**Box 2 Classification of 18 alleles from 16 pathogenic/likely pathogenic RIPDs, according to reason missed by 100kGP pipeline and mode of inheritance**

|  |  |  |
| --- | --- | --- |
| **Categorya** | **Reason missed by 100kGP** | Number of RIPD alleles in category |
| 1 | SNVs/indels in PanelApp genes that had been missed or filtered out by the variant caller | 6b |
| 2 | Variants in known developmental genes not rated Green in the PanelApp for CRS (± additional panels applied), at the time of the GMC’s analysis. To broaden the search space we scrutinised genes listed in G2PDD 29 and/or prioritised by Exomiser,23 and checked recently published medical literature for citations to additional candidate genes identified | 7 |
| 3 | Copy number variants (CNV) or structural variants (SV) annotated using one or both of the callers applied to the GEL data, ie Canvas (CNV) and Manta (CNV/SV) | 3 |
| 4 | Genes for which apparently pathogenic variants of a particular class were present in two or more unrelated individuals, whereas variants with similar predicted pathogenic effect were rare in gnomAD (classified as *research genes*) | 2 |
|  | **Mode of Inheritance**a |  |
| A | Sporadic case associated with *de novo* mutation (DNM) in the proband | 10c |
| B | Sporadic case with autosomal recessive (homozygous or compound heterozygous) inheritance | 4 |
| C | Ultra-rare pathogenic variant in a singleton | 1 |
| D | Affected parent and child with concordant segregation of ultra-rare genotype (dominant inheritance) | 2d |
| E | Incorrect disease segregation model applied, owing to phenocopies or non-penetrance | 1 |

aCGG researchers considered additional pathogenic mechanisms, such as affected sib pairs arising from biparental (autosomal recessive) inheritance or parental gonadal mosaicism for a DNM, but if no convincing pathogenic example was found, no number category is assigned here.

bThe missense allele in *MMP21*was detected, but only assigned to Tier 3 because the other allele was filtered out.

cThe *ERF* deletion was present in mosaic state in the unaffected father.

dThe *HOXC* duplication was present in mosaic state in the affected father.