

Supplementary Table 7. Detailed gene classification and BCA interpretations used in this study

Gene Classification	
Confirmed gene associated with dominant developmental disorders	Plausible disease-causing mutations* within, affecting or encompassing the functional region** of a single gene identified in multiple (≥ 3) unrelated cases/families with a dominant developmental disorder***
	Plausible disease-causing mutations within, affecting or encompassing cis-regulatory elements convincingly affecting the expression of a single gene identified in multiple (≥ 3) unrelated cases/families with a dominant developmental disorder
	As definition of Possible Gene (see below) with addition of functional evidence of causation (e.g. existence of animal model which recapitulates the human phenotype)
Possible gene associated with dominant developmental disorders	Plausible disease-causing mutations within, affecting or encompassing the functional region of a single gene identified in isolated (=2) unrelated cases/families or segregation within multiple individuals within a single large family with a dominant developmental disorder
	Plausible disease-causing mutations within, affecting or encompassing cis-regulatory elements convincingly affecting the expression of a single gene identified in isolated (=2) unrelated cases/families with a dominant developmental disorder
	Plausible disease-causing mutations within, affecting or encompassing the functional region or encompassing cis-regulatory elements convincingly affecting the expression of a single gene identified in a single case/family with a dominant developmental disorder, with addition of bioinformatic or functional evidence of causation (e.g. high intolerance to haploinsufficiency in controls)
Gene without evidence for association with dominant developmental disorders	No plausible disease-causing mutations reported within, affecting or encompassing the coding region of a gene in cases/families with a dominant developmental disorder
BCA interpretation	
Pathogenic	Genomic rearrangement affecting or encompassing the functional region** of at least one gene confirmed to be associated with dominant developmental disorders via LoF mutations
	Genomic rearrangement associated with genomic imbalances at breakpoints overlapping with microdeletions/microduplications reported in multiple (≥ 3) unrelated cases/families with a dominant developmental disorder
Likely Pathogenic	Genomic rearrangement affecting or encompassing the functional region** of at least one gene possibly associated with dominant developmental disorders via LoF mutations
	Genomic rearrangement associated with genomic imbalances at breakpoints overlapping with microdeletions/microduplications reported in isolated (=2) unrelated cases/families with a dominant developmental disorder
	Genomic rearrangement affecting or encompassing the functional region** of at one gene confirmed to be associated with dominant developmental disorders but via non-LoF mutations
	Genomic rearrangement affecting or encompassing cis-regulatory elements convincingly affecting the expression of a gene confirmed to be associated with dominant developmental disorders via LoF mutations
	Genomic rearrangement affecting or encompassing cis-regulatory elements predicted <i>in silico</i> only to affect the expression of a gene confirmed to be associated with dominant developmental disorders via LoF mutations; multiple (≥ 3) unrelated cases have been reported with similar positional effects
VUS	Genomic rearrangement affecting or encompassing cis-regulatory elements predicted <i>in silico</i> only to affect the expression of a gene confirmed to be associated with dominant developmental disorders via LoF mutations; no or isolated (=2) unrelated cases have been reported with similar positional effects
	Genomic rearrangement only affecting or encompassing the functional region** of genes not associated with dominant developmental disorders via LoF mutations
	Genomic rearrangement overall not affecting or encompassing the functional region** of genes

The gene classification re-uses gene classes proposed by the Deciphering Developmental Disorders consortium with minor modifications

LoF: loss-of-function mutations = nonsense, frame-shifting indel, essential splice site mutation, whole gene deletion or any other mutation where functional analysis demonstrates clear reduction or loss of function

*: Recurrent de novo mutations convincingly affecting gene function, rare, highly-penetrant mutations

** : open-reading frame in protein coding genes

***: Disorder in which the most prominent pathogenetic mechanism occurs during embryogenesis or early brain development, segregating as a dominant or X-linked disorder with high penetrance