HUWE1 related ID

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We previously reported on nonrecurrent overlapping duplications at Xp11.22 in individuals with nonsyndromic intellectual disability (ID) harboring HSD17B10, HUWE1, and the microRNAs miR-98 and let-7f-2 in the smallest region of overlap. Here, we describe six additional individuals with nonsyndromic ID and overlapping microduplications that segregate in the families. High-resolution mapping of the 12 copy-number gains reduced the minimal duplicated region to the HUWE1 locus only. Consequently, increased mRNA levels were detected for HUWE1, but not HSD17B10. Marker and SNP analysis, together with identification of two de novo events, suggested a paternally derived intrachromosomal duplication event. In four independent families, we report on a polymorphic 70 kb recurrent copy-number gain, which harbors part of HUWE1 (exon 28 to 3' untranslated region), including miR-98 and let-7f-2. Our findings thus demonstrate that HUWE1 is the only remaining dosage-sensitive gene associated with the ID phenotype. Junction and in silico analysis of breakpoint regions demonstrated simple microhomology-mediated rearrangements suggestive of replication-based duplication events. Intriguingly, in a single family, the duplication was generated through nonallelic homologous recombination (NAHR) with the use of HUWE1-flanking imperfect low-copy repeats, which drive this infrequent NAHR event. The recurrent partial HUWE1 copy-number gain was also generated through NAHR, but here, the homologous sequences used were identified as TcMAR-Tigger DNA elements, a template that has not yet been reported for NAHR. In summary, we showed that an increased dosage of HUWE1 causes nonsyndromic ID and demonstrated that the Xp11.22 region is prone to recombination- and replication-based rearrangements.