experiences with exome sequencing in a pediatric tertiary-care setting. They were able to document mosaicism in five probands, representing 4.3% of the cases in whom a genetic diagnosis could be established by sequencing. Gonzalez Garcia et al. report a Cornelia de Lange syndrome case for whom blood specimen sequencing did not identify a causative variant, but saliva specimens demonstrated ~60% mosaicism. Although there are many subtle genetic complexities that increase as our understanding becomes increasingly sophisticated, there are many unifying themes across rare pediatric conditions that allow us to learn common lessons that we can all apply to the understanding and care of children.

We want to thank the research community for its support of this journal that highlights the value of even single patients as we guide them on their journey to find the correct diagnosis and to use the information to improve their care. When we started this issue, none of us had ever heard of COVID-19. As we write this editorial, we can see that all of our lives have been and will be forever changed. We hope that in some cases we have learned a few lessons that will lead to improvement after COVID-19, particularly on the value of individual case studies in cataloging phenotypic complexity.

Competing Interest Statement

C.G. contributed to this article in her personal capacity. The views expressed are her own and do not necessarily represent the views of the National Institutes of Health or the United States Government.

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