<table>
<thead>
<tr>
<th>Variant</th>
<th>Prediction on protein</th>
<th>Inheritance</th>
<th>Segregation</th>
<th>Phenotype</th>
<th>Method</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.-84-1G&gt;C</td>
<td>p.?</td>
<td>sporadic</td>
<td>de novo</td>
<td>WS4 or PCWH (learning delay, hypotonia at birth; short segment HSCR)</td>
<td>Sanger</td>
<td></td>
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<tr>
<td>c.61del</td>
<td>p.(Arg21Alafs*11)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>PCW + olfactory bulbs agenesis</td>
<td>Sanger</td>
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<tr>
<td>c.89C&gt;A</td>
<td>p.(Ser30*)</td>
<td>familial</td>
<td>cosegregates</td>
<td>PCWH in index case and mother, isolated SNHL in sister</td>
<td>Sanger</td>
<td>Cassatella, Eur J Endocrinol 2018;178:377</td>
</tr>
<tr>
<td>c.236T&gt;G</td>
<td>p.(Val79Gly)</td>
<td>familial</td>
<td>de novo in father</td>
<td>PCWH (index case : demyelinating neuropathy, SNHL; son : peripheral neuropathy + HSCR + depigmentation, hearing is said to be normal)</td>
<td>Sanger</td>
<td></td>
</tr>
<tr>
<td>c.325A&gt;T</td>
<td>p.(Asn109Tyr)</td>
<td>sporadic</td>
<td>de novo</td>
<td>WS2 + anosmia</td>
<td>Sanger</td>
<td></td>
</tr>
<tr>
<td>c.331T&gt;C</td>
<td>p.(Phe111Leu)</td>
<td>sporadic</td>
<td>ND</td>
<td>WS2 or PCW (motor delay and ID), anosmia and hypoplastic olfactory bulbs</td>
<td>Sanger</td>
<td>Liu, Int J Pediatr Otorhinolaryngol 2019;130:109806</td>
</tr>
<tr>
<td>c.333C&gt;A</td>
<td>p.(Phe111Leu)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>WS2</td>
<td>NGS panel</td>
<td></td>
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<tr>
<td>c.335T&gt;C</td>
<td>p.(Met112Thr)</td>
<td>sporadic</td>
<td>de novo</td>
<td>WS2 + vestibular areflexia</td>
<td>NGS panel</td>
<td></td>
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<tr>
<td>c.335T&gt;C</td>
<td>p.(Met112Thr)</td>
<td>familial</td>
<td>de novo in mother</td>
<td>WS4 in 2 index case brothers (short segment HSCR), WS2 in mother</td>
<td>Sanger</td>
<td></td>
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<tr>
<td>c.335_336del</td>
<td>p.(Met112Serfs*21)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>WS2 + vestibular areflexia</td>
<td>Sanger</td>
<td></td>
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<tr>
<td>c.338T&gt;C</td>
<td>p.(Val113Ala)</td>
<td>familial</td>
<td>cosegregates</td>
<td>WS4 in 2 index case brothers, one has a possible hypogonadism; a third brother has SNHL; father has WS2</td>
<td>NGS panel</td>
<td></td>
</tr>
<tr>
<td>c.341G&gt;A</td>
<td>p.(Trp114*)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>WS4</td>
<td>NGS panel</td>
<td></td>
</tr>
<tr>
<td>c.342G&gt;A</td>
<td>p.(Trp114*)</td>
<td>familial</td>
<td>?</td>
<td>WS2</td>
<td>sanger</td>
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<tr>
<td>c.342G&gt;T</td>
<td>p.(Trp114Cys)</td>
<td>sporadic</td>
<td>de novo</td>
<td>WS2 + mild hypotonia</td>
<td>sanger</td>
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</tr>
<tr>
<td>c.355C&gt;G</td>
<td>p.(Arg119Gly)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>WS2</td>
<td>Sanger</td>
<td></td>
</tr>
<tr>
<td>c.356_357del</td>
<td>p.(Arg119Glnfs*14)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>WS2 or PCW, hyperpigmentation of hands</td>
<td>Sanger</td>
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<tr>
<td>cDNA Change</td>
<td>Protein Change</td>
<td>Dominance</td>
<td>Phenotype</td>
<td>Diagnosis</td>
<td></td>
<td></td>
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<tr>
<td>c.364C&gt;G</td>
<td>p.(Leu122Val)</td>
<td>sporadic</td>
<td>de novo</td>
<td>WS2</td>
<td></td>
<td></td>
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<tr>
<td>c.380del</td>
<td>p.(Pro127Argfs*19)</td>
<td>familial</td>
<td>ND</td>
<td>WS2</td>
<td></td>
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</tr>
<tr>
<td>c.383dup</td>
<td>p.(His128Glnfs*6)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>PCW</td>
<td></td>
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<tr>
<td>c.403A&gt;G</td>
<td>p.(Ser135Gly)</td>
<td>sporadic</td>
<td>ND</td>
<td>WS2 + KS</td>
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<tr>
<td>c.415G&gt;C</td>
<td>p.(Gly139Arg)</td>
<td>sporadic</td>
<td>de novo</td>
<td>WS2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.416_426del</td>
<td>p.(Gly139Glnfs*7)</td>
<td>familial</td>
<td>cosegregates</td>
<td>PCWH/PCW in the 2 index cases, father has WS2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.424T&gt;C</td>
<td>p.(Trp142Arg)</td>
<td>sporadic</td>
<td>de novo</td>
<td>WS2 + olfactory bulbs agenesis</td>
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</tr>
<tr>
<td>c.428+2T&gt;G</td>
<td>?</td>
<td>sporadic</td>
<td>ND</td>
<td>WS2 (+ dysmorphism and developmental delay suspectedly due to another cause)</td>
<td></td>
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<tr>
<td>c.467_469del</td>
<td>p.(Glu156del)</td>
<td>Sporadic</td>
<td>ND</td>
<td>SNHL (asymmetric) + KS + hyperpigmentation</td>
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</tr>
<tr>
<td>c.475del</td>
<td>p.(Arg159Glyfs*127)</td>
<td>Sporadic</td>
<td>parents not carriers</td>
<td>WS2</td>
<td></td>
<td></td>
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<tr>
<td>c.476G&gt;C</td>
<td>p.(Arg159Pro)</td>
<td>familial</td>
<td>cosegregates</td>
<td>WS4 without hearing loss (short segment HSCR) , father has WS2</td>
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<td></td>
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<tr>
<td>c.580G&gt;T</td>
<td>p.(Glu194*)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>WS2</td>
<td></td>
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<tr>
<td>c.667del</td>
<td>p.(Met223Cysfs*63)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>WS4, aortic coarctation</td>
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<tr>
<td>c.725dup</td>
<td>p.(Thr243Asnfs*38)</td>
<td>sporadic</td>
<td>parents not carriers</td>
<td>WS4 (short segment HSCR)</td>
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<tr>
<td>c.773_774delinsA</td>
<td>p.(Arg258Glnfs*28)</td>
<td>sporadic</td>
<td>ND</td>
<td>PCWH with extent depigmentation (short segment HSCR)</td>
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<tr>
<td>c.865del</td>
<td>p.(Met289Trps*22)</td>
<td>sporadic</td>
<td>ND</td>
<td>WS4</td>
<td></td>
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<tr>
<td>c.879del</td>
<td>p.(Gln299Hisfs*12)</td>
<td>sporadic</td>
<td>ND</td>
<td>PCWH (short segment HSCR)</td>
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<tr>
<td>c.900C&gt;A</td>
<td>p.(Tyr300*)</td>
<td>sporadic</td>
<td>ND</td>
<td>PCWH, severe</td>
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<tr>
<td>c.1091_1092delinsT</td>
<td>p.(Gln364Leufs*138)</td>
<td>parents not carriers</td>
<td>parents not carriers</td>
<td>WS2</td>
<td></td>
<td></td>
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<tr>
<td>c.1095del</td>
<td>p.(Pro367Hisfs*135)</td>
<td>Sporadic</td>
<td>parents not carriers</td>
<td>WS2</td>
<td></td>
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</tr>
</tbody>
</table>

- **WS2**: Williams Syndrome type 2
- **KS**: Klippel-Feil Syndrome
- **SNHL**: Sensorineural Hearing Loss
- **PCWH**: Posterior Column Wallerian Degeneration
- **NGS**: Next-Generation Sequencing
- **HSCR**: Hirschsprung Disease
- **WS1**: Williams Syndrome type 1
- **WS4**: Williams Syndrome type 4

Additional notes:
- Was initially suspected of having WS1 due to unexplained dystopia canthorum in the index case only
- Not expected: sent for WS1 (due to inherited hypertelorism)
- Initially sent for CHARGE syndrome
- Initially sent for WS1
- Pingault, *Hum Mutat* 2010;31:391
- Marcos, *J Clin Endocrinol Metab* 2014;99:E213
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Mutation</th>
<th>Mode of Inheritance</th>
<th>Other Features</th>
<th>Clinical Features</th>
<th>Detection Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1160_1179dup</td>
<td>p.(Ser394Thrfs*115)</td>
<td>Sporadic</td>
<td>ND</td>
<td>WS4 (short segment HSCR)</td>
<td>Sanger</td>
</tr>
<tr>
<td>c.1169C&gt;G</td>
<td>p.(Ser390*)</td>
<td>Familial</td>
<td>cosegregates</td>
<td>WS4 or PCWH (developmental delay but MRI is said to be normal) in twin brothers, a sister has HSCR and motor delay, father has SNHL and HSCR; no depigmentation reported in the whole family</td>
<td>Sanger, Somashekar, Clin Genet 2019;95:398</td>
</tr>
<tr>
<td>c.1302_1314del</td>
<td>p.(Leu435Serfs*63)</td>
<td>Sporadic</td>
<td>Parents not carriers</td>
<td>WS2</td>
<td>Sanger</td>
</tr>
<tr>
<td>c.1399T&gt;C</td>
<td>p.(<em>467Glnext</em>86)</td>
<td>Sporadic</td>
<td>Parents not carriers</td>
<td>PCWH, severe</td>
<td>Sanger</td>
</tr>
<tr>
<td>Genic rearrangements and copy number variations</td>
<td>p.?</td>
<td>Sporadic</td>
<td>Parents not carriers</td>
<td>SNHL, anosmia</td>
<td>NGS panel</td>
</tr>
<tr>
<td>c.698-351_1227del</td>
<td>p.?</td>
<td>Sporadic</td>
<td>Parents not carriers</td>
<td>SNHL, anosmia</td>
<td>NGS panel</td>
</tr>
<tr>
<td>dele5 (hg19:chr22:g38367276_38371138del)</td>
<td>Sporadic</td>
<td>ND</td>
<td>WS4 (short segment HSCR)</td>
<td>QM-PSF, MLPA</td>
<td></td>
</tr>
<tr>
<td>Full gene deletion, 1.6Mb including about 50 genes</td>
<td>Familial</td>
<td>Mocaicism in asymptomatic parent</td>
<td>WS4 (hypotonia with central abnormalities different from PCWH, possibly due to contiguous gene syndrome?) sister has small depigmentations and light hypotonia</td>
<td>QM-PSF, MLPA and array-CGH</td>
<td></td>
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<tr>
<td>Full gene deletion</td>
<td>Sporadic</td>
<td>Parents not carriers</td>
<td>WS2</td>
<td>QM-PSF, MLPA</td>
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<tr>
<td>Full gene deletion</td>
<td>Sporadic</td>
<td>Parents not carriers</td>
<td>WS2</td>
<td>QM-PSF, MLPA</td>
<td></td>
</tr>
<tr>
<td>Triplication 1Mb, about 30 genes from GGA1 to CBY (hg19:chr22:g38004181-38009846_39053183-39057638del)</td>
<td>Sporadic</td>
<td>De novo</td>
<td>Atypical WS with hypo and hyperpigmentation, bilateral deafness, hypotonia, polymalformation. Severe. Girl, no sex reversal.</td>
<td>QM-PSF, MLPA and array-CGH</td>
<td></td>
</tr>
<tr>
<td>Variants of unknown significance awaiting for larger familial segregation</td>
<td></td>
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<tr>
<td>c.356G&gt;T</td>
<td>p.(Arg119Leu)</td>
<td>familial</td>
<td>inherited from affected mother, a complement of clinical investigation and familial segregation has been asked for</td>
<td>WS2</td>
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<td>NGS panel</td>
<td></td>
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<tr>
<td>c.374A&gt;C</td>
<td>p.(Gln125Pro)</td>
<td>familial</td>
<td>ND</td>
<td>WS2</td>
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<td></td>
<td>anger</td>
<td>Not expected: sent for WS1</td>
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</tbody>
</table>

Supplemental table 1: Unpublished cases with heterozygous SOX10 variants of interest collected in our laboratory over the last years. When a mutation is already reported in an independent case, the reference is indicated in the comments column. p.? indicates that the consequence on the protein is difficult to predict. The other variants are newly described. ND: not determined. ID: intellectual deficiency. QM-PSF: Quantitative Multiplex PCR of Short Fluorescent Fragments. MLPA: Multiplex Ligation-dependent Probe Amplification.