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"New Twists in *MAGEL2*: Expanding the Phenotypic Spectrum Across the Lifespan"

Background: *MAGEL2* (MAGE family member 2) encodes a ubiquitin ligase enhancer that is required for endosomal protein recycling. It is an imprinted gene (paternally expressed) located within the Prader-Willi critical region on chromosome 15q11-q13. *MAGEL2* pathogenic variants have a wide spectrum of clinical, behavioral, and developmental consequences. Given the broad clinical variability, it is essential to recognize how presentations differ across the lifespan. Here, we report three patients with pathogenic variants in *MAGEL2*. One patient carries the most reported pathogenic variant, while the other two harbor novel variants, further expanding the currently limited literature on this rare condition.

Patient 1: The female patient was born at 37 weeks of gestation and presented with breathing difficulties, dysmorphic features, and neonatal hypoglycemia. As a child, she was diagnosed with central hypothyroidism, diabetes insipidus, growth hormone deficiency, precocious puberty, advanced bone age, bilateral myopia, and exotropia. As well as sleep disturbances, intellectual disabilities, abnormal weight gain, developmental nonverbal disorder, and neuromuscular scoliosis. Molecular testing identified a previously reported *de novo* pathogenic frameshift variant in *MAGEL2* (c.1996dupC; p. Gln666Pfs47). Upon her last evaluation, she continued to show increasing weight gain, insomnia, and developmental delays, but with no signs of regression. She is currently treated with growth hormone and desmopressin (DDAVP) daily.

Patient 2: The female patient was born at 31 weeks of gestation via an emergency C-section. In infancy, she presented with feeding difficulties, failure to thrive, avoidant restrictive food intake disorder, and developmental delays. As a child, she was diagnosed with bilateral myopia with pre-glaucoma, advanced bone disease, premature thelarche, and precocious puberty. Molecular testing identified a novel likely pathogenic nonsense variant in *MAGEL2* (c.1168C>T; p. Gln390*). On follow-up, she showed some improvement with eating, weight gain, and growth, but low BMI, chronic constipation, and intellectual disabilities persist. She is currently treated with a luteinizing hormone-releasing hormone (LHRH) analogue.

Patient 3: The male patient was born at 31 weeks and 5 days of gestation via C-section. He developed respiratory distress shortly after birth, with a prenatal history concerning polyhydramnios and a ventricular septal defect. Newborn exam revealed contractures of the extremities (rocker bottom-like feet), decreased tone, feeding difficulties, micrognathia, and bilateral undescended testes. Molecular testing identified a novel and de *novo* pathogenic nonsense variant in *MAGEL2* (c. 1852 Q>T, p.Q618*). At a later assessment, he was additionally diagnosed with diabetes insipidus, bronchopulmonary dysplasia, a patent foramen ovale, poor growth, and conductive hearing loss in the right ear with restricted hearing in the left. He remains hospitalized in the NICU.

Conclusion: This case series provides valuable insight into the wide phenotypic spectrum associated with *MAGEL2* variants. Although all three patients were confirmed to have truncating pathogenic variants, their clinical presentations vary considerably, thus highlighting the significant variability associated with this condition. These cases also demonstrate how manifestations of *MAGEL2* pathogenic variants differ across different stages of life. Additionally, we describe two previously unreported *MAGEL2* variants, adding to the limited research on this rare disorder. Recognition of this variability may aid diagnosis and improve clinical outcomes for individuals with *MAGEL2* pathogenic variants.