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INSIGHTS

Dadaism catches up with DADA2

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The early-20th-century artistic movement Dadaism challenged established norms of beauty and authority in art. In this issue of *JEM*, Wouters et al. (https://doi.org/10.1084/jem.20250499) challenge established genetic principles believed to govern DADA2, an inborn error of immunity.

DADA2 is known as a rare, monogenic, autosomal recessive autoinflammatory disease caused by biallelic mutations in the *ADA2* gene, which encodes adenosine deaminase 2 (Zhou et al., 2014). These mutations lead to ADA2 deficiency (DADA2) in patients who present with clinical features such as systemic inflammation, vasculitis, early-onset stroke, immunodeficiency, and bone marrow failure. Most individuals are identified within the first years of life, although some are diagnosed much later.

As with most recessively inherited disorders, heterozygous carriers were initially thought to be mostly symptom free. However, a few reports have noted that some carriers do present with DADA2-like phenotypes, albeit without molecular explanation. Genetically, this disorder was thus considered largely haplosufficient, meaning that a single WT allele was presumed sufficient to maintain adequate enzymatic activity for a healthy life.

In this study, Wouters et al. (2025) identified 10 patients from seven kindreds who presented with a DADA2-like phenotype, yet harbored only a single pathogenic *ADA2* variant. This discovery alone challenges the notion of a strictly recessive inheritance pattern.

Furthermore, the authors performed a series of in vitro and ex vivo assays. In one biochemical experiment, they simulated homozygous conditions by transfecting cells with a single *ADA2* variant plasmid and heterozygous (carrier) conditions by co-transfecting a mutant plasmid along with WT *ADA2*. They demonstrated decreased ADA2 secretion for most variants. More strikingly, the R169Q and H424N variants exhibited a pronounced dominant-negative effect on WT ADA2 secretion. Additionally, variants G47A, G47R, G47V, R169Q, E328K, H424N, and Y453C led to enzymatic activity levels below the expected 50% in heterozygous conditions—confirming their dominant-negative behavior.

The average age of disease onset in heterozygous individuals is significantly higher than in those with biallelic pathogenic variants, suggesting that the degree of dominant negativity influences disease onset. As is often the case in dominantly inherited disorders, incomplete penetrance is evident in the presented cases, as the authors discuss in depth. Their most intriguing hypothesis involves autosomal random monoallelic expression (Stewart et al., 2025) as a possible modifier of disease onset and penetrance—an idea that warrants careful evaluation.

Clinically, the authors rightly point out the current limitations of using serum ADA2 enzyme activity alone as a diagnostic marker for symptomatic carriers. Due to assay variability and insufficient sensitivity, individuals with suspected DADA2 and heterozygous variants should undergo biochemical allele-specific testing. This remains the most reliable method for predicting disease potential, despite the challenges posed by incomplete penetrance. For some patients, treatment with TNF-α inhibitors may lead to significant clinical improvement.

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Thus, while DADA2 has classically been defined as an autosomal recessive deficiency, it is also an autosomal dominant disorder.

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