**Online Supplement**

**Supplementary Methods**

*MUGQIC Bioinformatics Pipeline:*

Following sequencing on the Illumina® HiSeq 2000 platform, and base calling with the Illumina® CASAVA pipeline, sequencing reads were trimmed and aligned to the human reference genome version GRCh37 (hg19) using the Burrows Wheeler Aligner software version 0.6.2.1 Genome Analysis Toolkit (GATK) software version 2.7.2 was employed for realignment and quality control measures, along with Picard version 1.108 (http://broadinstitute.github.io/picard) for removal of duplicate reads.2 SNPs and INDELs were detected using samtools version 0.1.19 and bcftools.3-4 ANNOVAR was used to annotate these variants, which included annotations from the Database for Non-Synonymous SNPs Functional Predictions (dbNSFP version 2.0).5-6 Variants were aggregated into impact categories, and our research group at Memorial University completed further annotation and filtering.

References:

1. Li H, and Durbin R. Fast and accurate short read alignment with burrows-wheeler transform. *Bioinformatics* 2009; 25(14): 1754-1760.

2. McKenna A, Hanna M, Banks E, et al. The genome analysis toolkit: A MapReduce framework for analyzing next-generation DNA sequencing data. *Genome Res.* 2010; 20(9): 1297-1303.

3. Li H, Handsaker B, Wysoker A, et al. The sequence alignment/map format and SAMtools. *Bioinformatics* 2009; 25(16): 2078-2079.

4. Li H. A statistical framework for SNP calling, mutation discovery, association mapping and population genetical parameter estimation from sequencing data. *Bioinformatics* 2011; 27(21): 2987-2993.

5. Wang K, Li M, and Hakonarson H. ANNOVAR: Functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res.* 2010; 38(16): e164.

6. Liu X, Jian X, and Boerwinkle E. dbNSFP v2.0: A database of human non-synonymous SNVs and their functional predictions and annotations. *Hum. Mutat.* 2013; 34(9): E2393-2402.

**Supplementary Tables**

**Supplementary Table 1.** Remaining variants in family R1352 following application of filtering strategy.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Nucleotide Change** | **Amino Acid Change** | **rs ID** | **Number of Exomes with Variant** | **Variant Impact** | **Minor Allele Frequency (ExAC)** |
| *C4orf6* | c.A1G | p.M1V | *rs144117694* | 6/7 | High | 0% (0/21384) |
| *ATP1A4* | c.C1798T | p.P600S | *rs142338502* | 6/7 | Moderate | 0.2002% (246/122948) |
| *GIGYF2* | c.A3494G | p.H1165R | *rs72554081* | 6/7 | Moderate | 0.1586% (195/122946) |
| *RP1L1* | c.C202T | p.L68F | Unreported | 6/7 | Moderate | N/A |
| *MUC16* | c.G40588A | p.G13530S | Unreported | 7/7 | Moderate | N/A |
| *HSPBP1* | c.78\_79insGGCGGCGG | p.G25\_G26insAAD | Unreported | 7/7 | Moderate | N/A |

**Supplementary Table 2.** Remaining variants in family R1256 following application of filtering strategy.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Nucleotide Change** | **Amino Acid Change** | **rs ID** | **Number of Exomes with Variant** | **Variant Impact** | **Minor Allele Frequency (ExAC)** |
| *OCIAD1* | c.G-6+1A | N/A | *rs144048911* | 4/5 | High | 0.02851% (5/17538) |
| *CCDC3* | c.425delA | p.Tyr267ThrfsTer21 | Unreported | 4/5 | High | 0.2677% (290/108350) |
| *KIAA0319L* | c.A700G | p.T234A | *rs144951042* | 4/5 | Moderate | 0.0838% (103/122912) |
| *DYSF* | c.G1609A | p.V537M | *rs771062534* | 4/5 | Moderate | 0.006109% (5/81840) |
| *FAHD2A* | c.C281T | p.S94L | *rs200437887* | 4/5 | Moderate | 0.06028% (71/117782) |
| *RNF149* | c.A416G | p.N139S | *rs143827530* | 4/5 | Moderate | 0.1776% (199/112024) |
| *FANCD2* | c.G983A | p.R328Q | *rs35625434* | 4/5 | Moderate | 0.3032% (480/122080) |
| *SLC15A2* | c.A1301G | p.H434R | *rs748018463* | 4/5 | Moderate | 0.005767% (7/121370) |
| *MUC4* | c.G7189C | p.D2397H | *rs779985296* | 4/5 | Moderate | 0.04447% (11/24736) |
| *ABLIM2* | c.G481A | p.V161I | *rs370025292* | 4/5 | Moderate | 0.004107% (5/121740) |
| *FOXP4* | c.G97A | p.G33R | *rs41273784* | 4/5 | Moderate | 0.3616% (437/120854) |
| *GTF2E2* | c.A548G | p.K183R | *rs2978277* | 4/5 | Moderate | 0.3661% (449/122660) |
| *WRN* | c.C3785G | p.T1262R | *rs78488552* | 4/5 | Moderate | 0.2753% (338/122784) |
| *BRINP1* | c.C1046T | p.T349M | *rs142894245* | 4/5 | Moderate | 0.2099% (258/122902) |
| *ANTXRL* | c.A509G | p.N170S | *rs148029033* | 4/5 | Moderate | 0.07254% (12/16542) |
| *AGAP7* | c.T362C | p.L121S | *rs201609209* | 4/5 | Moderate | 0.3333% (219/65700) |
| *MYOF* | c.C4534T | p.R1512W | *rs201634420* | 4/5 | Moderate | 0.2305% (262/113648) |
| *LRRC56* | c.G655A | p.V219M | *rs138291757* | 4/5 | Moderate | 0.6479% (105/16206) |
| *LDHA* | c.G434C | p.G145A | *rs34305721* | 4/5 | Moderate | 0.2521% (310/122960) |
| *IFITM5* | c.G268A | p.A90T | *rs747064580* | 4/5 | Moderate | 0.004152% (5/120416) |
| *CPT1A* | c.C1436T | p.P479L | *rs80356779* | 4/5 | Moderate | 0.001627% (2/122898) |
| *C11orf30* | c.T2861G | p.L954R | *rs184345272* | 4/5 | Moderate | 0.1952% (237/121386) |
| *MOGAT2* | c.C299A | p.S100Y | *rs373540522* | 4/5 | Moderate | 0.01155% (14/121212) |
| *GSG1* | c.G391A | p.E131K | *rs148537880* | 4/5 | Moderate | 0.01546% (19/122894) |
| *OR11H4* | c.G55A | p.V19M | *rs142720326* | 4/5 | Moderate | 0.1199% (147/122594) |
| *LTBP2* | c.C2657A | p.T886K | *rs201591982* | 4/5 | Moderate | 0.07206% (70/97140) |
| *NIPA1* | c.40\_48delGCGGCGGCC | p.A14\_A16del | *rs549007670* | 4/5 | Moderate | 0.05244% (2/3814) |
| *MBP* | c.C194T | p.P65L | *rs149668522* | 4/5 | Moderate | 0.2069% (76/36732) |
| *ZNF816* | c.G1768C | p.E590Q | *rs61740548* | 4/5 | Moderate | 0.4302% (522/121346) |
| *AIM1L* | c.C28G | p.R10G | Unreported | 4/5 | Moderate | 0.004735% (1/21118) |
| *C2orf62* | c.G222C | p.E65Q | Unreported | 4/5 | Moderate | N/A |
| *ADPRH* | c.G91A | p.E31K | Unreported | 4/5 | Moderate | N/A |
| *MUC4* | c.A7183T | p.T2395S | Unreported | 4/5 | Moderate | 0.003966% (1/25216) |
| *MUC4* | c.C3053G | p.S1018C | Unreported | 4/5 | Moderate | 0.003766% (1/26552) |
| *MGST2* | c.C44T | p.S15L | Unreported | 4/5 | Moderate | N/A |
| *MCC* | c.60\_61insTCGGCGGCA | p.G20\_G21insSAA | Unreported | 4/5 | Moderate | N/A |
| *LAMA4* | c.G1546A | p.V516M | Unreported | 4/5 | Moderate | N/A |
| *TRPA1* | c.G1309A | p.V437M | Unreported | 4/5 | Moderate | N/A |
| *CCDC178* | c.C764G | p.A255G | Unreported | 4/5 | Moderate | N/A |
| *KIAA1210* | c.C263A | p.P88Q | Unreported | 4/5 | Moderate | 0.002018% (1/49550) |
| *KIAA0040* | c.217\_225delAAGAAGAAG | p.K73\_K75del | *rs150137790* | 5/5 | Moderate | 0.4964% (83/16720) |
| *LSG1* | c.C1039T | p.R347W | *rs114485048* | 5/5 | Moderate | 0.1805% (222/122962) |
| *SIM1* | c.C1082T | p.T361I | *rs145479047* | 5/5 | Moderate | 0.2145% (263/122600) |
| *ZMIZ2* | c.G1640A | p.S547N | *rs189007540* | 5/5 | Moderate | 0.09167% (112/122174) |
| *PSPH* | c.G268A | p.G90S | *rs75395437* | 5/5 | Moderate | 0.514% (608/118296) |
| *PSPH* | c.A249C | p.Q83H | *rs73343757* | 5/5 | Moderate | 0.8515% (997/117092) |
| *ANKRD30A* | c.G1232T | p.R411M | *rs202149101* | 5/5 | Moderate | 0.06915% (83/120022) |
| *GPR123* | c.G1283A | p.R428Q | *rs144212964* | 5/5 | Moderate | 0.2666% (45/16882) |
| *ZFPM1* | c.1334\_1339delCTCTGG | p.L446\_A447del | *rs149145771* | 5/5 | Moderate | 0% (0/118) |
| *PHF12* | c.C1473G | p.H491Q | *rs200985028* | 5/5 | Moderate | 0.1009% (124/122950) |
| *MYO18A* | c.C3704T | p.P1235L | *rs777985641* | 5/5 | Moderate | 0.000828% (1/120720) |
| *KANSL1* | c.G2698A | p.G900R | *rs74867664* | 5/5 | Moderate | 0.1078% (132/122452) |
| *DGCR6* | c.G392A | p.R131H | *rs146390355* | 5/5 | Moderate | 0.3033% (355/117050) |
| *POU3F1\** | c.82\_84delGCG | p.A28del | Unreported | 5/5 | Moderate | N/A |
| *MUC4\** | c.G7165A | p.D2389N | Unreported | 5/5 | Moderate | N/A |
| *MUC4\** | c.A7166G | p.D2389G | Unreported | 5/5 | Moderate | N/A |
| *MUC4\** | c.G7168C | p.A2390P | Unreported | 5/5 | Moderate | N/A |
| *MUC4\** | c.G2989A | p.D997N | Unreported | 5/5 | Moderate | N/A |
| *DSPP\** | c.2053\_2054insGTAGCAGTGACAGCAGCA | p.N685\_S686insSSSDSS | Unreported | 5/5 | Moderate | N/A |
| *MAML3\** | c.1468\_1470delCAG | p.Q490del | Unreported | 5/5 | Moderate | N/A |
| *DOPEY1\** | c.C6902T | p.A2301V | Unreported | 5/5 | Moderate | N/A |
| *CCDC3\** | c.C217G | p.L73V | Unreported | 5/5 | Moderate | N/A |
| *KNDC1\** | c.G2686T | p.A896S | Unreported | 5/5 | Moderate | N/A |
| *MTG1\** | c.C611T | p.P204L | Unreported | 5/5 | Moderate | N/A |
| *SPDYE4\** | c.C103T | p.P35S | Unreported | 5/5 | Moderate | N/A |
| *ZPBP2\** | c.A622T | p.T208S | Unreported | 5/5 | Moderate | N/A |
| *MUC16\** | c.G40588A | p.G13530S | Unreported | 5/5 | Moderate | N/A |
| *HSPBP1\** | c.78\_79insGGCGGCGG | p.G25\_G26insAAD | Unreported | 5/5 | Moderate | N/A |

\*These 15 moderate impact variants were included in validation stage of experiment, as highlighted in the manuscript.