MEDICOVER GENETICS

MOLECULAR GENETIC REPORT
GM19.12345

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Date: 16.03.2023

Report to:

Requesting Physician Name

Address

Contact Information

Order Number	**20 2009 1234**
Born	DD/MM/YYYY
Sex	
Date test requested:	27.02.2023
Sample collected:	27.02.2023
Sample / Specimen:	DNA from EDTA blood

Order: molecular genetic analysis of Intellectual disability_3.2
Additional Information /patient phenotype: Global developmental delay. Gemini ID panel requested.

RESULT SUMMARY:

POSITIVE – Consistent with Mental retardation, autosomal dominant 52 – heterozygous for a likely pathogenic variant

Result

The variant NC_000001.10:g.(155349907_155365249)_(155378193_155385534)del results in an out-of-frame deletion of the genomic region encompassing exon 7 of *ASH1L*, a gene that has been classified by ClinGen as having sufficient evidence for haploinsufficiency. This variant is expected to result in either an abnormal, truncated protein product or loss of protein from this allele through nonsense-mediated mRNA decay, which is a mechanism for disease.

ASH1L encodes a histone methyltransferase involved in epigenetic modification of chromatin. It associates with the transcribed region of genes important in development, including homeobox (HOX) genes. ASH1L catalyzes H3K36 methylation and plays important roles in development. It also contributes to nucleotide excision repair (NER) of DNA with cyclobutane pyrimidine dimer (CPD) lesions caused by ultraviolet (UV) irradiation. Pathogenic variants in this gene, usually occurring de novo, are a cause of autosomal dominant mental retardation.

Conclusion

The detected deletion encompassing *ASH1L* is consistent with the clinical diagnosis of mental retardation, autosomal dominant 52 and may with a high probability be regarded as causative for the patient's phenotype.

The reported CNV has been confirmed by the qPCR. The precise location and the breakpoints of the reported CNV are recommended to be determined by another method, if needed.

Offspring inherit CNV with a probability of 50%, each.

Recommended action

- Offer genetic counselling.
- Offer variant-specific genetic testing of biological relatives, the information from which can additionally be applied for segregation analysis for further evaluating the pathogenicity of the likely pathogenic variant.

CNV DETAILS

Region		Location on GRCh38	Size
NC_000001:g.(155349907_155365249)_(155378193_155385534)del Cytoband Notation: 1q22 (1:155365249-155378193)x1 Het Deletion		Chr1:155365248-155378193	12.9 Kb
Consequence	**Mode of inheritance**	**ACMG/AMP criteria** (Richards et al.; Ellard et al.)	**Classification**
Het Deletion	Unknown	1A, 3A, 2E	**Likely pathogenic**
Relevant Genomic Content: **This deletion includes 1 protein coding genes, which is relevant to this report:**			
Gene	**Disease**	**Mode of Inheritance**	**Decipher HI Index**
ASH1L (NM_018489.2)	Intellectual disability, autosomal dominant 52	Autosomal dominant	23.94

Report released by

John Doe 16.03.2023

johndoe@medicover.com

TEST METHODOLOGY

Sequencing	Enrichment	SNV and CNV Data analysis	data evaluation	Reference genome
Next Generation Sequencing (Illumina)	Twist Human Core Exome plus RefSeq SpikeIn	Illumina Dragen Bio-IT Platform VarSeq by GoldenHelix	VarSeq by GoldenHelix	hg38, NCBI GR38
Quality criteria	**SNV detection sensitivity**	**Classification of variants**	**in silico algorithms**	**Databases**
>30 (precision >99,9%) in min. 75% of bases	99.92 - 99.93 %; confirmation of reported SNV with Sanger sequencing, data analysis with SeqPilot	Richards et al. 2015, Genet Med 17:405; Ellard et al. "ACGS Best Practice Guidelines for Variant Classification 2020“	MaxEntScan, SpliceSiteFinder-like, REVEL	HGMD Professional release, ClinVar, gnomAD

PERCENTAGE OF SEQUENCED BASES WITH COVERAGE >20X

98.08%

ANALYZED GENES

AAAS(NM_015665.5), AARS(No Transcript), AASS(NM_005763.3), ABCC9(NM_005691.3), ABCD1(NM_000033.3), ABCD4(NM_005050.3), ABHD5(NM_016006.4), ACAD9(NM_014049.4), ACADM(NM_000016.5), ACADS(NM_000017.3), ACO2(NM_001098.2), ACOX1(NM_004035.6), ACSL4(NM_004458.2), ACTB(NM_001101.3), ACTG1(NM_001614.3), ACTL6A(NM_004301.4), ACTL6B(NM_016188.4), ACY1(NM_000666.2), ADAR(NM_001111.4), ADAT3(NM_138422.3), ADGRG1(NM_005682.6), ADK(NM_001123.3), ADNP(NM_015339.4), ADSL(NM_000026.3), AFF2(NM_002025.3), AFF4(NM_014423.3), AFG3L2(NM_006796.2), AGA(NM_000027.3), AGPS(NM_003659.3), AHDC1(NM_001029882.3), AHI1(NM_017651.4), AIFM1(NM_004208.3), AIMP1(NM_001142416.1), AKT3(NM_005465.4), ALDH18A1(NM_002860.3), ALDH3A2(NM_000382.2), ALDH4A1(NM_003748.3), ALDH5A1(NM_001080.3), ALDH7A1(NM_001182.4),

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NFU1(NM_001002755.2), NGLY1(NM_018297.3), NHS(NM_198270.3), NIPBL(NM_133433.3), NKAP(NM_024528.3), NKX2-1(NM_001079668.2), NLGN3(NM_181303.1), NONO(NM_007363.4), NPC1(NM_000271.4), NPC2(NM_006432.3),

NPHP1(NM_001128178.1), NR2F1(NM_005654.5), NRAS(NM_002524.4), NRXN1(NM_001135659.2), NSD1(NM_022455.4), NSD2(NM_001042424.2), NSDHL(NM_015922.2), NSUN2(NM_017755.5), NT5C2(NM_012229.4), NTNG2(NM_032536.2), NTRK1(NM_001007792.1), NTRK2(NM_006180.4), NUBPL(NM_025152.2), OCLN(NM_001205254.1), OCRL(NM_000276.3), ODC1(NM_002539.2), OFD1(NM_003611.2), OGT(NM_181672.2), OPA3(NM_025136.3), OPHN1(NM_002547.2), OSGEP(NM_017807.3), OTC(NM_000531.5), OTUD6B(NM_016023.3), OTX2(NM_172337.2), P4HTM(NM_177939.2), PACS1(NM_018026.3), PACS2(NM_001100913.2), PAFAH1B1(NM_000430.3), PAH(NM_000277.1), PAK1(NM_002576.4), PAK3(NM_002578.4), PARN(NM_002582.3), PAX6(NM_000280.4), PAX8(NM_003466.3), PBX1(NM_002585.3), PC(NM_001040716.1), PCCA(NM_000282.3), PCCB(NM_000532.4), PCDH12(NM_016580.3), PCDH19(NM_001184880.1), PCGF2(NM_007144.2), PCNT(NM_006031.5), PCYT2(NM_002861.4), PDE4D(NM_001104631.1), PDGFRB(NM_002609.3), PDHA1(NM_000284.3), PDHX(NM_003477.2), PDSS1(NM_014317.4), PDSS2(NM_020381.3), PEPD(NM_000285.3), PEX1(NM_000466.2), PEX10(NM_153818.1), PEX11B(NM_003846.2), PEX12(NM_000286.2), PEX13(NM_002618.3), PEX14(NM_004565.2), PEX16(NM_057174.2), PEX19(NM_002857.3), PEX2(NM_000318.2), PEX26(NM_017929.5), PEX3(NM_003630.2), PEX5(NM_001131025.1), PEX6(NM_000287.3), PEX7(NM_000288.3), PGAP1(NM_024989.3), PGAP2(NM_014489.3), PGAP3(NM_033419.4), PGK1(NM_000291.3), PGM3(NM_001199917.1), PHACTR1(NM_001322314.1), PHF21A(NM_001101802.1), PHF6(NM_032458.2), PHF8(NM_015107.2), PHGDH(NM_006623.3), PHIP(NM_017934.6), PIGA(NM_002641.3), PIGB(NM_004855.4), PIGG(NM_001127178.2), PIGL(NM_004278.3), PIGN(NM_176787.4), PIGO(NM_032634.3), PIGT(NM_015937.5), PIGU(NM_080476.4), PIGV(NM_017837.3), PIGW(NM_001346754.1), PIK3CA(NM_006218.3), PIK3R2(NM_005027.3), PITRM1(NM_014889.3), PLA2G6(NM_003560.2), PLAA(NM_001031689.2), PLCB1(NM_015192.3), PLK4(NM_014264.4), PLP1(NM_000533.4), PLPBP(NM_007198.3), PMM2(NM_000303.2), PMPCB(NM_004279.2), PNKP(NM_007254.3), PNPLA6(NM_001166111.1), POGZ(NM_015100.3), POLA1(NM_001330360.1), POLG(NM_002693.2), POLR2A(NM_000937.4), POLR3A(NM_007055.3), POLR3B(NM_018082.5), POMGNT1(NM_001243766.1), POMGNT2(NM_032806.5), POMT1(NM_007171.3), POMT2(NM_013382.5), PORCN(NM_203475.2), POU3F3(NM_006236.2), PPM1D(NM_003620.3), PPP1CB(NM_002709.2), PPP1R15B(NM_032833.4), PPP1R21(NM_001135629.2), PPP2CA(NM_002715.2), PPP2R1A(NM_014225.5), PPP2R5D(NM_006245.3), PPP3CA(NM_000944.4), PPT1(NM_000310.3), PQBP1(NM_005710.2), PRKD1(NM_002742.2), PRMT7(NM_019023.2), PRODH(NM_016335.4), PRPS1(NM_002764.3), PRR12(NM_020719.2), PRSS12(NM_003619.3), PRUNE1(NM_021222.2), PSAP(NM_002778.3), PSMD12(NM_002816.4), PSPH(NM_004577.3), PTCH1(NM_000264.3), PTCHD1(NM_173495.2), PTDSS1(NM_014754.2), PTEN(NM_000314.6), PTF1A(NM_178161.2), PTPN11(NM_002834.4), PTPN23(NM_015466.3), PTS(NM_000317.2), PUF60(NM_078480.2), PURA(NM_005859.4), PUS1(NM_025215.5), PUS3(NM_031307.3), PUS7(NM_019042.4), PYCR1(NM_006907.3), PYCR2(NM_013328.3), QARS(No Transcript), 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SCN3A(NM_006922.3), SCN8A(NM_001330260.1), SCO1(NM_004589.3), SCO2(NM_005138.2), SDCCAG8(NM_006642.3), SDHA(NM_004168.3), SDHAF1(NM_001042631.2), SEPSECS(NM_016955.3), SERAC1(NM_032861.3), SET(NM_001122821.1), SETBP1(NM_015559.2), SETD1B(NM_015048.1), SETD2(NM_014159.6), SETD5(NM_001080517.2), SGPL1(NM_003901.3), SGSH(NM_000199.3), SHANK2(NM_012309.4), SHANK3(NM_033517.1), SHH(NM_000193.3), SHOC2(NM_007373.3), SIK1(NM_173354.4), SIL1(NM_022464.4), SIN3A(NM_001145358.1), SIX3(NM_005413.3), SKI(NM_003036.3), SLC12A5(NM_020708.4), SLC12A6(NM_133647.1), SLC13A5(NM_177550.4), SLC16A2(NM_006517.4), SLC17A5(NM_012434.4), SLC19A3(NM_025243.3), SLC1A2(NM_004171.3), SLC1A4(NM_003038.4), SLC25A1(NM_005984.4), SLC25A12(NM_003705.4), SLC25A15(NM_014252.3), SLC25A22(NM_001191061.1), SLC2A1(NM_006516.2), SLC33A1(NM_004733.3), SLC35A1(NM_006416.4), SLC35A2(NM_001042498.2), SLC35C1(NM_018389.4), SLC39A14(NM_001128431.2), SLC39A8(NM_001135146.1), SLC46A1(NM_080669.5), SLC4A4(NM_001098484.2), SLC6A1(NM_003042.3), SLC6A17(NM_001010898.3), SLC6A19(NM_001003841.2), SLC6A3(NM_001044.4), SLC6A8(NM_005629.3), SLC6A9(NM_201649.3), SLC9A6(NM_001042537.1), SLX4(NM_032444.3), SMAD4(NM_005359.5), SMARCA2(NM_003070.4), SMARCA4(NM_001128849.1), SMARCB1(NM_003073.4), SMARCC2(NM_003075.4), SMARCD1(NM_003076.4), SMARCE1(NM_003079.4), SMC1A(NM_006306.3), SMC3(NM_005445.3), SMOC1(NM_001034852.2), SMPD1(NM_000543.4), SMPD4(NM_017951.4), SMS(NM_004595.4), SNAP25(NM_130811.3), SNAP29(NM_004782.3), SNRPB(NM_003091.3), SNX14(NM_153816.5), SON(NM_138927.2), SOS1(NM_005633.3), SOS2(NM_006939.3), SOX10(NM_006941.3), SOX11(NM_003108.3), SOX2(NM_003106.3), SOX3(NM_005634.2), SOX4(NM_003107.2), SOX5(NM_006940.5), SOX9(NM_000346.3), SPART(NM_015087.4), SPATA5(NM_145207.2), SPECC1L(NM_015330.4), SPG11(NM_025137.3), SPR(NM_003124.4), SPRED1(NM_152594.2), SPTAN1(NM_001130438.2), SPTBN2(NM_006946.2), SRCAP(NM_006662.2), SRD5A3(NM_024592.4), SSR4(NM_001204526.1), ST3GAL3(NM_006279.3), ST3GAL5(NM_003896.3), STAG1(NM_005862.2), STAG2(NM_001042750.1), STAMBP(NM_213622.2), STIL(NM_001048166.1), STRA6(NM_022369.3),

STRADA(NM_001003787.2), STX1B(NM_052874.4), STXBP1(NM_001032221.3), SUCLG1(NM_003849.3), SUMF1(NM_182760.3), SUOX(NM_001032386.1), SURF1(NM_003172.3), SVBP(NM_199342.3), SYN1(NM_133499.2), SYNGAP1(NM_006772.2), SYNJ1(NM_203446.2), SYP(NM_003179.2), SYT1(NM_005639.2), SZT2(NM_015284.3), TAF1(NM_001286074.1), TAF6(NM_005641.3), TANGO2(NM_152906.6), TAOK1(NM_020791.2), TAT(NM_000353.2), TAZ(NM_000116.4), TBC1D20(NM_144628.3), TBC1D23(NM_001199198.2), TBC1D24(NM_001199107.1), TBCD(NM_005993.4), TBCE(NM_003193.4), TBCK(NM_001163435.2), TBL1XR1(NM_024665.5), TBR1(NM_006593.3), TCF20(NM_005650.3), TCF4(NM_001083962.1), TCN2(NM_000355.3), TCTN2(NM_024809.4), TDP2(NM_016614.2), TECPR2(NM_014844.4), TELO2(NM_016111.3), TGIF1(NM_003244.3), TH(NM_199292.2), THOC2(NM_001081550.1), THOC6(NM_024339.4), THRA(NM_199334.3), TIMM50(NM_001001563.3), TLK2(NM_001284333.1), TMCO1(NM_019026.4), TMEM165(NM_018475.4), TMEM216(NM_001173990.2), TMEM237(NM_001044385.2), TMEM240(NM_001114748.1), TMEM5(No Transcript), TMEM67(NM_153704.5), TMEM70(NM_017866.5), TMEM94(NM_014738.5), TMTC3(NM_181783.3), TMX2(NM_015959.3), TOE1(NM_025077.3), TPP1(NM_000391.3), TRAF7(NM_032271.2), TRAIP(NM_005879.2), TRAPPC12(NM_016030.5), TRAPPC6B(NM_001079537.1), TRAPPC9(NM_001160372.3), TREX1(NM_033629.4), TRIM32(NM_012210.3), TRIM8(NM_030912.2), TRIO(NM_007118.3), TRIP12(NM_004238.2), TRIT1(NM_017646.5), TRMT1(NM_017722.3), TRMT10A(NM_152292.4), TRRAP(NM_001244580.1), TSC1(NM_000368.4), TSC2(NM_000548.4), TSEN2(NM_025265.3), TSEN34(NM_024075.4), TSEN54(NM_207346.2), TSFM(NM_005726.5), TSHB(NM_000549.4), TSPAN7(NM_004615.3), TTC19(NM_017775.3), TTC37(NM_014639.3), TTC8(NM_198309.3), TTI2(NM_001102401.2), TUBA1A(NM_006009.3), TUBB(NM_178014.3), TUBB2A(NM_001069.2), TUBB2B(NM_178012.4), TUBB3(NM_006086.3), TUBB4A(NM_006087.3), TUBG1(NM_001070.4), TUBGCP6(NM_020461.3), TUSC3(NM_006765.3), TWIST1(NM_000474.3), UBA5(NM_024818.4), UBE2A(NM_003336.3), UBE3A(NM_130838.1), UBE3B(NM_130466.3), UBR1(NM_174916.2), UBTF(NM_014233.3), UFM1(NM_016617.3), UMPS(NM_000373.3), UNC80(NM_032504.1), UPF3B(NM_080632.2), UROC1(NM_144639.2), USP9X(NM_001039590.2), VAMP1(NM_014231.4), VAMP2(NM_014232.2), VARS(No Transcript), VLDLR(NM_003383.4), VPS13B(NM_017890.4), VPS53(NM_001128159.2), VRK1(NM_003384.2), WAC(NM_016628.4), WARS2(NM_015836.3), WASF1(NM_003931.2), WDPCP(NM_015910.5), WDR26(NM_025160.6), WDR37(NM_014023.3), WDR45(NM_007075.3), WDR45B(NM_019613.3), WDR62(NM_001083961.1), WDR73(NM_032856.3), WDR81(NM_001163809.1), WWOX(NM_016373.3), XRCC4(NM_022406.3), YWHAG(NM_012479.3), YY1(NM_003403.4), ZBTB18(NM_205768.2), ZBTB20(NM_001164342.2), ZBTB24(NM_014797.2), ZC4H2(NM_018684.3), ZDHHC9(NM_016032.3), ZEB2(NM_014795.3), ZFYVE26(NM_015346.3), ZIC2(NM_007129.3), ZMIZ1(NM_020338.3), ZMYND11(NM_006624.5), ZNF142(NM_001105537.2), ZNF462(NM_021224.5), ZNF711(NM_021998.4), ZSWIM6(NM_020928.1)

LIST OF EXONS WITH COVERAGE <20X

Chr.	Pos.	Gene	Exon	Transcript	Mean Coverage (Min/Max)
Chr1	1447644..1447858	*ATAD3A*	Exon 01	NM_001170535.1	39.33 (12/60)
Chr1	39875933..39880226	*KIAA0754*	Exon 01	NM_015038.1	132.82 (9/276)
Chr1	63153893..63153940	*DOCK7*	Exon 01	NM_001271999.1	20.35 (18/22)
Chr1	228345455..228346784	*GJC2*	Exon 02	NM_020435.3	100.70 (4/188)
Chr2	16082182..16082981	*MYCN*	Exon 02	NM_005378.5	104.60 (8/196)
Chr2	86115942..86116033	*ST3GAL5*	Exon 01	NM_003896.3	29.77 (18/43)
Chr2	105471964..105473476	*POU3F3*	Exon 01	NM_006236.2	97.37 (2/212)
Chr3	49027685..49028048	*P4HTM*	Exon 01	NM_177939.2	59.86 (9/96)
Chr4	1242699..1242748	*CTBP1*	Exon 01	NM_001328.2	15.16 (12/16)
Chr4	108852795..108853294	*CYP2U1*	Exon 01	NM_183075.2	118.08 (14/214)
Chr5	14143830..14143996	*TRIO*	Exon 01	NM_007118.3	3.10 (0/10)
Chr5	14487568..14488374	*TRIO*	Exon 48	NM_007118.3	98.19 (12/170)
Chr5	60628095..60628780	*ZSWIM6*	Exon 01	NM_020928.1	31.18 (0/99)
Chr5	68830516..68830671	*OCLN*	Exon 05	NM_001205254.1	33.90 (12/53)
Chr5	68843752..68843933	*OCLN*	Exon 07	NM_001205254.1	14.03 (7/18)

Chr5	68847366..68847417	*OCLN*	Exon 08	NM_001205254.1	6.48 (4/8)
Chr5	92920725..92921197	*NR2F1*	Exon 01	NM_005654.5	93.05 (14/168)
Chr5	140998360..140998486	*DIAPH1*	Exon 01	NM_005219.4	18.41 (11/25)
Chr6	3154092..3155162	*TUBB2A*	Exon 04	NM_001069.2	89.85 (8/217)
Chr6	3224980..3226050	*TUBB2B*	Exon 04	NM_178012.4	93.17 (14/197)
Chr6	13014114..13014376	*PHACTR1*	Exon 01	NM_001322314.1	64.37 (18/91)
Chr6	13281656..13281790	*LOC100130357*	Exon 04	NM_001242698.1	1.68 (1/2)
Chr6	21594761..21596195	*SOX4*	Exon 01	NM_003107.2	104.71 (11/217)
Chr6	157099059..157100610	*ARID1B*	Exon 01	NM_020732.3	93.86 (11/194)
Chr7	193195..193809	*FAM20C*	Exon 01	NM_020223.3	71.97 (12/134)
Chr7	19156331..19156949	*TWIST1*	Exon 01	NM_000474.3	85.75 (0/158)
Chr7	101891687..101892327	*CUX1*	Exon 24	NM_181552.3	60.60 (2/124)
Chr7	153749901..153750153	*DPP6*	Exon 01	NM_130797.3	33.64 (9/66)
Chr8	42995635..42995762	*HGSNAT*	Exon 01	NM_152419.2	9.59 (4/12)
Chr8	133492389..133492784	*KCNQ3*	Exon 01	NM_004519.3	79.86 (8/136)
Chr8	145149998..145150136	*CYC1*	Exon 01	NM_001916.4	32.44 (12/51)
Chr9	2047224..2047489	*SMARCA2*	Exon 05	NM_003070.4	51.22 (2/127)
Chr9	98270438..98270648	*PTCH1*	Exon 01	NM_000264.3	48.62 (17/71)
Chr9	101470694..101471024	*GABBR2*	Exon 01	NM_005458.7	113.11 (4/205)
Chr9	133884597..133884979	*LAMC3*	Exon 01	NM_006059.3	76.31 (8/130)
Chr9	135117258..135117503	*NTNG2*	Exon 08	NM_032536.2	74.95 (8/141)
Chr9	140513476..140513506	*EHMT1*	Exon 01	NM_024757.4	2.84 (2/4)
Chr9	140772381..140772674	*CACNA1B*	Exon 01	NM_000718.3	78.53 (9/126)
Chr9	140917458..140918268	*CACNA1B*	Exon 19	NM_000718.3	82.66 (10/167)
Chr10	23481455..23482248	*PTF1A*	Exon 01	NM_178161.2	64.55 (9/146)
Chr10	26991086..26991128	*PDSS1*	Exon 02	NM_014317.4	0.00 (0/0)
Chr11	694754..695052	*DEAF1*	Exon 01	NM_021008.3	45.82 (10/82)
Chr11	65837953..65838318	*PACS1*	Exon 01	NM_018026.3	72.90 (13/103)
Chr11	70766131..70766149	*SHANK2*	Exon 11	NM_012309.4	0.00 (0/0)
Chr11	70776121..70776141	*SHANK2*	Exon 10	NM_012309.4	0.00 (0/0)
Chr11	70776133..70776155	*SHANK2*	Exon 09	NM_012309.4	0.00 (0/0)
Chr11	70785644..70785662	*SHANK2*	Exon 08	NM_012309.4	0.00 (0/0)
Chr11	118307223..118307664	*KMT2A*	Exon 01	NM_001197104.1	63.76 (9/103)
Chr13	31774217..31774296	*B3GLCT*	Exon 01	NM_194318.3	19.59 (18/22)

Chr13	77574588..77575109	*CLN5*	Exon 04	NM_006493.2	75.89 (15/132)
Chr13	100637572..100637941	*ZIC2*	Exon 03	NM_007129.3	56.59 (6/121)
Chr14	29236481..29237960	*FOXG1*	Exon 01	NM_005249.4	122.06 (8/222)
Chr14	58907934..58908066	*KIAA0586*	Exon 06	NM_001244189.1	0.00 (0/0)
Chr14	59010596..59010690	*KIAA0586*	Exon 33	NM_001244189.1	1.00 (1/1)
Chr14	99640483..99642537	*BCL11B*	Exon 04	NM_138576.3	140.57 (6/207)
Chr14	105715203..105715427	*BTBD6*	Exon 02	NM_033271.2	13.48 (0/58)
Chr15	40903671..40903714	*KNL1*	Exon 07	NM_144508.4	20.80 (19/22)
Chr15	90191481..90192010	*KIF7*	Exon 05	NM_198525.2	78.87 (15/173)
Chr16	128304..128337	*MPG*	Exon 01	NM_001015052.2	17.18 (15/21)
Chr16	4852523..4852577	*ROGDI*	Exon 01	NM_024589.2	12.89 (12/16)
Chr16	46918623..46918875	*GPT2*	Exon 02	NM_133443.3	72.35 (15/120)
Chr16	53656126..53656273	*RPGRIP1L*	Exon 23	NM_015272.4	37.80 (16/51)
Chr16	79632677..79633804	*MAF*	Exon 01	NM_005360.4	107.47 (0/239)
Chr16	89334881..89335076	*ANKRD11*	Exon 13	NM_013275.5	64.23 (13/93)
Chr17	7405832..7406025	*POLR2A*	Exon 16	NM_000937.4	52.92 (15/71)
Chr17	15903158..15903351	*TTC19*	Exon 01	NM_017775.3	58.67 (18/134)
Chr17	40688286..40688678	*NAGLU*	Exon 01	NM_000263.3	32.01 (14/54)
Chr17	65821836..65822458	*BPTF*	Exon 01	NM_182641.3	67.39 (2/184)
Chr17	73512637..73512702	*TSEN54*	Exon 01	NM_207346.2	9.14 (7/12)
Chr17	79860149..79860407	*NPB*	Exon 01	NM_148896.4	68.58 (7/156)
Chr17	79869138..79869236	*PCYT2*	Exon 01	NM_002861.4	15.59 (10/20)
Chr17	79989633..79989677	*RAC3*	Exon 01	NM_005052.2	17.96 (16/20)
Chr17	80710065..80710258	*TBCD*	Exon 01	NM_005993.4	86.94 (18/127)
Chr18	77439943..77440266	*CTDP1*	Exon 01	NM_004715.4	52.75 (19/93)
Chr19	1465149..1470217	*APC2*	Exon 15	NM_005883.2	133.15 (10/241)
Chr19	18272084..18272310	*PIK3R2*	Exon 06	NM_005027.3	25.40 (12/57)
Chr19	47249401..47249692	*STRN4*	Exon 01	NM_013403.2	34.73 (4/67)
Chr19	48901645..48902119	*GRIN2D*	Exon 02	NM_000836.2	39.16 (1/83)
Chr19	48945852..48947199	*GRIN2D*	Exon 13	NM_000836.2	42.24 (2/113)
Chr19	50831465..50832344	*KCNC3*	Exon 01	NM_004977.2	71.59 (0/197)
Chr20	442975..443054	*TBC1D20*	Exon 01	NM_144628.3	21.33 (16/24)
Chr20	62119646..62119783	*EEF1A2*	Exon 08	NM_001958.3	53.67 (19/73)
Chr22	19166088..19166191	*SLC25A1*	Exon 01	NM_005984.4	26.20 (8/40)

Chr22	43045296..43045326	*CYB5R3*	Exon 01	NM_000398.6	13.68 (10/14)
Chr22	51113065..51113137	*SHANK3*	Exon 01	NM_033517.1	16.63 (5/26)
Chr22	51135980..51135994	*SHANK3*	Exon 11	NM_033517.1	0.80 (0/4)
Chr22	51135987..51136148	*SHANK3*	Exon 12	NM_033517.1	11.54 (0/15)
Chr22	51158607..51160870	*SHANK3*	Exon 22	NM_033517.1	112.11 (6/216)
Chr22	51169144..51169745	*SHANK3*	Exon 23	NM_033517.1	73.56 (18/129)
ChrX	2871179..2871311	*ARSL*	Exon 05	NM_000047.2	29.72 (18/36)
ChrX	12701597..12701711	*FRMPD4*	Exon 06	NM_014728.3	28.59 (19/35)
ChrX	18597963..18598093	*CDKL5*	Exon 06	NM_003159.2	32.17 (17/38)
ChrX	18631267..18631400	*CDKL5*	Exon 15	NM_003159.2	25.17 (19/29)
ChrX	19379452..19379538	*MAP3K15*	Exon 28	NM_001001671.3	21.72 (18/24)
ChrX	19379606..19379716	*MAP3K15*	Exon 27	NM_001001671.3	18.18 (13/21)
ChrX	20179757..20179884	*RPS6KA3*	Exon 20	NM_004586.2	18.58 (13/22)
ChrX	20204409..20204489	*RPS6KA3*	Exon 10	NM_004586.2	28.77 (19/33)
ChrX	21958938..21958996	*SMS*	Exon 01	NM_004595.4	25.39 (16/34)
ChrX	24828010..24828052	*POLA1*	Exon 27	NM_001330360.1	24.95 (19/29)
ChrX	25031034..25031920	*ARX*	Exon 02	NM_139058.2	44.18 (0/108)
ChrX	40460009..40460138	*ATP6AP2*	Exon 08	NM_005765.2	35.98 (16/45)
ChrX	41029243..41029493	*USP9X*	Exon 19	NM_001039591.2	44.74 (14/70)
ChrX	41586275..41587295	*GPR82*	Exon 03	NM_080817.4	58.90 (18/83)
ChrX	43599923..43599990	*MAOA*	Exon 11	NM_000240.3	17.26 (16/19)
ChrX	53263396..53264371	*IQSEC2*	Exon 15	NM_001111125.2	50.24 (8/85)
ChrX	53449436..53449554	*SMC1A*	Exon 01	NM_006306.3	22.54 (15/28)
ChrX	67494575..67494656	*OPHN1*	Exon 05	NM_002547.2	23.17 (19/26)
ChrX	67518838..67518943	*OPHN1*	Exon 03	NM_002547.2	13.09 (10/16)
ChrX	70776525..70776635	*OGT*	Exon 09	NM_181672.2	24.09 (19/27)
ChrX	79945461..79945596	*BRWD3*	Exon 32	NM_153252.4	32.00 (18/40)
ChrX	108912258..108912407	*ACSL4*	Exon 10	NM_004458.2	29.15 (18/36)
ChrX	110435350..110435408	*PAK3*	Exon 12	NM_002578.4	19.58 (16/22)
ChrX	118975034..118975226	*UPF3B*	Exon 07	NM_080632.2	39.76 (13/53)
ChrX	119660611..119660716	*CUL4B*	Exon 20	NM_001079872.1	9.46 (7/12)
ChrX	122536840..122536954	*GRIA3*	Exon 08	NM_000828.4	7.37 (3/10)
ChrX	122778421..122778532	*THOC2*	Exon 15	NM_001081550.1	26.50 (19/35)
ChrX	123171372..123171478	*STAG2*	Exon 06	NM_001042750.1	25.42 (18/30)

ChrX	123182850..123182933	*STAG2*	Exon 10	NM_001042750.1	23.32 (17/28)
ChrX	135104740..135104861	*SLC9A6*	Exon 11	NM_006359.2	10.80 (7/14)
ChrX	135115568..135115657	*SLC9A6*	Exon 14	NM_006359.2	21.00 (16/24)
ChrX	139585880..139587230	*SOX3*	Exon 01	NM_005634.2	78.51 (11/131)
ChrX	148062263..148062325	*AFF2*	Exon 19	NM_002025.3	22.94 (17/26)
ChrX	152954025..152954296	*SLC6A8*	Exon 01	NM_005629.3	45.55 (15/67)
ChrX	152956754..152957013	*SLC6A8*	Exon 03	NM_005629.3	48.57 (17/75)
ChrX	153784375..153784596	*IKBKG*	Exon 03	NM_003639.4	0.77 (0/3)
ChrX	153786742..153786870	*IKBKG*	Exon 04	NM_003639.4	0.00 (0/0)
ChrX	153788617..153788779	*IKBKG*	Exon 05	NM_003639.4	1.99 (1/3)
ChrX	153789898..153790004	*IKBKG*	Exon 06	NM_003639.4	0.00 (0/0)
ChrX	153791020..153791173	*IKBKG*	Exon 07	NM_003639.4	0.00 (0/0)
ChrX	153791769..153791921	*IKBKG*	Exon 08	NM_003639.4	0.00 (0/0)
ChrX	153792169..153792240	*IKBKG*	Exon 09	NM_003639.4	18.47 (14/21)
ChrX	153792529..153792681	*IKBKG*	Exon 10	NM_003639.4	23.36 (11/44)
ChrX	154005069..154005147	*DKC1*	Exon 15	NM_001363.4	24.19 (19/28)

TECHNICAL LIMITATIONS

mosaics (<20%); indels >21bp; repeat expansions; repetitive regions; variants in: homopolymeric regions or regions of high sequence homology, unenriched regions (untranslated regions, introns, promoter and enhancer regions) or enriched but insufficiently covered regions; variants in mt-DNA (VAF<20%); determination of the phase of multiple variants in one gene; balanced genomic rearrangements

CLASSES OF VARIANTS

Class 5: pathogenic variant – are reported, posterior probability >99 %
Class 4: likely pathogenic variant – are reported, posterior probability >90 %
Class 3: uncertain significance – only be listed in the report if posterior probability is >67.5 %
Class 2: likely benign – not reported, posterior probability <10 %
Class 1: benign – not reported, posterior probability <0,1 %

ACMG CRITERIA

1. Criteria for pathogenic evidence
PVS1: Null variant in a gene where loss of function (LOF) is a known mechanism of disease; PS1: same amino acid change as a previously established pathogenic variant regardless of nucleotide change; PS2/PM6: de novo in a patient with the disease and no family history; PS3: well-established functional studies supportive of a damaging effect on the gene or gene product; PS4: the prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls/was identified in unrelated affected individuals; PM1: missense variant located in a mutational hot spot and/or critical and well-established functional domain; PM2: absent from controls (or at extremely low frequency) in Genome Aggregation Database (gnomAD); PM3: for recessive disorders, detected in homozygous state or together with another (not benign or likely benign) variant; PM4: protein length changes as a result of in-frame deletions/insertions in a non- repeat region or stop-loss variants; PM5: missense change at an amino acid residue where a different missense change determined to be (likely) pathogenic has been seen before; PP1: co-segregation with disease in multiple affected family members; PP2: missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease; PP3: multiple lines of computational evidence support a deleterious effect on the gene or gene product; PP4: patient's phenotype or family history is (highly) is specific for variations in the affected gene; PP5: reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation.

2. Criteria for benign evidence
BA1: allele frequency is >5% if recessive and 0.5% if dominant in gnomAD; BS1: allele frequency is greater than expected for disorder; BS2: observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age; BS3: well-established functional studies show no damaging effect on protein function or splicing; BS4: lack of segregation with disease; BP1: missense variant in a gene for which primarily truncating variants are known to cause disease OR for loss-of-function variants in a gene where the disease is caused by gain-of-function variants; BP2: observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern; BP3: in-frame deletions/insertions in a repetitive region without a known function; BP4: multiple lines of computational evidence suggest no impact on gene or gene product; BP5: variant found in a case with an alternate molecular basis for disease; BP6: reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation; BP7: a synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved.

According to Ellard et al. 2020, the strength level of criteria PVS1, PS1, PS2, PS3, PS4, PM1, PM3, PM4, PM5, PP1, PP4, BP2, and BP4 can be modified depending on the cogency of the evidence.

ALLELE FREQUENCIES

This value corresponds to the maximum frequency of all reference populations (POPMAX).

Report released by

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