Variant Classification Schema

<table>
<tr><th>Variant ranking</th><th>Initial bioinformatic classification</th><th colspan="2">Final classification</th></tr>
<tr><td>Class 5 = pathogenic</td><td>Genomic coordinates fed to VEP on ENSEMBL 75:
"splice_donor_variant"
"splice_acceptor_variant"
"stop_gained"
"frameshift_variant"</td><td>Transcript abrogating variants (nonsense, frameshift, consensus splice site) with previous reports of pathogenicity</td><td>Missense variants with functional characterisation demonstrating a functional effect relevant to the disease phenotype and multiple independent reports of pathogenicity.</td></tr>
<tr><td>Class 4 = likely pathogenic</td><td>"stop_lost"
"initiator_codon_variant"
"inframe_insertion"
"inframe_deletion"
“missense variant” and 1000 genomes project combined MAF < 0.01 and VEST3 call deleterious</td><td>Previously unreported variants predicted to lead to protein truncation (nonsense, frameshift, consensus splice site, initiator codon, non-stop). Variants predicted to abrogate the transcript but occurring in the last exon were called class 3 unless a functional effect or pathogenicity had been previously demonstrated.</td><td>Missense variants with supporting functional evidence, but lacking multiple independent reports of pathogenicity.</td></tr>
<tr><td>Class 3 = uncertain significance</td><td>MAF < 0.01 and
"splice_region_variant"
"incomplete_terminal_codon_variant"
“missense variant” and 1000 genomes project combined MAF < 0.01 and VEST3 call not available</td><td colspan="2">Class 3 variants all have a minor allele frequency <0.01 and include in-frame indels, splice region variants and missense variants with predicted deleterious consequence according to VEST3 or conflicting reports of pathogenicity.</td></tr>
<tr><td>Class 2 = probable non-pathogenic</td><td>1000 genomes combined MAF > 0.01 and/or “missense variant” and VEST3 call tolerated</td><td colspan="2" rowspan="2">Class 1 and class 2 variants are comprised of missense variants which either have a MAF < 0.01 but are predicted to be benign or a MAF ≥0.01, synonymous variants and non-coding variants (intronic, UTR, down- and up-stream).</td></tr>
<tr><td>Class 1 = non-pathogenic</td><td>"synonymous_variant"
"stop_retained_variant"
"coding_sequence_variant"
"5_prime_UTR_variant"
"3_prime_UTR_variant"
"non_coding_exon_variant"
"nc_transcript_variant"
"intron_variant"
"NMD_transcript_variant"
"upstream_gene_variant"
"downstream_gene_variant"
"TFBS_ablation"
"TFBS_amplification"
"TF_binding_site_variant"
"regulatory_region_variant"
"regulatory_region_ablation"
"intergenic_variant"</td></tr>
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