Female Fertility and Polymorphism Panel

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

INDICATION FOR TESTING

Proband, Mrs. XX is married and has a history of failed IVF stimulations. Proband Mrs. XX has been evaluated for pathogenic and polymorphic variations.

RESULTS

FEMALE FERTILITY SINGLE NUCLEOTIDE VARIATION ANALYSIS

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

List of polymorphic variants (SNP) identified:

Gene Name	RsID	Variant	Genotype	Zygosity	Observed Phenotype	Recommendations
FSHR	rs1394205	c.-29G>A	GA	Heterozygous	intermediate estradiol concentrations, Lower FSH consumption, intermediate number of preovulatory follicles [4-5]	Require higher gonadotropin dose [4-5]
AMH	rs10407022	c.146G>T	GT	Heterozygous	Associated with reduced bioactivity of AMH, low oocyte numbers in untreated	DHEA supplementation is reported to augment

					females, and poor response to controlled ovarian stimulation [6-8].	ovarian stimulation in poor responders, especially in women with low AMH [6-8].

FEMALE INFERTILITY GENES - 679 GENES

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, HGD, HGSNAT, HLCS, HMGCL, HMOX1, HOGA1, HPD, HPS1, HPS3, HPS4, HSD3B2, HYLS1, IDS, IDUA, IKBKAP, 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, 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, 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), 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, 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

FEMALE POLYMORPHISM GENES (30 Genes)

LHCGR, IL10, IL19, IL21, MTHFR, AMH, MTRR, KISS1, MDM2, ESR1, FSHR, AMHR2, BMP15, KISS1R, LHB, SERPINE1, TNF, VEGFA, F5, F13A1, ITGB3, GP1BA, ITGA2B, ITGA2, ITGB3, APOB, APOE, MTR, AGTR1, GSTP1, F2

Recommendations

- Genetic counseling is recommended.

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 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 (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.

Sequence data attributes

Total reads generated	11.14 Gb
Data ≥ Q30	95.59 %

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 [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.

References

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