Veritas
The Genome Company

myNewbornDNA Gene Panel Test

Name	Veritas myNB Demo	Sample Type	Saliva
DOB	May 05 1950	Sample Collected	Nov 7 2018
Sex	Female	Sample Received	Nov 12 2018
Provider	Veritas Doctor	Batch ID	mNB1234
Date of Report	Dec 14 2018	Customer ID	12345678

POSITIVE RESULT

FAH c.520C>T (p.Arg174*), NM_000137, homozygous, pathogenic variant

ADDITIONAL FINDINGS

No additional variants of clinical significance were detected.

CLINICAL NOTE

Please note that this individual is homozygous for a pathogenic *FAH* variant. Pathogenic variants in this gene are associated with autosomal recessive tyrosinemia type I (also known as *FAH* deficiency or Fumarylacetoacetase deficiency). Additional information regarding this condition can be found at GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1515/. It is recommended that these results be interpreted with this individual's previous biochemical testing and presentation. Parental testing is advised to clarify recurrence risk and confirm biallelic inheritance.

INTERPRETATION

Variant Information

***FAH* c.520C>T (p.Arg174*; also referred to as R174X)** is a pathogenic variant associated with autosomal recessive tyrosinemia type I. This variant introduces a premature stop codon at amino acid position 174. At this position, this is expected to result in absent protein (loss of function) which is an established mechanism of disease for *FAH*. This variant has been identified in 1 affected individual in the homozygous state (Dursun 2011). This variant was detected in 1/30782 South Asian chromosomes by the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org, dbSNP rs781496816) and is present in ClinVar (ID: 188751, accessed 1/18/18). In summary, the p.Arg174* variant meets criteria (ACMG, Richards 2015) to be classified as pathogenic for autosomal recessive tyrosinemia type I.

REFERENCES

23289006, 17574969, 22889855, 21473589, 23867111

METHODS AND LIMITATIONS

Veritas' myNewborn test is a screening test for newborn babies and children, covering 407 genes that lead to highly penetrant, actionable disease. The test is performed on saliva, cord blood or whole blood. Extracted genomic DNA is processed by a capture-based assay and sequenced on a next-generation sequencer (Illumina). For sample tracking and quality assurance, each sample is also assessed with the Infinium QC Array-24 microarray (Illumina). Sequencing is performed in Veritas Genetics' CLIA licensed and CAP accredited laboratory. Sequencing data are aligned to the hg19 (build 37.1) human reference genome. Data analysis is performed with Veritas Genetics' custom bioinformatics pipeline, which uses both Bayesian and Heuristic-based statistical variant callers.

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

METHODS AND LIMITATIONS

[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) as well as HGMD (Human Gene Mutation Database, Stenson et al., 2017). Variant interpretation is restricted to the set of 407 genes strongly associated with pediatric onset disorders. For these genes, any novel loss of function variants as well as variants with at least one ClinVar entry with a classification of likely pathogenic or pathogenic or an HGMD label of "DM" will be fully interpreted by Veritas using ACMG standards (Richards et al., 2015). The 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 variants (pathogenic and likely pathogenic variants) are confirmed with Sanger sequencing). Carrier state for recessive disorders is not reported.

Certain types of variations 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 disease specific test providing coverage of all necessary variant types should be considered. Negative results do not exclude the possibility of an undetected pathogenic variant. False negatives or positives can occur for a variety of reasons including technical issues, human error, and limited available scientific and clinical knowledge on data interpretation.

References

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

Mandelker D et al. Navigating highly homologous genes in a molecular diagnostic setting: a resource for clinical next-generation sequencing. Genet Med 2016;18:1282-1289. PMID: 27228465

Landrum MJ et al. ClinVar: public archive of interpretations of clinically relevant variants. Nuc Acids Res 2016;44(1):D862–D868. doi: 10.1093/nar/gkv1222. PMID 26582918

Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-424. PMID 25741868

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

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GENES TESTED

ABCC8, ABCC9, ABCD1 (95.7%), 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 (97.0%), 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 (92.1%), CPS1, CPT1A, CPT2, CTNS, CYBA, CYBB, CYP11B1 (87.0%), CYP11B2 (87.0%), CYP1B1, CYP27A1, CYP27B1, DBT, DCLRE1C, DHCR7, DLD, DNAAF1, DNAAF5 (95.8%), DNAH11, DNAH5, DNAI1, DNAJB13, DNMT3B, DOCK8, DRC1, DSP, DUOX2 (96.5%), DUOXA2, DYX1C1, EDN3, ELANE, ELN, ELP1, EPB42, ERCC6, ESRRB, ETFA, ETFB, ETFDH, ETHE1, EYA1 (93.3%), F10, F11, F13A1, F13B, F2, F5, F7, F8 (99.4%), F9, FAH, FANCA, FANCB, FANCC, FANCD2 (96.6%), FANCG, FANCI, FBN1, FBP1, FGF3, FGFR3, FKTN, FOLR1, G6PC, G6PD, GAA, GALE, GALK1, GALNS, GALT, GAMT, GAS8, GATA1, GATA2, GATM, GBA (70.3%), 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 (83.0%), IDUA, IGSF1, IL2RA, IL2RG, IL7R, ILDR1, INS, ITGA2B, ITGB3 (96.3%), ITK, IVD, IYD, JAG1, JAK3, KCNH2, KCNJ10, KCNJ11, KCNJ5, KCNQ1, KCNQ2, KCNQ4 (85.9%), 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 (98.2%), MYO6, MYO7A, NAGS, NDUFS6, NF1, NFKB2, NKX2-1, NKX2-6, NLRP3, NOTCH2 (95.4%), NPC1, NPC2, NPHS1, NPHS2, OAT, OTC, OTOA (65.4%), 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 (92.6%), 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 (98.8%), 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 (16.9%), TAT, TAZ, TBC1D24, TBX19, TCIRG1, TCN2, TCOF1, TECTA, TG, TGFB3, TH, THRA, TMC1, TMIE, TMPRSS3, TP53, TPO, TRHR, TRIOBP (56.8%), TRMU, TSC1, TSC2, TSFM, TSHB, TSHR, TTC25, TTPA, UGT1A1, UNC13D, USH1C, USH1G, USH2A, VHL, WHRN, WT1, ZAP70, ZMYND10

AUTHORIZED SIGNATURES

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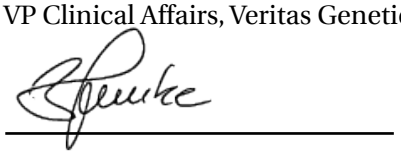

DISCLAIMER

This test was developed and its performance characteristics determined by Veritas Genetics. The analytical validation of this test meets CLIA and CAP requirements. The test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The Veritas Genetics laboratory is regulated under CLIA as qualified to perform high-complexity testing. If you have any questions about this report or wish to speak with one of Veritas Genetics' genetic counselors, please call 888-507-6619