SETD5 Syndrome

At a Glance — A Guide for Families & New Providers

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WHAT IS SETD5 SYNDROME?

SETD5 Syndrome is a rare genetic neurodevelopmental disorder caused by a change (variant) in the **SETD5 gene** on chromosome 3 (3p25.3). This gene regulates how other genes are switched on and off during development. When one copy doesn't function correctly, gene regulation is disrupted — this is called **haploinsufficiency**. Most cases arise *de novo* (a spontaneous change, not inherited from a parent), though it can be inherited in some families. Parental genetic testing is recommended after diagnosis to determine recurrence risk. You may see it listed as **SETD5 haploinsufficiency**, **MRD23**, or **Intellectual Disability-Facial Dysmorphism Syndrome due to SETD5 Haploinsufficiency** — all refer to the same condition. The condition was first described in medical literature in 2014.

FEATURES REPORTED IN SETD5 SYNDROME

Not every individual will have all features listed. Severity varies widely, even among people with the same variant type.

Neurodevelopmental & Behavioral	Neurological, Physical & Growth
• Intellectual disability (mild to moderate in most; some near-typical)	• Hypotonia (low muscle tone); gait abnormalities including toe-walking
• Global developmental delay	• Coordination difficulties; motor development delays
• 'Spiky' cognitive profile: strengths alongside challenges	• Epilepsy or seizures in some; EEG abnormalities
• Working memory and short-term memory difficulties	• Sleep disturbances common
• Speech and language delay (nearly universal); expressive more affected than receptive	• Short stature; feeding difficulties in infancy
• Some individuals are minimally verbal; AAC may be beneficial	• Triangular face; hypertelorism; synophrys; depressed nasal bridge
• ADHD features: inattention, hyperactivity, impulsivity	• High-arched or cleft palate; micrognathia in some
• Autism spectrum features in some	• Congenital heart defects in some
• Anxiety; behavioral rigidity; difficulty with transitions	• Eye anomalies: strabismus, nystagmus, ptosis
• Sensory sensitivities; repetitive movements or behaviors	• Hearing impairment in some
• Affectionate, sociable disposition often reported	• Scoliosis, kyphosis, joint laxity; reduced bone mineral density in some

GENE	INHERITANCE	PREVALENCE	OMIM	REGISTRY
SETD5 (chromosome 3p25.3)	Typically de novo; can be inherited (AD)	Fewer than 100 in published literature; ~1,100 in patient community	#615761	Simons Searchlight

More information, plain-language research summaries, and a medical terms guide are available at

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