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50 Years Ago in *The Journal of Pediatrics*

Syndromic Intellectual Disability: A Never-Ending Genomic Odyssey

Palant DI, Feingold M, Berkman MD. Unusual Facies, Cleft Palate, Mental Retardation, and Limb Abnormalities in Siblings - A New Syndrome. J Pediatr 1971;78:686-9.

Intellectual disability is often associated with abnormalities in other systems, resulting in a recognizable syndrome. In 1971, Palant et al described 2 female siblings with global developmental delay, microcephaly, short stature, dysmorphic features including almond-shaped eyes with upslanted palpebral fissures, epicanthal folds, bulbous nasal tip, midline cleft of the hard and soft palate, clinodactyly of fourth and fifth fingers, and nonbony prominences in the ulnar aspect of bilateral wrist. A chromosomal analysis was normal. An autosomal recessively inherited syndrome was considered (Online Mendelian Inheritance in Man 260150). No further reports of similar phenotype have been described to date. Also, although a single gene disorder is more likely in this family in view of 2 affected individuals in 1 generation, the possibility of chromosomal abnormalities too small to be detected on a karyotype cannot be ruled out.

Significant advances in the last 50 years in clinical genetics have enhanced our understanding and unraveled the genetic etiology and underlying pathophysiology of many intellectual disability syndromes and several monogenic syndromes. The development of robust databases for standard vocabulary for description of phenotypic abnormalities (human phenotype ontology); online genetic and phenotypic data like Online Mendelian Inheritance in Man, London Medical Database, POSSUM web; tools for semantic similarity search like Phenomizer; and artificial intelligence based next-generation phenotyping applications like Face2Gene play a complementary role in phenotype analysis and aid the clinical diagnosis of several genetic disorders.

In addition, more advanced cytogenetic and molecular techniques for genetic diagnosis currently available can provide a more precise diagnosis. Advances in clinical cytogenetic testing methodologies like chromosomal microarray have enabled the study of genome wide abnormalities at a greater resolution, making the diagnosis of rare submicroscopic deletions and duplications possible; these would otherwise have been missed on conventional karyotyping. Chromosomal microarray is now used as the first-tier diagnostic test in children with intellectual disability with or without multiple congenital anomalies owing to a higher diagnostic yield of 15%-20%.[1] The advent of next-generation sequencing technology has made the diagnosis and discovery of single gene disorders easier by facilitating massive parallel sequencing of the whole exome or genome. In most chromosomal microarray negative patients with intellectual disability/multiple congenital anomalies, exome or genome sequencing studies have shown a yield of 28%-68%.[2] The genomic journey continues to enlighten our minds regarding the remaining intellectual disability syndromes.

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