"A Case Report and Literature Review of Gabriele-de Vries Syndrome"

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Introduction

Ying and Yang 1 (*YY1*) is a zinc-finger transcription factor that both represses and activates genes. Pathogenic variants in *YY1* can lead to a rare autosomal dominant disorder – Gabriele-de Vries syndrome (GADEVS).

The phenotypic spectrum is variable and continues to expand. Currently, the primarily reported findings of GADEVS include developmental delay/intellectual disability, facial dysmorphisms, intrauterine growth restriction, and feeding difficulties.

Gabriele et. al. reported the first 10 cases of GADEVS in 2017. Since then, only 32 other cases have been published. Here we present an additional case along with a literature review to further characterize the current phenotypic spectrum of this rare genetic disorder.

Case

A 5-year-old male was referred to the Genetics Clinic at Children's Hospital of New Orleans for re-evaluation. First seen at 5 weeks old, initial testing included a chromosome micro array (normal).

He has a significant medical history with prominent phenotypic findings that are noted in Table 1.

Upon re-evaluation and after a neurodevelopmental disorder panel was non-diagnostic, whole exome and mitochondrial sequencing (GeneDx XomeDxPlus) were recommended and identified a Likely Pathogenic variant in *YY1*, c.1106 A>G p. (Asn369Ser), which is shown in Figure 1.

Literature Review

A case from Dos Santos et. al. was identified whose variant is identical to our case. They reported novel and infrequent findings such as non-febrile seizures, severe scoliosis, hearing impairments, and chorioretinitis.

Our case shares major features with Dos Santos et. al.'s case which is compared in Table 1.

Our case also demonstrates features not present in the published case such as cardiac (6/33), renal (4/33), and sleep disturbances (4/33) which are also infrequent findings reported in GADEVS.

Figure 1

Gene	Disease	Mode of Inheritance	Variant	Zygosity	Inherited* From	Classification
YY1	YY1-related neurodevelopmental disorder	Autosomal Dominant	c.1106 A>G p.(N369S)	Heterozygous	Unknown	Likely Pathogenic Variant

Figure 1: Results of exome sequencing
*Only the mother of the patient was tested.

Table 1

Phenotypic Findings	Our case	Dos Santos' Case	Total frequency (33)*
Developmental delay	X	X	33/33
Facial dysmorphisms	X	X	33/33
Feeding difficulties	X	X	25/33
Behavior issues	X	X	21/33
Eye abnormalities	X	X	22/33
Hypotonia	X	X	14/33
Vomiting	X	X	2/33
Pneumonia	X	X	2/33
Seizure like activity	X	X	5/33
Scoliosis		X	4/33
Hearing impairment		X	1/33
Chorioretinitis		X	1/33
Cardiac abnormalities	X		6/33
Renal abnormalities	X		4/33
Sleep disturbances	X		4/33

Table 1: Our case compared against Dos Santos' case who had the same Likely Pathogenic variant in *YY1*, c.1106 A>G p. (Asn369Ser). while noting the total phenotypic frequencies.

* 33 cases have been reported in literature. This number includes our case as well. All phenotypic findings were based out of 33.

Yellow Highlight: This indicates how our case had different phenotypic findings than Dos Santos' case even though they shared the same variant. Moreover, these features are also infrequent findings of GADEVS, as shown by the frequencies.

Discussion

A complete loss of *YY1* in mice resulted in peri-implantation lethality, but heterozygous mice showed neurulation defects and developmental restrictions, which suggest haploinsufficiency of *YY1* to be the cause for GADEVS.

Additionally, *YY1* haploinsufficiency leads to loss of acetylation, allowing methylation of lysine 27 on histone 3 (H3K27) via polycomb repressive complex 2 (PRC2) which inhibits gene expression.

In all, this case study and literature review contributes to the characterization and expansion of the phenotypic and clinical spectrum of GADEVS while demonstrating that patients with identical variants may display a variable phenotype.

Future directions include clarifying the pathophysiology of this rare syndrome via functional studies, especially for infrequent, multisystemic features such as sleep, renal, and cardiac abnormalities.

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