

Splice Mutations and Digital Anomalies Extend the Genotypic and Phenotypic Spectrum of Kim-Gusella Syndrome in *PHF21A* Patients

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Kim-Gusella syndrome (KGS) is a rare neurodevelopmental disorder caused by heterozygous mutations in the *PHF21A* gene at 11p11.2. In 2012, *PHF21A* was identified as the causative gene for intellectual disability (ID) and craniofacial anomalies (CFA) through breakpoint mapping of balanced translocations and comparative deletion mapping. This discovery explained these two partial phenotypes observed in Potocki-Shaffer syndrome (PSS), a contiguous gene disorder resulting from the minimal 2.1 Mb interstitial deletion of 11p11.2. PSS also exhibits additional skeletal anomalies, including multiple exostoses caused by *EXT2* and parietal foramina caused by *ALX4*. These three genes in the PSS region at 11p11.2 manifest full spectrum of PSS phenotypes.

Subsequent to the identification of *PHF21A* by positional cloning, 14 intragenic mutations in *PHF21A* were reported in KGS patients with additional clinical features, including autism, ADHD, and epilepsy. These mutations consisted of 11 frameshift, two nonsense, and one missense alterations.

In our present study, we present 14 unrelated KGS patients with novel variants in *PHF21A*, including six frameshift (resulting from four nucleotide deletions, one nucleotide duplication, and one nucleotide insertion), three nonsense, two missense, and three splice mutations. Notably, the identification of splice variants in *PHF21A* is novel and further supports the loss-of-function mechanism associated with KGS.

Most KGS patients exhibited developmental delay, intellectual disability, learning disabilities, and language/speech delays. Additionally, several patients displayed digital anomalies such as clinodactyly, syndactyly, and tapering fingers, confirming previously reported phenotypes, and establishing these digital anomalies as novel features associated with KGS.

Our findings expand the genotypic and phenotypic spectrum of KGS and enhance our understanding of the role of *PHF21A* in the pathogenesis and potentially improve diagnostic and therapeutic strategies.