

## Trio exome sequencing identifies ultra-rare case of Skraban Deardorff syndrome

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### Abstract

#### *Presentation*

Individual (female) presented at 2 years of age due to concerns of developmental delay.

#### *Diagnosis*

Following multi-disciplinary assessment, she was diagnosed with autism spectrum disorder (ASD) and global developmental delay (GDD). Initial investigations for metabolic and genetic testing (microarray, Fragile X testing, and singleton exome sequencing) were normal, and MRI brain identified mild thinning of corpus callosum. However, trio exome sequencing identified a pathogenic de novo heterozygous variant in *WDR26* gene (C.523-10A>G), confirming Skraban-Deardorff syndrome (SKDEAS).

#### *Treatment*

As for many children with global developmental delay, despite advancements in targeted precision therapies, management is supportive (including multi-disciplinary team input).

#### *Discussion*

In this article, we add to the spectrum of cases described by this ultra-rare syndrome while highlighting the rationale and utility of *repeat* genetic testing for patients with global developmental delay.

### Introduction

Genetic testing has become standard practice in patients with unexplained global developmental (GDD) or intellectual disability (ID). Chromosomal microarray is widely utilized as a first-line investigation with a yield of 15% in unexplained GDD/ID<sup>1</sup>. Exome sequencing further increases diagnostic yield (28 to 43%), with its benefit recently acknowledged in a

report by American Academy of Paediatrics (June 2025)<sup>2</sup>. Despite this, a proportion of patients remain without a confirmed aetiology, contributing to parental stress and anxiety, and an unclear prognosis.

In this report, we describe a female individual with GDD who was subsequently diagnosed with an ultra-rare disorder called SKDEAS following using trio exome sequencing. This novel case adds to the molecular and clinical spectrum of existing reports of SKDEAS internationally, with this ultra-rare disorder described in only approximately 30 cases to date<sup>3, 4</sup>.

### Case report

A 2-year-old (female) presents with global delay (gross and fine motor, language) on a previously unremarkable birth history (term baby, normal antenatal/postnatal history). Relevant background includes developmental dysplasia hip (managed conservatively). Notable delay in milestones included sitting unsupported (12 months), standing (2 years), walking (2.5 years), first words (3 years). By age 4 years 11 months, her expressive vocabulary consisted of approximately 40 words, mostly single-word speech. Additionally observed clinical features included autistic stereotypic behaviours. At 6 years, she was independent in many activities of daily living (including feeding and dressing oneself), with relatively age-appropriate toileting (occasional nocturnal enuresis). On examination, she was non-dysmorphic, normocephalic and thriving, with a normal neurological examination. Similarly, examination across cardiovascular, respiratory and abdominal systems was unremarkable.

Initial investigations included metabolic (serum amino acids, ammonia, lactate, urinary organic acids, uric acid, acylcarnitine) and genetic testing (chromosomal microarray, Fragile X testing) which were negative. Singleton exome sequencing (performed by CeGaT, including exome analysis of 700+ genes) was also negative. MRI brain identified mild thinning of corpus callosum. Interestingly, repeat genetic analysis (age 5 years) including *trio* exome sequencing (CeGaT) identified a likely pathogenic variant in *de novo* heterozygous *WDR26* gene (c.523 – 10 A>G, Chr 1:224619293 T > C (hg)), previously reported in a patient with neurodevelopmental delay<sup>5</sup>.

The patient was assessed by a regional Children's Disability Network Team, formally diagnosed with GDD and ASD, and developed following multi-disciplinary input. She now attends main-stream school (in ASD specific stream), with mild intellectual disability. Her childhood course was also complicated by three episodes of simple febrile seizures, with no long-term use of anti-epileptic medications.

## Discussion

This case highlights the utility trio exome sequencing in neurodevelopmental syndromes of uncertain aetiology. The variant detected in our patient was initially identified on singleton exome analysis and interpreted as a variant of unknown significance. The *de novo* nature of the variant was clinically relevant however, and following trio exome approach, the likelihood of pathogenicity increased (see criteria PS2 Richards et al. ACMG guidelines)<sup>6</sup>. In addition, the expanding international database data contributed to a pathogenic interpretation in our patient, as this WDR26-related variant was reported in a separate patient with GDD<sup>5</sup>.

WDR26-related disorder, or SKDEAS, is an ultra-rare and recently discovered neuro-developmental syndrome caused by *de novo* loss-of-function variants or microdeletions in the WDR26 gene (MIM 617424) gene located at 1q42.12<sup>3,4,7</sup>. Like many neuro-developmental syndromes, phenotypic variability exists, and clinical manifestations include febrile seizures, epilepsy, hypotonia, structural brain abnormalities (ventriculomegaly, polymicrogyria, corpus callosum thinning), skeletal anomalies, facial dysmorphism, microcephaly, in addition to global developmental delay and intellectual disability<sup>8</sup>.

## Declarations of Conflicts of Interest:

None declared.

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