

Category	Description
Confirmed DD Gene	Plausible disease-causing mutations* within, affecting or encompassing an interpretable functional region** of a single gene identified in multiple (>3) unrelated cases/families with a 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 developmental disorder
	As definition 1 and 2 of Probable DD Gene (see below) with addition of convincing bioinformatic or functional evidence of causation e.g. known inborn error of metabolism with mutation in orthologous gene which is known to have the relevant deficient enzymatic activity in other species; existence of animal model which recapitulates the human phenotype
Probable DD Gene	Plausible disease-causing mutations within, affecting or encompassing an interpretable functional region of a single gene identified in more than one (2 or 3) unrelated cases/families or segregation within multiple individuals within a single large family with a developmental disorder
	Plausible disease-causing mutations within, affecting or encompassing cis-regulatory elements convincingly affecting the expression of a single gene identified in more than one (2 or 3) unrelated cases/families with a developmental disorder
	As definitions of Possible DD Gene (see below) with addition of convincing bioinformatic or functional evidence of causation e.g. known inborn error of metabolism with mutation in orthologous gene which is known to have the relevant deficient enzymatic activity in other species; existence of animal model which recapitulates the human phenotype
Possible DD Gene	Plausible disease-causing mutations within, affecting or encompassing an interpretable functional region of a single gene identified in one case or segregation within multiple individuals within a small family with a developmental disorder
	Plausible disease-causing mutations within, affecting or encompassing cis-regulatory elements convincingly affecting the expression of a single gene identified in one case/family with a developmental disorder
	Possible disease-causing mutations within, affecting or encompassing an interpretable functional region of a single gene identified in more than one unrelated cases/families or segregation within multiple individuals within a single large family with a developmental disorder
Not DD Gene	No plausible disease-causing mutations within, affecting or encompassing the coding region in a developmental disorder AND not an IF gene
Both DD and IF	Plausible disease-causing mutations within, affecting or encompassing the coding region of a single gene identified in multiple (>3) unrelated cases/families with both a developmental disorder and an incidental (non-developmental) disorder

*
Plausible disease-causing mutation

Recurrent de novo mutations convincingly affecting gene function
Rare, fully-penetrant mutations - relevant genotype never seen in controls

**
Interpretable functional region

ORF in protein coding genes
miRNA stem or loop

Developmental Disorder

Disorder in which the most prominent pathogenetic mechanism occurs during embryogenesis or early brain development
Early onset degenerative disorders that may mimic above definition are included; for example Sanfilippo syndrome which can mimic global developmental delay

Category	Description
Monoallelic	Plausible disease-causing mutations identified on one allele in all or the vast majority of with specific developmental disorder
Biallelic	Plausible disease-causing homozygous or compound heterozygous mutations identified on both alleles in the majority of with specific developmental disorder
Both	Plausible disease-causing mutations identified on either one or both alleles in a specific developmental disorder where the mono allelic cases cannot be accounted for by false negative screens on the other allele
Imprinted	Plausible disease-causing mutations identified on one allele with the parent of origin determining the specific developmental disorder
Digenic	Plausible disease-causing mutations identified on one or both alleles of two different genes causing a specific developmental disorder where similar mutations of either gene would not
Hemizygous	Plausible disease-causing mutations identified on the X chromosome in a male as a cause of a specific developmental disorder, the disorder being predominantly recessive in female carriers
X-linked dominant	Plausible disease-causing mutations identified one copy of the X chromosome in females as a cause of a specific developmental disorder, includes disorders where heterozygous females and hemizygous males are similarly affected e.g. SMC1A mutations
Mosaic	Plausible disease-causing mutations identified on one allele in a proportion of cells with the others being wild-type as a cause of a specific developmental disorder
Mitochondrial	Plausible disease-causing mutations identified on mitochondrial DNA where homoplasmy or heteroplasmy are associated with a specific developmental disorder
Uncertain	Plausible disease-causing mutations in which the allele status is not recorded or is unclear with specific developmental disorder

Category	Description
Loss of function	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
All missense/in frame	Where all the mutations described in the data source are either missense or in frame deletions and there is no evidence favoring either loss-of-function, activating or dominant negative effect
Dominant negative	Mutation within one allele of a gene that creates a significantly greater deleterious effect on gene product function than a monoallelic loss of function mutation
Activating	Mutation, usually missense that results in a constitutive functional activation of the gene product
Increased gene dosage	Copy number variation that increases the functional dosage of the gene
Cis-regulatory or promotor mutation	Mutation in cis-regulatory elements that lies outwith the known transcription unit and promotor of the controlled gene
Uncertain	Where the exact nature of the mutation is unclear or not recorded