Whole Exome Sequencing Analysis

Patient name	:	**Master. XXX**	**PIN**	:	**XX**
Gender/ Age	:	**Male/ 8 Years**	**Sample number**	:	**XX**
Referring clinician	:	**XX**	**Sample collection date**	:	**XX**
Specimen	:	**Peripheral Blood**	**Sample receipt date**	:	**XX**
			Report date	:	**XX**

Clinical history

Proband, Master. XXX was born to non-consanguineous parents with history of jaundice till one month of age. He is presented with chief complaints of difficulty in speaking after 1 year of age, myopia, nipples retroverted, cafe au lait spots, spine ?sacral dimple, high total T3, low vitamin D, IgE high and delayed bone age. His mother was diagnosed with childhood hypothyroidism, prone to bronchial asthma and has giant cafe au lait spots. His father was diagnosed with asthma. Proband's maternal grandmother has features of early onset dementia and paternal family has history of thyroid disorders, gall bladder, renal stone diseases, asthma and his paternal aunt's family has history of early breast cancer. Proband has an elder sister, alive and healthy. He is suspected to be affected with multiple endocrine neoplasia with neurocutaneous syndromes, congenital disorders of glycosylation with multiple autoimmune polyendocrinopathy and autism. Proband, Master. XXX has been evaluated for pathogenic variations.

Results

Variant of uncertain significance related to the given phenotype was detected

List of uncertain significant variant identified to the related phenotype:

Gene	Region	Variant*	Allele Status	Disease	Classification*	Inheritance pattern
RET (+)	Exon 3	c.406G>A **(p.Glu136Lys)**	Heterozygous	Multiple endocrine neoplasia IIA **(OMIM#171400)** Multiple endocrine neoplasia IIB	**Uncertain significance**	Autosomal Dominant

				(OMIM#162300) Pheochromocytoma **(OMIM#171300)** Medullary thyroid carcinoma **(OMIM#155240)** {Hirschsprung disease, protection against}/ {Hirschsprung disease, susceptibility to, 1} **(OMIM#142623)**		

*Genetic test results are based on the recommendation of American college of Medical Genetics [1].
No other variant that warrants to be reported for the given clinical indication was identified.

Interpretation

***RET*: c.406G>A**

Variant summary: A heterozygous missense variation in exon 3 of the *RET* gene (chr10: g.43102410G>A, NM_020975.6, Depth: 118x) that results in the amino acid substitution of Lysine for Glutamic acid at codon 136 (p.Glu136Lys) was detected.

Population frequency: This variant has minor allele frequency of 0.003% gnomAD database and has not been reported in 1000 genomes databases.

ClinVar evidence: This variant has been classified as uncertain significance in ClinVar database [3].

***In-silico* prediction**: The *in-silico* predictions of the variant are damaging by SIFT and LRT. The reference codon is conserved across mammals in PhyloP and GERP++ tools.

OMIM phenotype: Multiple endocrine neoplasia IIA (OMIM#171400) and Multiple endocrine neoplasia IIB (OMIM#162300) are caused by heterozygous mutation in the *RET* gene (OMIM*164761). Pheochromocytoma (OMIM#171300) is caused by mutation in the *RET* gene (OMIM*164761). Medullary thyroid carcinoma (OMIM#155240) occurs from mutation in the *RET* gene (OMIM*164761). {Hirschsprung disease, protection against} / {Hirschsprung disease, susceptibility to, 1} (OMIM#142623) is associated with variation in the *RET* gene (OMIM*164761). These diseases follow autosomal dominant pattern of inheritance [2].

Variant classification: Based on the evidence, this variant has been classified as a variant of uncertain significance**. In this view, clinical correlation and familial segregation analysis are strongly recommended to establish the significance of the finding. If the results do not correlate, additional testing may be considered based on the phenotype observed**.

Additional Variant(s)

The additional variants identified may not be related to patient's phenotype. Phenotype – genotype correlation is recommended.

List of additional variants identified:

Gene	Region	Variant*	Allele Status	Disease	Classification*	Inheritance pattern
CLCN7 (-)	Exon 13	c.1147G>A **(p.Val383Met)**	Heterozygous	Hypopigmentation, organomegaly, and delayed myelination and development **(OMIM#618541)**	**Uncertain significance**	Autosomal dominant
				Osteopetrosis, autosomal dominant 2 **(OMIM#166600)**		
				Osteopetrosis, autosomal recessive 4 **(OMIM#611490)**		Autosomal recessive

Recommendations

- Sequencing the variant(s) in the parents and the other affected and unaffected members of the family is recommended to confirm the significance.
- Alternative test is strongly recommended to rule out the deletion/duplication.
- Genetic counselling is advised.

Methodology

DNA extracted from the blood was used to perform whole exome using whole exome capture kit. The targeted libraries were sequenced to a targeted depth of 80 to 100X using GenoLab M sequencing platform. This kit has deep exonic coverage of all the coding regions including the difficult to cover regions. The sequences obtained are aligned to human reference genome (GRCh38.p13) using Sentieon aligner and analyzed using Sentieon for removing duplicates, recalibration and re-alignment of indels. Sentieon DNAscope has been used to call the variants. Detected variants were annotated and filtered using the VarSeq software with the workflow implementing the ACMG guidelines for variant classification. The variants were annotated using 1000 genomes (V2), gnomAD (v3.1,2.1.1), ClinVar, OMIM, dbSNP, NCBI RefSeq Genes. *In-silico* predictions of the variant was carried out using VS-SIFT, VS-PolyPhen2, PhyloP, GERP++, GeneSplicer, MaxEntScan, NNSplice, PWM Splice Predictor. Only non-synonymous and splice site variants found in the coding regions were used for clinical interpretation. Silent variations that do not result in any change in amino acid in the coding region are not reported.

Sequence data attributes

Total reads generated	9.37 Gb
Data ≥ Q30	96.59%

Genetic test results are reported based on the recommendations of American College of Medical Genetics [1], as described below:

Classification	Interpretation
Pathogenic	A disease-causing variation in a gene which can explain the patients' symptoms has been detected. This usually means that a suspected disorder for which testing had been requested has been confirmed
Likely Pathogenic	A variant which is very likely to contribute to the development of disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion of pathogenicity.
Variant of Uncertain Significance	A variant has been detected, but it is difficult to classify it as either pathogenic (disease causing) or benign (non- disease causing) based on current available scientific evidence. Further testing of the patient or family members as recommended by your clinician may be needed. It is probable that their significance can be assessed only with time, subject to availability of scientific evidence.

Disclaimer

- The classification of variants of unknown significance can change over time. Anderson Diagnostics and Labs cannot be held responsible for it.
- Intronic variants, UTR, Promoter region variants and CNV are not assessed using this assay.
- Certain genes may not be covered completely, and few mutations could be missed. Variants not detected by this assay may impact the phenotype.
- The variations have not been validated by Sanger sequencing.
- The above findings and result interpretation was done based on the clinical indication provided at the time of reporting.
- It is also possible that a pathogenic variant is present in a gene that was not selected for analysis and/or interpretation in cases where insufficient phenotypic information is available.
- Genes with pseudogenes, paralog genes and genes with low complexity may have decreased sensitivity and specificity of variant detection and interpretation due to inability of the data and analysis tools to unambiguously determine the origin of the sequence data in such regions.

- Incidental or secondary findings that meet the ACMG guidelines can be given upon request [4].

References

1. 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. Genetics in medicine: official journal of the American College of Medical Genetics. 17.5 (2015): 405-424.
2. Amberger J, Bocchini CA, Scott AF, Hamosh A. McKusick's Online Mendelian Inheritance in Man (OMIM). Nucleic Acids Res. 2009 Jan;37(Database issue):D793-6. doi: 10.1093/nar/gkn665. Epub 2008 Oct 8.
3. https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000216727.20
4. Kalia S.S. et al., Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med., 19(2):249-255, 2017.

This report has been reviewed and approved by:

Sivasankar.S, Ph.D Molecular Biologist	Muthukumaran. S, Ph.D Clinical Bioinformatician	Sachin. D.Honguntikar, Ph.D, Molecular Geneticist	Dr. G. Suriyakumar Director

Gene list based on phenotypes used for screening of pathogenic and likely pathogenic variants:

ADK, ADPRS, ALG9, AP1S2, AP4B1, AP4E1, AP4M1, AP4S1, APC2, ASPA, ATAD3A, ATP10A, ATP1A1, ATP6V0A2, ATP6V1A, ATP6V1B2, ATP6V1E1, BRF1, CAD, CAMK2G, CASZ1, CCDC22, CDC42, CDON, CHKB, CHMP1A, CHMP2B, CHSY1, CIC, CLIC2, CNTNAP2, COG8, TDGF1, CSF1R, CTNNB1, DAG1, DIAPH1, DISP1, DLAT, DLL1, DOCK7, DYM, DYRK1A, EIF2S3, EXT2, FBXL3, FDXR, FGF12, FGF8, FGFR1, FKRP, FMN2, FOXH1, FOXP2, FOXRED1, FRMD4A, GABRD, GAMT, GAS1, GATA4, GATAD2B, GJC2, GLI2, GMPPB, GNPTAB, GPR88, GRN, GUSB, HDAC8, HEPHL1, HNRNPK, HS6ST2, HSPG2, IFNG, INPP5E, IQSEC2, KANSL1, KAT6A, KCNAB2, KIF14, KMT2B, LARGE1, LAS1L, LRPPRC, LUZP1, MAN1B1, MAPT, MED13L, MED25, MID1, MID2, MRPS2, MTO1, NAA20, NAGS, NALCN, NDST1, NDUFA13, NDUFA6, NDUFS1, NGLY1, NODAL, NONO, NUBPL, OCA2, ODC1, OPHN1, PAK1, PAK3, PDPN, PIGC, PIGH, PLPBP, POMK, POMT1, POMT2, PPP1R15B, PPP2R1A, PPP2R5D, PRDM16, PRKCZ, PSEN1, PTCH1, PUS3, PYCR2, RAB39B, RAC1, RERE, RILPL1, RLIM, RNASET2, SARDH, SASS6, SATB2, SET, SHH, SIX3, SKI, SLC19A3, SLC35A1, SLC39A14, SLC39A8, SLC6A17, SMARCA2, SMC1A, SMC3, SNAP25, SNRPN, SOBP, SPEN, SQSTM1, STAG2, STIL, SYNGAP1, SYT1, TAF2, TAF6, TBCD, TBCK, TELO2, TGIF1, TMEM106B, TRAPPC10, TRAPPC11, TREM2, TRIO, TRMT10A, TRMT5, TRRAP, TSC1, TSC2, TUBB3, TUBB4A, UBE2A, UBE3A, UBE4B, UNC80, UQCC2, VCP, VLDLR, VPS11, WDR45, WDR73, WIPI2, YME1L1, ZEB2, ZIC2, ZNF148, ACOX2, ALDH18A1, COL7A1, CTNS, DNAJC21, DZIP1L, EFL1, ELN, FARSB, FBLN5, FGF23, FOCAD, GALNT2, GALT, GATA1, GPR35, HLA-DQA1, HLA-DQB1, MMP1, MST1, MTTP, OCRL, PKHD1, PTH1R, RPL11, RPS10, SBDS, SEMA4D, SLC10A1, SLC37A4, SLC51B, SRP54, TCF4, UROS, AEBP1, AFF3, ANK1, ARID1B, ASXL1, B3GLCT, B9D2, BAP1, BAZ1B, BCL7B, BICD2, BUD23, CAPN15, CCL2, CD96, CDK10, CLIP2, COLEC10, COX7B, CPLX1, CTBP1, CTCF, DCHS1, DEAF1, DHCR7, DHPS, DICER1, DNAJC30, DVL1, DVL3, EBP, EIF4H, ERI1, EXTL3, FANCB, FANCF, FAT4, FGFRL1, FKBP6, FUZ, FZD2, GNB2, GTF2IRD1, H4C5, HCCS, HIC1, HOXA13, IL6ST, KCNK9, KMT2A, LETM1, LIG4, LIMK1, MAN2C1, MASP1, MED12, METTL27, MLXIPL, NADSYN1, NCAPG2, NDUFB11, NELFA, NSD2, NSUN2, NXN, OTUD6B, PAFAH1B1, PIGG, POLA1, PRMT7, PRR12, PSMD12, RAB23, RFC2, ROR2, RPL10, SCARF2, SETD5, SHANK3, SMC5, SMG9, SMOC1, SPOP, STX1A, SUGCT, TAF1, TBL2, TBX4, TBX5, TBXT, TMCO1, TMEM270, USP9X, VANGL1, VANGL2, VPS37D, WLS, WNT5A, YWHAE, ZIC3, ZNF699, ABCB6, ABCC9, AKT1, APC, ARL6IP6, ATM, BLM, BRAF, BRCA1, BRCA2, BRIP1, BUB1, BUB1B, BUB3, CBL, CDKN1C, CEP57, CIB1, CLCN7, COPB1, CREBBP, CWC27, DHX30, EP300, ERCC4, ESCO2, FANCA, FANCC, FANCD2, FANCE, FANCG, FANCI, FANCL, GNA11, HEPACAM, HMGA2, IGF1, IGF2, IL7, KDM5C, KDM6A, KDM6B, KITLG, KLLN, KMT2D, KRAS, LZTR1, MAD2L2, MAP2K1, MAP2K2, MAPK1, MAX, MEN1, MLH1, MSH2, MSH6, MTOR, NBN, NF1, NF2, NRAS, PALB2, PCNT, PDE11A, PIK3CA, PLAG1, PLXND1, PMS2, POLE, PPP1CB, PRKAR1A, PTEN, PTPN11, RAD51, RAD51C, RAF1, RBBP8, RET, RFWD3, RFX7, SDHB, SDHC, SDHD, SEC23B, SETBP1, SH3PXD2B, SHOC2, SLC9A1, SLF2, SLX4, SOX10, SPRED1, STEAP3, TMC6, TMC8, TMEM127, TOMM7, TOP3A, TP63, TRIP13, TWIST2, UBAP2L, UBE2T, USF3, VHL, 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RHAG, RHCE, RHD, RINT1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SERPINA1, SETD2, SLC16A2, SLC25A13, SLC26A4, SLC2A1, SLC30A10, SLC44A1, SLC4A1, SLC5A5, SLCO1B1, SMAD4, SMPD1, SP110, SPIB, SPINK1, SPTA1, SPTB, SPTBN1, STX11, STXBP2, TBX19, TFAM, TG, TNFSF15, TNPO3, TP53, TPI1, TPO, TREX1, TRHR, TRMU, TSHB, TSHR, TULP3, UGT1A1, UNC13D, UNC45A, USP53, VIPAS39, VPS33B, YARS1, ZFYVE19, AARS1, ABCB7, ACTL6B, ADNP, ADSL, AHDC1, ALAD, ALDH5A1, ALG13, ALG14, ANKRD11, AP3B2, ARCN1, ARL6, ARNT2, ARV1, ARVCF, ASXL3, ATP1A2, ATP1A3, ATRX, BBIP1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BCKDK, BRD4, CACNA1A, CACNA1B, CACNA1C, CACNA2D1, CDK13, CDK19, CELF2, CEP19, CFAP418, CHD7, CHD8, CHRNA7, CLTC, CNKSR2, COMT, CYFIP2, DALRD3, DHDDS, DNM1, DPYD, DPYS, EEF1A2, EHMT1, EIF4A2, FBXO28, FGF13, FLCN, FLG, FMR1, FOXG1, FTCD, FTSJ1, FZR1, GABBR2, GABRA2, GABRA5, GABRB2, GABRG2, GATM, GJA5, GJA8, GLRA2, GNB1, GP1BB, GRIA3, GRIN2D, HCN1, HDAC4, HECTD4, HERC2, HIRA, IFT172, IFT27, IFT74, IL1RAPL1, 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PPOX, PPP1R21, PPT1, PRDM5, PRIMPOL, PUF60, PURA, RAB28, RBM10, RECQL4, RHO, RHOA, RIN2, RNF113A, RP1, RP2, RPE65, RPGR, SAG, SCO2, SLC12A6, SLC24A1, SLC25A4, SLC2A10, SLC39A5, SLITRK6, SMARCA4, SMARCAL1, SMARCB1, SMARCC2, SMARCD1, SMARCE1, SMS, SON, SOX11, SOX4, SOX5, SOX9, SPATA7, SPTSSA, SRCAP, TARS1, TBC1D24, TBC1D7, TCF20, TDO2, TEAD1, TFAP2A, TFAP2B, TFE3, TGFBI, THG1L, THOC6, TIMM8A, TKFC, TLK2, TMEM63A, CLCN7, TMEM94, TNPO2, TPP1, TRIT1, TRNT1,

TRPM1, TSPAN7, TTLL5, TTR, TUB, TULP1, TYR, UBE3B, UCHL1, UNC119, USH2A, USP7, VARS1, VCAN, VPS13B, VPS50, WAC, WDR19, WDR26, WDR35, WHRN, XYLT1, XYLT2, ZMYM3, ZNF408, ZNF469, ZNF644, ZSWIM6, ADA, CAMK2B, CARD11, CARMIL2, CDSN, CPN1, CSTA, CTLA4, DOCK8, DPP9, DSG1, FOXP1, FOXP3, JAK1, KRT74, PGM3, PLCG2, PSTPIP1, RBM8A, SIK3, SLC19A1, SLC27A4, SMAD2, SOX6, SPINK5, STAT6, TGM5, ALG11, ALG12, ALG2, ALG3, ALG8, ATN1, C18orf32, DLK1, DPM1, EBF3, EZH2, JARID2, MGAT2, RFT1, RTL1, SLC25A46, SLC35A2, SRD5A3, STT3A, TBX3, DPM3, ALG1, SSR4, MOGS, COG4, MAGT1, MPI, DPM2, PGM1, COG1, COG5, COG2, DOLK, GNE, DDOST, MPDU1, STT3B, TUSC3, COG6, GMPPA, TMEM165, PIGN, TMEM199, CHEK2, FH, IPMK, EGFR, NTHL1, ARMC5, CDH1, POLD1, SDHAF2, MUTYH, GPR101, SDHA, BARD1, RAD51D, KIF1B, AIP, CDKN1B, CDK4, EPCAM, STK11, CDH23, RECQL, MET, NR0B1, CYP17A1, KCNJ11, SLC2A2, THRA, THRB, INSR, SLC16A1, ABCC8, CYP11B1, GLUD1, GLIS3, GCK, HADH