**Supplementary Table 3: X-chromosomal variants in individuals 1 and 2 which passed the filter criteria.**

Except for one, none of the genes affected by X-chromosomal variants were listed as disease-associated in OMIM or in the in-house curated list of X-chromosomal disease-associated genes (column “Disease-associated gene?”). The gene [*CCDC22*](https://ihgseq3.helmholtz-muenchen.de/cgi-bin/mysql/snv-vcf/searchGene.pl?g.genesymbol=CCDC22) which is affected by a maternally inherited missense variant in Individual 2 is associated with an ID syndrome, Ritscher-Schinzel syndrome 2 (MIM #300963300963). However, the variant has been classified as not disease-associated for two reasons: a) the clinical picture of Individual 2 differs considerably from Ritscher-Schinzel syndrome 2 (e.g. no congenital heart defect, no cranial MRI anomalies, no short stature, different craniofacial dysmorphism), b) the variant is rather frequent (dbSNP: 0.60%, ExAC European (Non-Finnish): 0.48%, ExAC African: 0.16%) and many control persons are also hemizygous for this variant (ExAC European (Non-Finnish): N=81, ExAC African: N=2).

MAF: minor allele frequency; ExAC ea: European (Non-Finnish); ExAC aa: African; NA: not applicable

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Individual** | **Gene** | **Disease-associated gene?** | **Chromosomal position**  **of variant (hg19)** | **Consequence** | **dbSNP 142** | **ExAC ea MAF (N hemizygotes)** | **ExAC aa MAF  (N hemizygotes)** | **CADD**  **Score** | **SIFT (Score)** | **PolyPhen (Score)** |
| **#1** | ***LOC100129520*** | no | chrX:124454140 | NM\_001195272.1:c.172C>T (p.(Arg58Trp)) |  | 0.04% (0) | 0.00% | 2.63 | NA | NA |
| **#1** | ***BCORL1*** | no | chrX:129149906 | NM\_021946.2:c.3158A>G (p.(Lys1053Arg)) | rs35470604 | 0.67% (125) | 0.05% (0) | 8.73 | tolerated (0.45) | benign (0.12) |
| **#1** | ***NHSL2*** | no | chrX:71359920 | NM\_001013627.2:c.2522C>T (p.(Pro841Leu)) |  | 0.002% (1) | 0.00% | 20.50 | tolerated (0.20) | benign (0.15) |
| **#2** | ***MAP7D3*** | no | chrX:135307018 | NM\_001173516.1:c.2107C>T (p.(Arg703Trp)) |  | 0.002% (1) | 0.00% | 24.20 | damaging (0.00) | possibly damaging (0.80) |
| **#2** | ***ACRC*** | no | chrX:70811974 | NM\_052957.4:c.62A>G (p.(Tyr21Cys)) | rs36115715 | 0.002% (0) | 0.00% | 10.00 | damaging (0.00) | benign (0.00) |
| **#2** | ***CCDC22*** | yes: MIM 300963 (Ritscher-Schinzel syndrome 2) | chrX:49104709 | NM\_014008.3:c.1150C>T (p.(Arg384Cys)) | rs143790434 | 0.48% (81) | 0.16% (2) | 29.50 | damaging (0.00) | probably damaging (1.00) |