Male Fertility and Polymorphism Panel

Patient name	:	**Mr. XXX**	**PIN**	:	**XX**
Gender/ Age	:	**Male/ 29 years**	**Sample number**	:	**XX**
Hospital/Clinic	:	**XX**	**Sample collection date**	:	**XX**
Specimen	:	**Peripheral blood**	**Sample receipt date**	:	**XX**
			Report date	:	**XX**

CLINICAL HISTORY

Mr. XXX and Mrs. YYY are a non-consanguineous couple presented with a history of pregnancy losses. Their previous pregnancy was miscarried at 14 weeks GA. Chromosomal Microarray Analysis in Product of Conception was indicative of Trisomy 21. Peripheral Blood Karyotyping in both the partners was indicative of normal chromosome complement. Genetic Thrombophilia Recurrent Pregnancy Loss panel in the female partner was indicative of heterozygous polymorphism in Factor V gene. Mr. XXX have been evaluated for carrier status of pathogenic variations.

RESULTS

MALE FERTILITY SINGLE NUCLEOTIDE VARIATION

No pathogenic or likely pathogenic variant causative of the reported phenotype was detected

*Genetic test results are based on the recommendation of American college of Medical Genetics [1-3].
No other variant that warrants to be reported for the given clinical indication was identified.

MALE POLYMORPHISM ANALYSIS

THROMBOPHILIA AND NAIT PANEL (Neonatal Alloimmune Thrombocytopenia) [4-9]			
DISORDER/COMMON NAME	**VARIANT**	**ZYGOSITY/GENOTYPE**	**DESCRIPTION/RECOMMENDATIONS**
Factor V Leiden	F5: c.1601G>A (p.Arg534Gln)	Normal	
Factor VR2	F5:c.3980A>G (p.His1327Arg)	Normal	
Factor XIII	F13A1:c.103G>T (p.Val35Leu)	Homozygous wild type	
HPA-1	ITGB3:c.176T>C (p.Leu59Pro)	Normal	
HPA-2	GP1BA:c.482C>T (p.Thr161Met)	Normal	
HPA-3	ITGA2B):c.2621T>G (p.lle8745er	Normal	
HPA-4	ITGB3:c.506G>A (p.Arg169Gln)	Normal	
HPA-5	ITGA2:c.1600G>A (p.Glu534Lys)	Heterozygous	
HPA-6	ITGB3:c.1544G>A (p.Arg515Gln)	Normal	
PAI-1 4G/5G	SERPINE1:c-820G[(4_5)]		
MTHFR	MTHFR:c.665C>T (p.Ala222Val)	Normal	
MTHFR	MTHFR:c.1286A>C (p.Glu429Ala)	Heterozygous	
ACE (I/D)	ACE:c.2306-117 2306-116insAF118569.1: g.14094_14382		
Apo B	APOB:c.10580G>A (p.Arg3527Gln)	Normal	

Apo E	APOE:c.526C>T (p.Arg176Cys)	Normal	
Apo E	APOE:c.388T>C (p.Cys130Arg)	Normal	
MTR	MTR:c.2756A>G (p.Asp919Gly)	Heterozygous	
MTRR	MTRR:c.66A>G (p.lle22Met)	Heterozygous	
AGT	AGT:c.803T>C (p.Met268Thr)		
AGTR1	AGTR1:c.*86A>C	Normal	
GSTP1	GSTP1:c.313A>G (p.lle105Val)	Normal	
Prothrombin	F2:c.*97G>A	Normal	

Male Infertility conditions			
DISORDER/COMMON NAME	**VARIANT**	**ZYGOSITY/GENOTYPE**	**DESCRIPTION/RECOMMENDATION**
Impaired Spermatogenesis	***CATSPER1*:c.1954G>A** ***CATSPER1*: c.1222C>A**		High risk for Asthenospermia Clinical Correlation
	FSHR:* c.2039G>A, *FSHB	Homozygous wild type	Variable – Oligo/Astheno/Terato r-FSH improves seminal parameters
Testicular Volume			
Sperm DNA Fragmentation (DFI)	***FSHR:* c.2039G>A, *FSHB***	Homozygous wild type	Elevated DFI risk r-FSH may reduce DFI
Sperm Function			
Bilateral absence of Vas Deferens			
Androgen Insensitivity			

Erectile / Ejaculation dysfunction			
Male Hormones			
Idiopathic Male Infertility			
Fertility / ART implications			
ART protocols	***CATSPER1*:c.1954G>A** ***CATSPER1*: c.1222C>A**		Carriers suitable for ART ICSI for favorable results
			Improved response to r-FSH therapy Post r-FSH therapy improves ART
Fertilization Rates			
Aneuploidy Risk			
Pregnancy loss & Other			
Recurrent Pregnancy Loss	***FSHR:* c.2039G>A, *FSHB***	Homozygous wild type	Elevated RPL risk due to high DFI r-FSH therapy helpful

MALE INFERTILITY GENES - 751 GENES

PROKR2,ANOS1,FGFR1,CHD7,SEMA3A,CYP17A1,CYP21A2,PATL2,TUBB8,TRIP13,ZP3,CBS,ZP1,ZP2,PADI6,TLE6,KHDC3L,NLRP7,NLRP5,BTG4,CHEK1,WEE2,PANX1,LHX1,WNT4,SHOX,HNF1B,TBX6,WNT9B,TBC1D1,AMH,AMHR2,CLPP,HSD17B4,DNAH5,DNAI1,DNAI2,DNAL1,BRCA1,CFTR,LHCGR,DLX3,FGG,LIG4,COX4I2,AR,CBX2,CYP11A1,CYP19A1,DHH,FGF8,FSHB,HESX1,HSD17B3,LHB,LHX3,LHX4,MAP3K1,NR0B1,NSMF,POU1F1,PROP1,SRD5A2,AAAS,ABCA12,ABCA4,ABCB11,ABCB4,ABCC6,ABCC8,ABCD1,ACAD9,ACADM,ACADS,ACADSB,ACADVL,ACAT1,ACOX1,ACSF3 ADA,ADAMTS2,ADGRG1,AGA,AGL,AGPS,AGXT,AIRE,ALDH3A2,ALDH7A1,ALDOB,ALG6,ALPL,AMT,AP1S1,AQP2,ARG1,ARSA,ARSB,ASL,ASNS,ASPA,ASS1,ATM,ATP6V1B1,ATP7A,ATP7B,ATP8B1,ATRX,BBS1,BBS10,BBS2,BBS4,BBS9,BCHE,BCKDHA,BCKDHB,BCS1L,BLM,BRIP1,BSND,BTD,BTK,CANT1,CAPN3,CASQ2,CC2D1A,CDH23,CEP290,CERKL,CHM,CHRNE,CHRNG,CIITA,CLN3,CLN5,CLN6,CLN8,CLRN1,CNGA3,CNGB3,COL11A2,COL4A3,COL4A4,COL4A5,COL7A1,CPS1,CPT1A,CPT2,CRB1,CTNS,CTSC,CTSD,CTSK,CYBA,CYBB,CYP11B2,CYP1B1,CYP27A1,CYP27B1,DBT,DCLRE1C,DDB2,DHCR7,DHDDS,DKC1,DLD,DMD,DOK7,DPYD,DYSF,EDA,EDAR,EIF2AK3,EMD,ERCC2,ERCC3,ERCC4,ERCC5,ERCC8,ESCO2,ETFA,ETFB,ETFDH,ETHE1,EVC,EVC2,EXOSC3,EYS,F11,F2,F8,F9,FAH,FAM161A,FANCA,FANCC,FANCG,FH,FKRP,FKTN,G6PC,G6PD,GAA,GALC,GALE,GALK1,GALNS,GALNT3,GAMT,GBA,GBE1,GCDH,GCH1,GDF5,GFM1,GH1,GHRHR,GJB1,GJB2,GJB3,GJB6,GLA,GLB1,GLDC,GLE1,GNE,GNPTAB,GNPTG,GNS,GORAB,GP1BA,GP1BB,GP9,GRHPR,GUCY2D,GUSB,HADHA,HADHB,HAX1,HBA1,HBA2,HBB,HEXA,HEXB,HFE,HFE2(HJV),HGD,HGSNAT,HLCS,HMGCL,HMOX1,HOGA1,HPD,HPS1,HPS3,HPS4,HSD3B2,HYLS1,IDS,IDUA,IKBKAP(ELP1),IL2RG,ITGB3,IVD,KCNJ11,LAMA2,LAMA3,LAMB3,LAMC2,LCA5,LDLR,LDLRAP1,LIFR,LIPA,LIPH,LOXHD1,LPL,LRPPRC,LYST,MAN2B1,MAT1A,MCCC1,MCCC2,MCOLN1,MECP2,MED17,MEFV,MESP2,MFSD8,MKS1,MLC1,MLYCD,MMAA,MMAB,MMACHC,MMADHC,MOCS1,MPI,MPL,MPV17,MRE11,MTHFR,MTM1,MTRR,MTTP,MUT(MMUT),MYO15A,MYO7A,NAGLU,NAGS,NBN,NDRG1,NDUFAF5,NDUFS4,NDUFS6,NEB,NEU1,NPC1,NPC2,NPHP1,NPHS1,NPHS2,NR2E3,NTRK1,OAT,OCRL,OPA3,OTC,PAH,PANK2,PC,PCCA,PCCB,PCDH15,PDHA1,PDHB,PEPD,PET100,PEX1,PEX10,PEX12,PEX2,PEX6,PEX7,PFKM,PHGDH,PIGN,PKHD1,PLA2G6,PNPO,POLG,POLH,POMGNT1,POR,PPT1,PREPL,PRPS1,PSAP,PTS,PUS1,PYGM,RAB23,RAG1,RAG2,RAPSN,RARS2,RDH12,RLBP1,RMR

P(NME1),RNASEH2C,RPE65,RPGRIP1L,RS1,RTEL1,SACS,SAMD9,SAMHD1,SBDS,SEPSECS,SERPINA1,SGCA,SGCB,SGCD,SGCG,SGSH,SLC12A3,SLC12A6,SLC17A5,SLC19A2,SLC22A5,SLC25A13,SLC25A15,SLC25A20,SLC26A2,SLC26A3,SLC26A4,SLC35A3,SLC37A4,SLC39A4,SLC3A1,SLC45A2,SLC4A11,SLC6A8,SLC7A7,SLC7A9,SMARCAL1,SMN1,SMPD1,ST3GAL5,STAR,STRC,SUCLA2,SUMF1,SURF1,TAT,TCIRG1,TECPR2,TFR2,TGM1,TH,TMC1,TMEM216,TPO,TPP1,TREX1,TRIM32,TRMU,TSEN54,TSFM,TSHB,TSHR,TTC37,TTN,TTPA,TYMP,TYR,TYRP1,UGT1A1,UPB1,USH1C,USH2A,VPS13A,VPS13B,VPS45,VPS53,VRK1,VSX2,VWF,WAS,WISP3(CCN6),WNT10A,WRN,XPA,XPC,ZFYVE26,AKR1C4,AXL,BBS5,BBS7,CAPN10,DUSP6,EIF2B1,EIF2B3,F10,F12,F13A1,F13B,F2R,F5,F7,FGA,FGB,FGF17,FGFR2,GNAS,HOXA13,HS6ST1,INS,INSR,IRS1,IRS2,ITGA2,KLKB1,LEP,LEPR,LMNA,MTR,NOS1,PCSK1,PLAT,PLG,PRLR,PROC,PROCR,PROS1,RSPO1,SEMA3E,SERPINC1,SERPINE1,SERPINF1,SHBG,SOX10,SOX9,SPRY4,SRA1,THBD,TTC8,WWOX,ABCA3,AFF2,AHI1,ANO10,ARX,CC2D2A,CCDC88C,CLCN1,DYNC2H1,ELP1,FMO3,FMR1,FXN,G6PC1(G6PC),GALT,GRIP1,L1CAM,LRP2,MCPH1,MID1,MMUT,MVK,NAGA,OCA2,PLP1,PMM2,PRF1,RNASEH2B,RPGR,SCO2,SLC19A3,TF,TNXB,APC,MYH11,ACTA2,TMEM43,DSP,PKP2,DSG2,DSC2,BRCA2,SCN5A,RYR2,FLNC,MYBPC3,COL3A1,APOB,MYH7,TPM1,PRKAG2,TNNI3,MYL3,MYL2,ACTC1,RET,PALB2,ENG,ACVRL1,MAX,TMEM127,PCSK9,BMPR1A,SMAD4,TNNT2,TP53,TGFBR1,TGFBR2,SMAD3,TRDN,KCNQ1,KCNH2,MLH1,MSH2,MSH6,PMS2,RYR1,CACNA1S,FBN1,HNF1A,MEN1,MUTYH,NF2,SDHD,SDHAF2,SDHC,SDHB,STK11,PTEN,RB1,TSC1,TSC2,VHL,WT1,FSHR,SRY,CYP11B1,NOBOX,GDF9,DLK1,DNMT1,FOXL2,SOHLH1,C3,FIGLA,BMP15,MCM8,MCM9,PSMC3IP,TRIM37,TG,IGSF10,MRPS22,NR5A1,MSH5,ERCC6,BMPR1B,GREM1,NOTCH2,STAG3,CAV1,NUP107,ATG7,ATG9A,ESR2,KHDRBS1,PGRMC1,SPIDR,POF1B,EIF2B2,EIF2B4,EIF2B5,HFM1,SYCE1,TGFBR3,POU5F1,CITED2,NANOS3,EIF4ENIF1,NOG,C14orh39,RAD51B,NPPC,FANCL,TP63,BUB1B,IL17RD,FLRT3,POLR3A,TUBB3,RAB3GAP2,SLC29A3,DCAF17,ALMS1,BBS12,MKKS,RAB3GAP1,PHF6,ARL6,FEZF1,PROK2,NDNF,KISS1R,GNRHR,KISS1,CCDC141,WDR11,TAC3,SOX2,TACR3,GNRH1,CADM1

MALE THROMBOPHILIA & NAIT PANEL - 27 GENES

Genes: NM_000130.4(*F5*):c.1601G>A (p.Arg534Gln). NM_000130.4(*F5*):c.3980A>G (p.His1327Arg). NM_000129.3(*F13A1*):c.103G>T (p.Val35Leu). NM_000212.2(ITGB3):c.176T>C (p.Leu59Pro). NM_000173.7(GP1BA):c.482C>T (p.Thr161Met). NM_000419.5(ITGA2B):c.2621T>G (p.Ile874Ser). NM_000212.2(ITGB3):c.506G>A (p.Arg169Gln). NM_002203.4(ITGA2):c.1600G>A (p.Glu534Lys). NM_000212.2(ITGB3):c.1544G>A (p.Arg515Gln). NM_000602.5(SERPINE1):c.-820G[(4_5)]. NM_005957.5(MTHFR):c.665C>T (p.Ala222Val). NM_005957.4(MTHFR):c.1286A>C (p.Glu429Ala). NM_000789.3(ACE):c.2306-117_2306-116insAF118569.1:g.14094_14382. NM_000384.3(APOB):c.10580G>A (p.Arg3527Gln). NM_000041.2(APOE):c.526C>T (p.Arg176Cys). NM_000041.4(APOE):c.388T>C (p.Cys130Arg). NM_000254.2(MTR):c.2756A>G (p.Asp919Gly). NM_002454.3(MTRR):c.66A>G (p.Ile22Met). NM_000029.4(AGT):c.803T>C (p.Met268Thr). NM_031850.3(AGTR1):c.*86A>C. NM_000852.4(GSTP1):c.313A>G (p.Ile105Val). NM_000506.5(F2):c.*97G>A, NM_000233.4(*LHCGR*): c.56_57insC(p.Pro19_Pro20insCysSer), , NM_000233.4(*LHCGR*): c.935A>G(p. Asn312Ser), NM_000145.4(*FSHR*): c.-29G>A, NM_000145.4(*FSHR*): c.919G>A(p. Ala307Thr), NM_000145.4(*FSHR*): c.2039G>A(p. Ser680Asn)

Methodology: Single Nucleotide Variation - Single Nucleotide Polymorphism

SNV analysis: DNA extracted from the blood, was used to perform targeted gene capture using a custom capture kit. The targeted libraries were sequenced to a targeted depth of 80 to 100X using Illumina 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 (3.1.2,2.1.1), 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.

SNP analysis: Variant analysis and interpretation is done using VarSeq Software. Extensive scientific literature, Information from variant analysis and disease specific databases, population specific research are used to interpret and recommend. All results are finally approved by medical geneticists.

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 [3].
- Result interpretation was done based on the literature evidence available at the time of reporting. The clinical significance of the polymorphic variants tested can change over time and Anderson Diagnostics & Labs cannot be held responsible for this.
- This is not a diagnostic test and so not to be considered as diagnosis of any disease. This test is meant only for understanding the polymorphism at a given position and its association with various clinical parameters.

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This report has been reviewed and approved by:

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