**Table 1** **Researcher-identified potential diagnoses (RIPDs) submitted by CGG for patients with CRS recruited to 100kGP.a**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case** | **Researcher category (Box 2** | **Panels applied in addition to CRS** | | **Gene** | | **cDNA change** | | **protein change** | | **Tier** | **Exomiser rank** | **Inheritance** | | **Gene Green on original/**  **updated panel?** | | **Pathogenicity** | | **Also identified by GE/GMC?** | | **Currently identifiable by NHSE pipeline?** | |
| **Tier 1, 2 or A variants** | | | |  | |  | |  | |  |  |  | |  | |  | |  | |  | |
| 1 | N/Ab | 5 | | *MAN2B1* | | c.[1830+1G>C];[2248C>T] | | p.[(?)];[(Arg750Trp)] | | Tier 1;  Tier 2 | 2 | Recessive | | original | | Pathogenic | | Y | | Y | |
| 2 | N/A | 10 | | 3.4 Mb Chr 6 del | | - | | - | | Tier A | Unranked | *De novo* | | N/A | | Pathogenic | | Y | | Y | |
| **Monoallelic Tier 3 variants** | | | | | |  | |  | |  |  |  | |  | |  | |  | |  | |
| 3 | N/A | 0 | | *KMT5B* | | c.557T>A | | p.(Leu186\*) | | Tier 3 | 1 | *De novo* | | no | | Pathogenic | | Y | | Y | |
| 4 | 2A | 1 | | *SMAD2* | | c.1223T>C | | p.(Leu408Pro) | | Tier 3 | 2 | *De novo* | | no | | VUSb | | N/A | | N/A | |
| 5 | 2A | 0 | | *SMAD6* | | c.40T>C | | p.(Trp14Arg) | | Tier 3 | 1 | *De novo* | | updated | | Likely pathogenic | | N | | Y | |
| 6 | 2A | 0 | | *CDK13* | | c.2563G>C | | p.(Asp855His) | | Tier 3 | 2 | *De novo* | | no | | Likely pathogenic | | N | | Y | |
| 7 | 2A | 7 | | *HNRNPK* | | c.1291G>T | | p.(Glu431\*) | | Tier 3 | 1 | *De novo* | | updated | | Pathogenic | | N | | Y | |
| 8 | 2A | 1 | | *FBXO11* | | c.2731\_2732insGACA | | p.(Thr911Argfs\*5) | | Tier 3 | 3 | *De novo* | | updated | | Likely pathogenic | | N | | Y | |
| 9 | 4A | 1 | | *SOX6* | | c.242C>G | | p.(Ser81\*) | | Tier 3 | 2 | *De novo* | | no | | Pathogenic | | N | | Y | |
| 10 | 4C | 1 | | *SOX6* | | c.277C>T | | p.(Arg93\*) | | Tier 3 | 63 | Parents not available | | no | | Likely Pathogenic | | N | | N | |
| 11 | 2A | 0 | | *BRWD3* | | c.4012C>T | | p.(Gln1338\*) | | Tier 3 | 1 | *De novo* | | no | | Pathogenic | | N | | Y | |
| 12 | 2A | 1 | | *PTCH1* | | c.290del | | p.(Asn97Thrfs\*20) | | Tier 3 | 1 | *De novo* | | no | | Pathogenic | | N | | Y | |
| 13 | 2A | 1 | | *ALX1* | | c.541C>A | | p.(Gln181Lys) | | Tier 3 | 5 | *De novo* | | no | | VUS | | N/A | | N/A | |
| **Untiered small variants** | | | |  | |  | |  | |  |  |  | |  | |  | |  | |  | |
|  |  |  | |  | |  | |  | |  |  |  | |  | |  | |  | |  | |
| 14 | 1B;1B | 1 | | *MEGF8* | | c.4496G>A(;)7766\_7768del | | p.(Arg1499His)(;)  (Phe2589del) | | Both untiered | 96;  unranked | Compound heterozygous | | original | | Pathogenic/likely pathogenic | | N | | N | |
| 15 | 1B;1B | 3 | | *MMP21* | | c.[671\_684del];[775C>G] | | p.[(Val224Glyfs\*29)];  [(His259Asp)] | | Untiered; Tier 3 | Both unranked | Compound heterozygous | | original | | Pathogenic/likely pathogenic | | N | | N | |
| 16 | 1A | 1 | | *ARID1B* | | c.3594delinsCCCCCA | | p.(Gly1199Profs\*14) | | Untiered | Unranked | *De novo* | | original | | Pathogenic | | N | | N | |
| 17 | 2A | 1 | | *TRAF7* | | c.1885A>G | | p.(Ser629Gly) | | Untiered | 3 | *De novo* | | updated | | Likely pathogenic | | N | | Yc | |
| 18 | 1E | 1 | | *TCF12* | | c.1870C>T | | p.(Leu624Phe) | | Untiered | Unranked | *De novo* | | original | | Pathogenic | | N | | Y | |
| 19 | N/A | 3 | | *OGT* | | c.539A>G | | p.(Tyr180Cys) | | Untiered | 1 | *De novo* | | updated | | Pathogenic | | Y | | Y | |
| **Untiered copy number and structural variants** | | | | | | | |  | |  |  |  | |  | |  | |  | |  | |
| 20 | 3D | 0 | | 13.4 Mb Chr 7 inv (*TWIST1*) | | - | | - | | Untiered | Unranked | Dominant (proband, affected mother) | | original | | Pathogenic | | N | | N | |
| 21 | 3A | 1 | | 314 kb Chr 19 del (*ERF*) | | - | | - | | Untiered | Unranked | Dominant (mildly affected father) | | original | | Pathogenic | | N | | Y | |
| 22 | 3D | 2 | | 285 kb Chr 12 dup | | - | | - | | Untiered | Unranked | Dominant (mosaic in affected father) | | no | | Likely pathogenic | | N | | N | |
|  |  | |  | |  | |  | |  | | | |  | |  | |  | |  | |  | | 4 |  |
| aFor a more detailed version of the content of this table, please see Table S4.  bN/A, not applicable; VUS, variant of unknown significance.  cIn an updated *de novo* analysis dataset (V9, Sept 2020), one read is allowed in either parent so the variant would be called. | | | | | | | | | | | | | | | | |  | |  | |  | | 16 |  |