Critical exon indexing improves clinical interpretation of copy number variants in neurodevelopmental disorders

**Objective** To evaluate a new tool to aid interpretation of copy number variants (CNVs) in individuals with neurodevelopmental disabilities.

**Methods** Critical exon indexing (CEI) was used to identify genes with critical exons (CEGs) from clinically reported CNVs, which may contribute to neurodevelopmental disorders (NDDs). The 742 pathogenic CNVs and 1,363 variants of unknown significance (VUS) identified by chromosomal microarray analysis in 5,487 individuals with NDDs were subjected to CEI to identify CEGs. CEGs identified in a subsequent random series of VUS were evaluated for relevance to CNV interpretation.

**Results** CEI identified a total of 2,492 unique CEGs in pathogenic CNVs and 953 in VUS compared with 259 CEGs in 6,965 CNVs from 873 controls. These differences are highly significant (*p* < 0.00001) whether compared as frequency, average, or normalized by CNV size. Twenty-one percent of VUS CEGs were not represented in Online Mendelian Inheritance in Man, highlighting limitations of existing resources for identifying potentially impactful genes within CNVs. CEGs were highly correlated with other indices and known pathways of relevance. Separately, 136 random VUS reports were reevaluated, and 76% of CEGs had not been commented on. In multiple cases, further investigation yielded additional relevant literature aiding interpretation. As one specific example, we discuss GTF2I as a CEG, which likely alters interpretation of several reported duplication VUS in the Williams-Beuren region.

**Conclusions** Application of CEI to CNVs in individuals with NDDs can identify genes of potential clinical relevance, aid laboratories in effectively searching the clinical literature, and support the clinical reporting of poorly annotated VUS.

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Identification of TYW3/CRYZ and FGD4 as susceptibility genes for amyotrophic lateral sclerosis

**Objective** A 2-stage genome-wide association was conducted to explore the genetic etiology of amyotrophic lateral sclerosis (ALS) in the Chinese Han population.

**Methods** Totally, 700 cases and 4,027 controls were genotyped in the discovery stage using Illumina Human660W-Quad BeadChips. Top associated single nucleotide polymorphisms from the discovery stage were then genotyped in an independent cohort with 884 cases and 5,329 controls. Combined analysis was conducted by combining all samples from the 2 stages.

**Results** Two novel loci, 1p31 and 12p11, showed strong associations with ALS. These novel loci explained 2.2% of overall variance in disease risk. Expression quantitative trait loci searches identified TYW/CRYZ and FGD4 as risk genes at 1p13 and 12p11, respectively.

**Conclusions** This study identifies novel susceptibility genes for ALS. Identification of TYW3/CRYZ in the current study supports the notion that insulin resistance may be involved in ALS pathogenesis, whereas FGD4 suggests an association with Charcot-Marie-Tooth disease.

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