Female Fertility and Polymorphism Panel

Patient name	:	**Mrs. XXX**	**PIN**	:	**XX**
Gender/ Age	:	**Female/ 26 years**	**Sample number**	:	**XX**
Hospital/Clinic	:	**XX**	**Sample collection date**	:	**XX**
Specimen	:	**Peripheral blood**	**Sample receipt date**	:	**XX**
			Report date	:	**XX**

CLINICAL HISTORY

Mr. YYY and Mrs. XXX 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. Mrs. XXX have been evaluated for carrier status of pathogenic variations.

RESULTS

FEMALE 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.

FEMALE POLYMORPHISM ANALYSIS

THROMBOPHILIA AND NAIT PANEL (Neonatal Alloimmune Thrombocytopenia) [4-9]			
DISORDER/COMMON NAME	**VARIANT**	**ZYGOSITY/GENOTYPE**	**DESCRIPTION**
Factor V Leiden	F5: c.1601G>A (p.Arg534Gln)	Heterozygous	Heterozygous Polymorphism
Factor VR2	F5:c.3980A>G (p.His1327Arg)	Normal	
Factor XIII	F13A1:c.103G>T (p.Val35Leu)	Normal	
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)	Normal	
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)	Normal	
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)	Heterozygous	Heterozygous polymorphism
MTR	MTR:c.2756A>G (p.Asp919Gly)	Heterozygous	Heterozygous polymorphism
MTRR	MTRR:c.66A>G (p.lle22Met)	Normal	
AGT	AGT:c.803T>C (p.Met268Thr)		
AGTR1	AGTR1:c.*86A>C		
GSTP1	GSTP1:c.313A>G (p.lle105Val)	Normal	
Prothrombin	F2:c.*97G>A	Normal	

FEMALE POLYMORPHISM - FSHR & LHCGR [10-25]

DISORDER/COMMON NAME	VARIANT	ZYGOSITY/GENOTYPE	DESCRIPTION
LHCGR	c.54_55ins6bp (ins18LQ)	-/ ins6bp	No association with controlled ovarian hyperstimulation No association with PCOS
		-/-	Susceptible to IVF failure
		ins6bp/ins6bp	Lower AMHR2 No association with controlled ovarian hyperstimulation Protective genotype for PCOS
LHCGR	c.935 A>G (Asn312Ser)	A/G	Increased risk for PCOS No association with IVF
		A/A	Increased risk for PCOS High basal FSH Protective effect on IVF
		G/G	Susceptible to IVF Failure Risk of developing PCOS

FSHR	c.-29G>A	G/A	Lower FSH consumption
		A/A	Increased testosterone level Reduced FSHR level Lower number of oocytes and low pregnancy rate Require high rFSH dose Poor responders to ovarian hyperstimulation
		G/G	Increased androstenedione Reduced AMH level Require high rFSH dose per oocyte Poor responders to ovarian hyperstimulation
FSHR	c.919G>A (Ala307Thr)	G/A	Stimulation duration is longer
		A/A	More oocytes retrieved after controlled ovarian hyperstimulation Stimulation duration is shorter
		G/G	Lower AMHR2 Higher LHCGR Low pregnancy rate Poor responders to ovarian hyperstimulation
FSHR	c.2039G>A (Ser680Asn)	G/A	Require high rFSH dose Generate higher number of follicles and oocytes No association with controlled ovarian hyperstimulation
		A/A	Lower LHCGR Lower levels of estradiol, follicle and oocytes High risk for ovarian hyperstimulation syndrome No association with controlled ovarian hyperstimulation Risk of developing PCOS
		G/G	Poor response to FSH stimulation Lower rate of oocyte retrieval after ovarian stimulation Lower AMHR2 Higher LHCGR Increased basal FSH level; Require high rFSH dose Resistance to insulin in PCOS Low pregnancy rate Risk of endometriosis in fertile women

**This test panel covers only the most common LHCGR and FSHR polymorphisms associated with infertility.*

Ovarian and Uterine Conditions			
DISORDER/COMMON NAME	**VARIANT**	**ZYGOSITY/GENOTYPE**	**DESCRIPTION/RECOMMENDATION**
Premature Ovarian Insufficiency - POI			
Follicle Count and Quality	ESR1(: c.453-397T>C)		May have low follicle count Higher gonadotropin dose favorable
Polycystic Ovarian Syndrome – PCOS(LHCGR)	*LHCGR*(c.935A>G)		2-3 fold elevated risk for PCOS Clinical Correlation
Endometriosis			
Fertility / ART implications			
DISORDER/COMMON NAME	**VARIANT**	**ZYGOSITY/GENOTYPE**	**DESCRIPTION/RECOMMENDATION**
Idiopathic Female Infertility			
Controlled Ovarian Stimulation - COS	*LHCGR*(: c.935A>G)		Slow response to ovarian stimulation LH stimulation favorable
	ESR1(: c.453-397T>C)		Poor response to ovarian stimulation Higher gonadotropin dose favorable
Ovarian Hyper Stimulation Syndrome			
Oocyte Number and Quality	*LHCGR*(c.935A>G)		Immature oocytes may be retrieved LH stimulation favorable
	ESR1(: c.453-397T>C)		Immature oocytes may be retrieved
Oocyte Maturation			
ART Fertilization Rates			
Embryo Quality and Development			
Aneuploidy Risk			
Implantation Rates	MDM2(: c.-412T>G)		RIF risk–High Oxidative Stress Supplementation of Anti Oxidants

	IL10: c.-627A>C		RIF risk-Dysregulated immunity Anti-inflammatory Immune support
	IL21: c.204+1115G>T		RIF risk-Dysregulated immunity Anti-inflammatory Immune support
	MTHFR: c.665C>T		RIF risk-Dysregulated thrombophilia Anti-Coagulant therapy favourable
Genuine Empty Follicle Syn - GEFS			

Pregnancy loss & Other

DISORDER/COMMON NAME	VARIANT	ZYGOSITY/GENOTYPE	DESCRIPTION/RECOMMENDATION
Recurrent Pregnancy Loss	MDM2(: c.-412T>G)		RPL risk–High Oxidative Stress Supplementation of Anti Oxidants
	MTHFR:c.665C>T		RIF risk-Dysregulated thrombophilia Anti-Coagulant therapy favourable
	IL10: c.-627A>C		RIF risk-Dysregulated immunity Anti-inflammatory Immune support
	IL21: c.204+1115G>T		RIF risk-Dysregulated immunity Anti-Coagulant therapy favourable
Fetal Neural Defects	MTHFR:c.665C>T		High risk for Neural Tube Defects Folic acid supplement & B12 helpful
Ectopic Pregnancy	MTHFR:c.665C>T		Higher risk of Ectopic pregnancy EP responsive to MTX injection
Premature Membrane Rupture	MTHFR:c.665C>T		Elevated Risk for PROM Preventive Management
Pre-Eclampsia			
Intra hepatic Cholestasis			
Gestational Diabetes			

FEMALE 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)

FEMALE INFERTILITY GENES - 679 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,RMRP(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,P

LP1,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

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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