Polycystic Ovary Syndrome Report

Introduction

The Polycystic ovary syndrome test is based on Whole Genome Sequencing Test. As such, it analyzes all Common and Rare Variants associated with Polycystic ovary syndrome instead of a limited set of genes. Polycystic ovary syndrome (PCOS) is a condition that affects a woman's hormone levels. This condition causes an increase in the amount of hormones, causing a hormonal imbalance making the pregnancy more difficult. PCOS also causes hair growth on the face and body, and baldness, it can contribute to long-term health problems like diabetes and heart disease. Genes, insulin resistance, and inflammation have all been linked to excess androgen production.

In our analysis, we found pathogenic or likely pathogenic variants related to:

- Congenital heart disease

Genes/Locations included in report:

AR (3)	FTO (1)	FSHB (0)	FSHR (0)	INSR (1)	KRR1 (0)	SUOX (0)
TOX3 (0)	YAP1 (0)	AOPEP (0)	ERBB4 (0)	GATA4 (4)	HMGA2 (0)	LHCGR (0)
RAB5B (0)	RAD50 (0)	THADA (0)	DENND1A (0)	SUMO1P1 (0)		

Variants Found:

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
GATA4	chr8:11606312	rs3735819	Congenital heart disease	HOM	T>C	0.87161	pathogenic	
GATA4	chr8:11617240	rs12458	Congenital heart disease	HET	A>T	0.39996	pathogenic	
AR	X:66766356	rs746853821	Androgen resistance syndrome	HET	TGGCGGC>T		uncertain significance	★
AR	X:66766356	rs746853821	Androgen resistance syndrome	HET	TGGCGGC>T		uncertain significance	★
INSR	19:7116711	rs71177157	Leprechaunism syndrome	HET	C>CAAAAAAAA		uncertain significance	★
AR Rare	X:66765158	rs200185441	Malignant tumor of prostate	HOM	TGCAGCA>T	0	uncertain significance	★★
GATA4	chr8:11616338	rs867858	Unknown	HET	A>C	0.36142	uncertain significance	
FTO	chr16:53800954	rs1421085	OBESITY (BMIQ14)	HET	T>C	0.22863	risk factor	
GATA4	chr8:11612698	rs804280	Congenital heart disease	HOM	C>A	0.73443	conflicting interpretations of pathogenicity	

Individual Variant Interpretations:

rs1421085 - NM_001080432.3(FTO):c.46-43098T>C

Dina et al. (2007) identified 2 potentially functional SNPs in intron 1 of the FTO gene that were consistently strongly associated with early-onset and severe obesity (BMIQ14; 612460) in 2,900 affected individuals and 5,100 controls (p = 1.67 x 10 (-26) for the C allele of rs1421085 and p = 1.07 x 10 (-24) for the G allele of rs17817449). The at-risk haplotype yielded a proportion of attributable risk of 22% for common obesity.

Meyre et al. (2009) analyzed genomewide association data from 1,380 Europeans with early-onset and morbid adult obesity and 1,416 age-matched normal-weight controls and found the strongest association signal in the first intron of the FTO gene for the imputed SNP rs1421085 (p = 3 x 10(-12)). Subsequent analysis confirmed the association in an additional 14,186 European individuals (combined p = 1.2 x 10(-28)).

In a study examining the contribution of a risk haplotype for obesity involving 3 SNPs in introns 1 and 2 of the FTO gene (rs1421085, rs9930506, and rs1558902), Claussnitzer et al. (2015) obtained the highest phylogenetic module complexity analysis (PMCA) score for rs1421085, which they noted is in perfect linkage disequilibrium with the most significant reported SNP, rs1558902. Analysis of the rs1421085 T-C alteration revealed that it disrupts a conserved motif for the regulatory gene ARID5B (608538), causing derepression of a potent preadipocyte enhancer and doubling of IRX3 (612985) and IRX5 (606195) expression during early adipocyte differentiation. This results in a cell-autonomous developmental shift from energy-dissipating beige (brite) adipocytes to energy-storing white adipocytes, with a 5-fold reduction in mitochondrial thermogenesis and an increase in lipid storage. Inhibition of Irx3 in adipose tissue in mice reduced body weight and increased energy dissipation without a change in physical activity or appetite. Knockdown of IRX3 or IRX5 in primary adipocytes from homozygous carriers of risk alleles at rs1421085, rs9930506, and rs1558902 restored thermogenesis, increasing it by a factor of 7, whereas overexpression of these genes had the opposite effect in adipocytes from carriers homozygous for the nonrisk variant of these 3 SNPs. Repair of the ARID5B motif in primary adipocytes from a patient with the risk alleles restored IRX3 and IRX5 repression, activated browning expression programs, and restored thermogenesis, increasing it by a factor of 7. Claussnitzer et al. (2015) concluded that the FTO SNP rs1421085 represents the causal variant that disrupts a pathway for adipocyte thermogenesis involving ARID5B, IRX3, and IRX5, providing a mechanistic basis for the genetic association between FTO and obesity.

PubMed PMID: 17496892
PubMed PMID: 19151714
PubMed PMID: 26287746

List of Conditions:

- Congenital heart disease

Methods

Extraction

Before sequencing, DNA extraction and library preparation processes were carried-out by automated liquid handling robots. Sequencing was completed using the NovaSeq 6000 instrument (Illumina).

The Nextera DNA Flex (Illumina) library was used during sequencing.

Analysis

Primary and secondary analysis was performed on the Illumina DRAGEN platform. Our secondary analysis extends the GATK 'best practices' pipeline. This includes Variant Quality Score Recalibration

It is important to note that applying a filter will not remove any data from the VCF file; it will just annotate the "FILTER" column. Variants with the "PASS" annotation are considered high quality and may, therefore, be used for advanced downstream analysis.

Sequence data is primarily aligned to the GATK GRCh37 reference genome and mitochondria is aligned to the Revised Cambridge Reference Sequence (NC_012920.1). Additional references may have been requested though tertiary analysis is not conducted on variant calls using references other than GRCh37.

Limitations

Test results are not interpretations. All variants reported in the genes included in the panel are reported.

Rare polymorphisms may lead to false-negative or false-positive results.

Due to limited read length and other contributing technical limitations, repeat expansions (e.g. in the Huntington gene, the SCA-genes, the myotonic dystrophy repeat region, and other similar regions) cannot be assessed with the applied method

Disclaimer

Any preparation and processing of a sample from saliva collection kit to Dante Labs by a customer is assumed to belong to the email used by the customer at the moment of kit registration on the Dante Labs Genome Manager platform before the shipment of the specimen to the laboratory.

The analysis and reporting conducted by Dante Labs are based on information from one or more published third-party scientific and medical studies.

Because of scientific and medical information changes over time, your risk assessment for one or more of the conditions contained within this report may also change over time. For example, opinions differ on the importance and relative weights given to genetic factors. Also, epidemiological data isn't available for some conditions, and this report may not be able to provide definitive information about the severity of a particular condition. We recommend asking your healthcare provider to correctly interpret them. Therefore, this report may not be 100% accurate (e.g., new research could mean different results) and may not predict actual results or outcomes.

This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The US Food and Drug Administration (FDA) has determined that clearance or approval of this method is not necessary and thus neither have been obtained.

Contact

Please contact contact@dantelabs.com for more information on the contents of this report, our analysis methodology, and the limitations of this process.