Table SV. Classification and evidence of 47 variants.

| Gene | AA change | Classification | PVS1 Truncation variants | PS3 Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product | PM1 Located in functional domain | PM2 gnomAD (East Asian) | PM2 1000 genomes (CHB) | PM3 A pathogenic variant detected in trans | PM4 Protein length changing variant | PM5 Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before | PP1 Cosegregation with disease in multiple affected family members | PP3 In silico prediction | PP5 Reputable source recently reports variant as pathogenic | BS3 Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing | BP4 Multiple lines of computational evidence suggest no impact on gene or gene product |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *TSHR* | p.R450H | P | | Yes (Narumi et al., 2011) | | 0.002597 | 0.0049 | Yes (Narumi et al., 2011) | | | | D | Yes | | |
| *TSHR* | p.K618* | P | Yes | | | 0 | 0 | Yes (this study) | | | | D | Yes | | |
| *DUOX2* | IVS28+1G>T | P | Yes | | | 0.001537 | 0 | Yes (Chen et al., 2018) | | | | | | | |
| *DUOX2* | p.R1110Q | P | | Yes (Narumi et al., 2011) | | 0.002597 | 0.0025 | Yes (this study) | | | | D | Yes | | |
| *DUOX2* | p.E879K | P | | Yes(Jin et al., 2014) | EF hand | 0.000954 | 0 | Yes (this study and Fu et al., 2015) | | | Yes(Maruo et al.,2008) | D | Yes | | |
| *DUOX2* | p.T803fs | P | Yes | | | 0 | 0 | | | | | D | Yes | | |
| *DUOX2* | p.R625* | P | Yes | | | 0 | 0 | Yes (this study) | | | | D | | | |
| *DUOX2* | p.G624fs | P | Yes | | | 0.0004638 | 0 | Yes (this study) | | | | D | | | |
| *DUOX2* | p.K530* | P | Yes | | Heme peroxidase-like | 0.009274 | 0.009244 | Yes (this study) | | | Yes(Maruo et al.,2008) | | Yes | | |
| *DUOX2* | p.R434* | P | Yes | | Heme peroxidase-like | 0.000116 | 0 | | | | | D | | | |
| *DUOX2* | p.R434_S440del | P | Yes | | Heme peroxidase-like | 0 | 0 | | YES | | Yes (Vigone et al., 2005) | D | | | |
| *TPO* | p.E757* | P | Yes | | | 0.00159 | 0 | | | | Yes(Niu et | D | Yes | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | al.,2002) | | |
| *TG* | p.E955fs | P | Yes | | type-1 8 | 0.00005798 | 0 | Yes (this study) | | | D | | |
| *TG* | p.L2282fs | P | Yes | | ACHE-like domain | 0 | 0 | Yes (this study) | | | D | | |
| *DUOX2* | p.G1521* | LP | | | NADPH binding | 0.001044 | 0.000809 | Yes (this study) | | | | | |
| *DUOX2* | p.Y1415C | LP | | | NADPH binding | 0.00008334 | 0 | Yes (this study) | | | D | | |
| *DUOX2* | p.R432H | LP | | | Heme peroxidase-like | 0.0004769 | 0.0007 | Yes (this study) | | | D | | |
| *DUOX2* | p.D137E | LP | | | Heme peroxidase-like | 0 | 0 | Yes (this study) | | | D | | |
| *TSHR* | p.C176R | LP | | | Leucine-rich repeat domain | 0 | 0 | Yes (this study) | | | D | | |
| *TSHR* | p.R528S | LP | | | | 0 | 0 | Yes (this study) | | | | Yes | |
| *DUOX2* | p.A1206T | LP | | Yes (Liu et al., 2016) | | 0.0001739 | 0 | | | | | | |
| *DUOX2* | p.R885L | LP | | | EF hand | 0.005777 | 0.0049 | Yes (this study) | Yes | Yes(Zheng et al.,2017) | | Yes | |
| *DUOX2* | p.R376W | LP | | | Heme peroxidase-like | 0 | 0 | Yes (Vigone et al., 2005) | | Yes (Vigone et al., 2005) | | Yes | |
| *TPO* | p.R361L | LP | | Yes (Yoshizawa-Ogasawara, et al., 2016) | | 0.009273 | 0.0194 | | | | | | |
| *DUOX2* | p.V779M | VUS | | | | 0.004094 | 0.0056 | | | | | | |
| *DUOX2* | p.F591S | VUS | | | | 0.00007081 | 0 | | | | D | | |
| *DUOX2* | p.V407F | VUS | | | Heme peroxidase-like | 0 | 0 | | | | | | |
| *DUOX2* | p.E389K | VUS | | | Heme peroxidase-like | 0 | 0 | | | | | | B |
| *DUOXA2* | p.R94C | VUS | | | | 0 | 0 | Yes (this study) | | | | | |
| *SLC5A5* | p.Q639* | VUS | | | | 0 | 0 | | | | | | B |
| *TPO* | p.S309P | VUS | | | | 0 | 0 | | | | | | |
| *TPO* | p.S571R | VUS | | | | 0 | 0 | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *TPO* | p.R846W | VUS | | 0.00159 | 0.0049 | | | | |
| *PROP1* | p.G51V | VUS | | 0.002151 | 0 | | | | |
| *SLC26A4* | p.Y78H | VUS | | 0 | 0 | | Yes (Guo et al., 2010) | D | |
| *SLC26A4* | p.A434T | VUS | SLC26A/SulP transporter domain | 0 | 0 | | | | |
| *SLC26A4* | p.Y578H | VUS | STAS domain | 0 | 0 | | | D | |
| *TRHR* | p.I168M | VUS | | 0.00212 | 0.0049 | | | | |
| *TG* | p.N212S | VUS | type-1 3 | 0.002122 | 0 | | | | |
| *TG* | p.R896Q | VUS | type-1 7 | 0.0007431 | 0.0049 | | | | |
| *TG* | p.V1738I | VUS | Type IIIB | 0.001325 | 0.0097 | | | | B |
| *TG* | p.S1912N | VUS | Type IIIA | 0 | 0 | | | | B |
| *TG* | p.I1931V | VUS | Type IIIA | 0.002391 | 0.0146 | | | | B |
| *TG* | p.I2394M | VUS | ACHE-like domain | 0.00005798 | 0 | | | | |
| *TG* | p.R2585W | VUS | ACHE-like domain | 0.005379 | 0.0049 | | | | |
| *TPO* | p.P883S | LB | | 0.005409 | 0.0146 | Yes (Ma et al., 2015) | | B (Yoshizawa-Ogasawara, et al., 2016) | B |

P, pathogenic; LP, likely pathogenic; VUS, variants of uncertain significance; LB, likely benign; D, damaged; B, benign; CHB, Han Chinese in Beijing, China; PVS1, null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multi-exons deletion) in a gene where LOF is a known mechanism of disease; PS3, well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product; PM1, located in a mutational hot spot and/or critical and well-established functional domain; PM2, Absent from controls (or at extremely low frequency if recessive) in public population databases; PM3, for recessive disorders, detected in trans with a pathogenic variant; PM4, protein length changes as a result of in-frame deletions/insertions in a non-repeat region, or stop-loss variants; PM5, Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before; PP1, Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease; PP3, multiple lines of computational evidence support a deleterious effect on the gene or gene product (detailed prediction results shown in Tables S6); PP5, Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation; BS3, Well-established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing; BP4, Multiple lines of computational evidence suggest no impact on gene or gene product (including conservation, evolutionary and splicing impact).