Name	Sample ID
Date of birth	Sample collected
Sex	Sample received
Provider	Report date
Sample type	

POSITIVE RESULT

SLC12A3 c.1928C>T (p.Pro643Leu), NM_000339, Heterozygous, likely pathogenic

SLC12A3 c.2891G>A (p.Arg964Gln), NM_000339, Heterozygous, pathogenic

CLINICAL NOTES

From Our Clinical Team

Please note that this newborn child is heterozygous for two variants in the SLC12A3 gene: c.2891G>A (p.Arg964Gln) pathogenic variant and c.1928C>T (p.Pro643Leu) likely pathogenic variant. Variants in SLC12A3 are associated with autosomal recessive Gitelman syndrome. To determine whether these variants are in cis configuration (on the same chromosome) or in trans configuration (on opposite chromosomes) in the child, it is necessary to study these variants in the parents. When present in trans configuration, individuals may present with Gitelman syndrome. Parental testing is recommended to determine the configuration of these variants in this child. Clinical correlation and genetic counseling are also recommended.

INTERPRETATION

SLC12A3 c.1928C>T (p.Pro643Leu) is a likely pathogenic variant associated with autosomal recessive Gitelman syndrome. This variant has been reported in at least 18 unrelated affected individuals in the homozygous or compound heterozygous state (Cruz 2001, Pantanetti 2002, Glaudemans 2011, Vagas-Poussou 2011, Fava 2007, Nakhoul 2011, Talaulikar 2005), and segregated with disease in one sibling (Nakhoul 2011). This variant has been identified in 18/10354 Ashkenazi Jewish chromosomes by the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org; dbSNP rs140012781) and is present in ClinVar (ID: 417863, accessed 7/11/18). In summary, the p.Pro643Leu variant meets criteria (ACMG, Richards 2015) to be classified as likely pathogenic for autosomal recessive Gitelman syndrome.

SLC12A3 c.2891G>A (p.Arg964Gln; also referred to as R955Q) is a pathogenic variant associated with autosomal recessive Gitelman syndrome. This variant has been reported in at least 13 affected individuals in the homozygous or compound heterozygous state (Fujimura 2019, Ito 2012, Simon 1996) and segregated with disease in 1 individual (Fujimura 2019). In vitro functional studies showed that this variant affects normal protein localization (De Jong 2002). This variant has been detected in 18/10370 Ashkenazi Jewish chromosomes by the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org; dbSNP rs202114767) and is present in ClinVar (ID: 417864, accessed 7/3/19). In summary, the p.Arg964Gln variant meets criteria (ACMG, Richards 2015) to be classified as pathogenic for autosomal recessive Gitelman syndrome.

Pathogenic and likely pathogenic variants in myNewborn genes are associated with an increased risk for mainly childhood onset genetic disease. The disease risk differs from gene to gene.

Accurate risk assessment of inherited childhood onset disease(s) requires comprehensive medical and family history evaluation by a certified genetic counselor or other qualified medical professional. Any changes in screening or medical management based on these results should only be done through consultation with a physician.

REFERENCES

11168953, 11940055, 22009145, 21415153, 17654016, 22169961, 15976513, 30596175, 22214629, 12039972, 8528245

METHODS AND LIMITATIONS

myNewborn is a screening test for newborns and children up to 10 years of age, covering 407 genes responsible of diseases that are highly penetrant, typically of pediatric onset, and/or meet Veritas' selection criteria. The test is performed on saliva, cord or whole blood samples. Extracted genomic DNA is processed by a capture-based assay and sequenced on a next-generation sequencer (Illumina). Sequencing data is processed using bioinformatics pipeline with both Bayesian and Heuristic-based statistical variant callers developed for this intended use. Mapping and analysis are based on the human genome build UCSC hg19 reference sequence.

Regions with high sequence homology (as defined in PMID: 27228465) or with technical limitations for Next Generation Sequencing are not analyzed, see gene list for reference. Positions with less than 10X coverage are excluded from reporting unless confirmed by an alternative technology.

Analytic sensitivity is 99.9%, 95% CI [99.7%, 100%] for SNVs and 93.6%, 95% CI [88.2%, 97.0%] for small insertions/deletions. Analytical positive predictive value is 99.1%, 95% CI [98.8%, 99.4%] for SNVs and 94.9%, 95% CI [89.8%, 97.9%] for small insertions/deletions. Only inherited (germline) variants are detected, and not somatic variants, mosaicism, or heteroplasmy.

Initial filtering of variants is based on population frequency, variant type, and variant classifications in ClinVar (Landrum et al., 2015) and HGMD (Human Gene Mutation Database, Stenson et al., 2017). Variant interpretation is restricted to the 407 genes included in the panel. Any novel loss of function variant and variants with at least one ClinVar entry with classification of likely pathogenic / pathogenic or an HGMD label of “DM”, will be fully interpreted by Veritas according to the ACMG standards (Richards et al., 2015). Final classification may differ from ClinVar. Variants classified as pathogenic or likely pathogenic are reported. Benign variants, likely benign variants and variants of uncertain significance (VUS) are not reported.

All reported pathogenic and likely pathogenic variants are confirmed with Sanger sequencing when necessary. Carrier status for recessive disorders is not reported.

Certain types of variant are not analyzed, including but not limited to repeat expansions, inversions, deletions, duplications, translocations and large structural rearrangements. Therefore, for genetic diseases known to be associated with such variant types, a specific test for all variant types should be considered. Negative results do not exclude the possibility of an undetected pathogenic variant. As for all screening tests false negative or positive results can occur for a variety of reasons including technical or biological issues and limited scientific and clinical knowledge available for data interpretation.

A DNA sample from one or both of the biological parents might be requested to help interpreting gene sequencing results of the child (proband). In this case, targeted testing will be used to only evaluate variants identified in the proband. As such, no independent interpretation of parental results will be performed, and no separate reports will be issued.

References

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Stenson PD et al. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet 2017;136:665-677. PMID: 28349240

Zook JM. et al. Extensive sequencing of seven human genomes to characterize benchmark reference materials. Sci Data 2016;3:160025 doi: 10.1038/sdata.2016.25. PMID: 27271295

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GENES TESTED

ABCC8, ABCC9, ABCD1, ABCG5, ACADM, ACADVL, ACAT1, ACSF3, ACTG1, ADA, ADGRV1, ADK, AGA, AGL, AGXT, AIP, AIRE, AK2, AKR1D1, ALB, ALDH7A1, ALDOB, ALMS1, ALPL, ANK1, APC, APOB, AQP2, ARG1, ARMC4, ARSA, ARSB, ASL, ASPA, ASS1, ATP6V1B1, ATP7A, ATP7B, AUH, AVPR2, BCHE, BCKDHA, BCKDHB, BLM, BMPR1A, BSND, BTD, C21ORF59, CACNA1C, CACNA1S, CALM1, CALM2, CARD11, CASQ2, CASR, CBS, CCDC114, CCDC151, CCDC39, CCDC40, CCDC65, CCNO, CD3D, CD3E, CD40LG, CDC73, CDH23, CFTR, CIB2, CLDN14, CLRN1, CNGA3, CNGB3, COL11A1, COL1A1, COL1A2, COL2A1, COL3A1, COL4A3, COL4A4, COL4A5, COL9A1, CORO1A, CPS1, CPT1A, CPT2, CTNS, CYBA, CYBB, CYP11B1, CYP11B2, CYP1B1, CYP27A1, CYP27B1, DBT, DCLRE1C, DHCR7, DLD, DNAAF1, DNAAF5, DNAH11, DNAH5, DNAI1, DNAJB13, DNMT3B, DOCK8, DRC1, DSP, DUOX2, DUOXA2, DYX1C1, EDN3, ELANE, ELN, ELP1, EPB42, ERCC6, ESRRB, ETFA, ETFB, ETFDH, ETHE1, EYA1, F10, F11, F13A1, F13B, F2, F5, F7, F8, F9, FAH, FANCA, FANCB, FANCC, FANCD2, FANCG, FANCI, FBN1, FBP1, FGF3, FGFR3, FKTN, FOLR1, G6PC, G6PD, GAA, GALE, GALK1, GALNS, GALT, GAMT, GAS8, GATA1, GATA2, GATM, GBA, GBE1, GCDH, GCH1, GCK, GGCX, GH1, GIF, GIPC3, GJB2, GJB6, GLA, GLUD1, GP1BB, GP6, GP9, GPSM2, GRHPR, GSS, GYS2, HADH, HADHA, HADHB, HAX1, HBB, HEXA, HLCS, HMGCL, HMGCS2, HNF1A, HNF4A, HOGA1, HPD, HPS1, HPS3, HPS4, HSD11B2, HSD17B10, HSD3B2, HSD3B7, IDS, IDUA, IGSF1, IL2RA, IL2RG, IL7R, ILDR1, INS, ITGA2B, ITGB3, ITK, IVD, IYD, JAG1, JAK3, KCNH2, KCNJ10, KCNJ11, KCNJ5, KCNQ1, KCNQ2, KCNQ4, LAMA2, LAMP2, LDLR, LHX3, LIPA, LMBRD1, LOXHD1, LPL, LRPPRC, LRRC6, LRTOMT, MARVELD2, MAT1A, MAX, MCCC1, MCCC2, MCEE, MCIDAS, MCOLN1, MEFV, MEN1, MITF, MKS1, MLYCD, MMAA, MMAB, MMACHC, MMADHC, MPI, MPL, MTR, MTRR, MTTP, MUT, MYH9, MYO15A, MYO6, MYO7A, NAGS, NDUFS6, NF1, NFKB2, NKX2-1, NKX2-6, NLRP3, NOTCH2, NPC1, NPC2, NPHS1, NPHS2, OAT, OTC, OTOA, OTOF, OTOG, OTOGL, P2RY12, PAH, PAX3, PAX8, PCBD1, PCCA, PCCB, PCDH15, PDX1, PHGDH, PHKA2, PHKB, PHKG2, PIK3CD, PJVK, PKHD1, PLAU, PMM2, PNPO, POLR1D, POU1F1, POU3F4, PPT1, PROC, PROP1, PROS1, PRRT2, PTEN, PTPN11, PTPRC, PTPRQ, PTS, PYGL, PYGM, QDPR, RAB23, RAG1, RAG2, RB1, RET, RIT1, RMRP, RPL11, RPL5, RPS19, RPS24, RPS26, RPS29, RSPH1, RSPH3, RSPH4A, RSPH9, RYR1, S1PR2, SACS, SCN2A, SCN5A, SCN8A, SCNN1A, SCNN1B, SDHB, SIX1, SLC12A3, SLC12A6, SLC17A5, SLC19A2, SLC19A3, SLC22A5, SLC25A13, SLC25A15, SLC25A20, SLC26A2, SLC26A4, SLC2A1, SLC2A9, SLC37A4, SLC39A4, SLC46A1, SLC4A1, SLC5A5, SLC7A7, SLITRK6, SMAD4, SMPD1, SMPX, SNAI2, SOX10, SPAG1, SPG11, SPR, SRY, STAR, STAT3, STK11, STRC, TAT, TAZ, TBC1D24, TBX19, TCIRG1, TCN2, TCOF1, TECTA, TG, TGFB3, TH, THRA, TMC1, TMIE, TMPRSS3, TP53, TPO, TRHR, TRIOBP, TRMU, TSC1, TSC2, TSFM, TSHB, TSHR, TTC25, TTPA, UGT1A1, UNC13D, USH1C, USH1G, USH2A, VHL, WHRN, WT1, ZAP70, ZMYND10

Note: The number in parentheses indicates the percentage of the coding region sequenced at a coverage greater than 20x in those genes in which such coverage cannot be achieved in the whole coding region for technical reasons.

VALIDATION

Technical Director: Medical Director: Approved by: