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

Introduction: Gabriele-de Vries syndrome (GADEVS) (OMIM 617557) is rare autosomal dominant disorder caused by Pathogenic variants in Yin and Yang 1 (*YY1*) (OMIM 600013), a zinc-finger transcription factor that both represses and activates genes. GADEVS is characterized primarily by developmental delay/intellectual disability, facial dysmorphisms, intrauterine growth restriction, and feeding difficulties. Other reported features include hypotonia, abnormal movements, behavioral, skeletal, eye, cardiac, and renal abnormalities. In 2017, Gabriele et. al. reported the first 10 cases, and since then, a total of 32 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 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 continued to have developmental delay, dysmorphic features, micrognathia, feeding difficulties with gastrostomy tube in place, hypotonia, ADHD (attention deficit hyperactivity disorder), strabismus, patent foramen ovale, hypercalciuria, bilaterial nephrolithiasis, seizure like activity, vomiting, recurrent pneumonia, and obstructive sleep apnea. 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).

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 such as developmental delay (33/33), facial dysmorphisms (33/33), feeding difficulties (25/33), behavior issues, eye abnormalities, hypotonia, vomiting, and pneumonia. They both also had seizure like activities, an uncommon feature of GADEVS (5/33). 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.

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.