Sjögren's Syndrome

Introduction

The Sjögren's Syndrome test is based on the Whole Genome Sequencing Test. As such, it analyses all Common and Rare Variants associated with Sjögren's Syndrome instead of a limited set of genes. Sjögren's syndrome is an autoimmune disease. This means that your immune system attacks parts of your own body by mistake. In Sjögren's syndrome, it attacks the glands that make tears and saliva. This causes a dry mouth and dry eyes. You may have dryness in other places that need moisture, such as your nose, throat, and skin. Sjögren's can also affect other parts of the body, such as your joints, lungs, kidneys, blood vessels, digestive organs, and nerves. Along with environmental factors, Genetics plays a key role in the regulation of Sjögren's Syndrome. - 11 genes analyzed - 100% of genomic regions covered - Intragenic and intergenic regions analyzed - All variants reported.

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

- Rheumatoid arthritis

Genes/Locations included in report

Genes in which variants of interest have been detected are listed in bold

ALDH3A2, IFNA1, IFNB1, IRF1, IRF2, ***IRF5 (2)****, IRF7, PTPRC, SIL1, STAT4, TNFSF4*

Clinical Variants Found:

#	Gene/Loc	Chr: Pos	rsID, Variant Description	Variation ID	Phenotype Name	Zygosity	Genomic Variant	Allele Frequency	Significance	Review Status
1	*IRF5*	chr7:128578301	rs2004640 - NM_001098629.3(IRF5):c.-12+198=	3396	• Rheumatoid arthritis • Systemic lupus erythematosus 10	HET	G>T	0.41354	pathogenic	

Informational Variants Found:

#	Gene/Loc	Chr: Pos	rsID, Variant Description	Variation ID	Phenotype Name	Zygosity	Genomic Variant	Allele Frequency	Significance	Review Status
1	*IRF5*	chr7:128589427	rs10954213 - NM_001098629.3(IRF5):c.*555G>A	3397	• Systemic lupus erythematosus 10	HET	G>A	0.53594	risk factor	

Individual Clinical Variant Interpretations:

#	
1	**rs2004640 - NM_001098629.3(IRF5):c.-12+198=** In an analysis of SNPs in genes of the type I interferon pathway in cases and controls, Sigurdsson et al. (2005) identified SNPs in the IRF5 gene that displayed strong signals in joint analysis of linkage and association with SLE (SLEB10; 612251). In joint linkage and association analysis, the SNP rs2004640 achieved a combined P of 2.4 x 10(-7). Graham et al. (2006) replicated the association of the IRF5 T allele of rs2004640 with SLE found by Sigurdsson et al. (2005) in 4 independent case-control cohorts and by family-based transmission disequilibrium test analysis. The T allele creates a 5-prime donor splice site in exon 1B of the IRF5 gene, allowing expression of several unique IRF5 isoforms. In a study of IRF5 SNPs in Swedish patients with rheumatoid arthritis (RA; 180300), Sigurdsson et al. (2007) found association with rs2004640 (p = 0.0067) and an even stronger association (p = 0.00063) with rs3807306, which was in linkage disequilibrium (r(2) = 0.67) with rs2004640. The authors noted that the minor alleles of these 2 SNPs are on the same protective haplotype in both SLE and RA. In a study of 485 Swedish SLE patients and 563 controls, Sigurdsson et al. (2008) performed logistic regression analysis conditioned on the CGGGG indel polymorphism in the promoter of the IRF5 gene (607218.0001), and found that the CGGGG indel accounts for the association signal previously observed with rs2004640. PubMed PMID: 15657875 PubMed PMID: 16642019 PubMed PMID: 17599733 PubMed PMID: 18063667

Individual Informational Variant Interpretations:

#	
1	**rs10954213 - NM_001098629.3(IRF5):c.*555G>A** Cunninghame Graham et al. (2007) identified 2 overtransmitted IRF5 haplotypes and a single undertransmitted haplotype among 380 UK SLE (SLEB10; 612251) nuclear families. The strongest association was with a TCTAACT haplotype, which carried all the overtransmitted alleles in the study. The TAT haplotype showed a dose-dependent relationship with mRNA expression. A differential expression pattern was seen between 2 expression probes located on each side of rs10954213 in the 3-prime untranslated region (UTR). rs10954213 showed the strongest association with RNA expression levels. The A allele of rs10954213 created a functional polyadenylation site, and the A genotype correlated with increased expression of a transcript variant containing a shorter 3-prime UTR. Expression levels of transcript variants with the shorter or longer 3-prime UTRs were inversely correlated. The authors proposed a new mechanism by which an IRF5 polymorphism may control the expression of alternate transcript variants, which may have different effects on interferon signaling. In a study of 485 Swedish SLE patients and 563 controls, Sigurdsson et al. (2008) performed logistic regression analysis conditioned on the CGGGG indel polymorphism in the promoter of the IRF5 gene (607218.0001), and found that the CGGGG indel accounts for the association signal previously observed with rs10954213. Systemic lupus erythematosus (SLE) is a chronic disease that causes inflammation in connective tissues, such as cartilage and the lining of blood vessels, which provide strength and flexibility to structures throughout the body. The signs and symptoms of SLE vary among affected individuals, and can involve many organs and systems, including the skin, joints, kidneys, lungs, central nervous system, and blood-forming (hematopoietic) system. SLE is one of a large group of conditions called autoimmune disorders that occur when the immune system attacks the body's own tissues and organs.SLE may first appear as extreme tiredness (fatigue), a vague feeling of discomfort or illness (malaise), fever, loss of appetite, and weight loss. Most affected individuals also have joint pain, typically affecting the same joints on both sides of the body, and muscle pain and weakness. Skin problems are common in SLE. A characteristic feature is a flat red rash across the cheeks and bridge of the nose, called a "butterfly rash" because of its shape. The rash, which generally does not hurt or itch, often appears or becomes more pronounced when exposed to sunlight. Other skin problems that may occur in SLE include calcium deposits under the skin (calcinosis), damaged blood vessels (vasculitis) in the skin, and tiny red spots called petechiae. Petechiae are caused by a shortage of cell fragments involved in clotting (platelets), which leads to bleeding under the skin. Affected individuals may also have hair loss (alopecia) and open sores (ulcerations) in the moist lining (mucosae) of the mouth, nose, or, less commonly, the genitals.About a third of people with SLE develop kidney disease (nephritis). Heart problems may also occur in SLE, including inflammation of the sac-like membrane around the heart (pericarditis) and abnormalities of the heart valves, which control blood flow in the heart. Heart disease caused by fatty buildup in the blood vessels (atherosclerosis), which is very common in the general population, is even more common in people with SLE. The inflammation characteristic of SLE can also damage the nervous system, and may result in abnormal sensation and weakness in the limbs (peripheral neuropathy); seizures; stroke; and difficulty processing, learning, and remembering information (cognitive impairment). Anxiety and depression are also common in SLE.People with SLE have episodes in which the condition gets worse (exacerbations) and other times when it gets better (remissions). Overall, SLE gradually gets worse over time, and damage to the major organs of the body can be life-threatening. PubMed PMID: 17189288 PubMed PMID: 18063667

List of Conditions:

- Rheumatoid arthritis

Glossary

Symbol		Description
AD	Autosomal dominant	One mutated copy of the gene in each cell is sufficient for a person to be affected by an autosomal dominant disorder. In some cases, an affected person inherits the condition from an affected parent. In others, the condition may result from a new mutation in the gene and occur in people with no history of the disorder in their family.
AR	Autosomal recessive	In autosomal recessive inheritance, both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Autosomal recessive disorders are typically not seen in every generation of an affected family.
X-linked dominant	X-linked	Dominant X-linked dominant disorders are caused by mutations in genes on the X chromosome, one of the two sex chromosomes in each cell. In one of the two sex chromosomes in each cell. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell causes the disorder. In most cases, males experience more severe symptoms of the disorder than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).
Y-linked	Y-linked	A condition is considered Y-linked if the mutated gene that causes the disorder is located on the Y chromosome, one of the two sex chromosomes in each of a male's cells. Because only males have a Y chromosome, in Y-linked inheritance, a mutation can only be passed from father to son.
Mitochondrial	Mitochondrial	Mitochondrial inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. Mitochondria, which are structures in each cell that convert molecules into energy, each contain a small amount of DNA. Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial mutations to their children. Conditions resulting from mutations in mitochondrial DNA can appear in every generation of a family and can affect both males and females, but fathers do not pass these disorders to their daughters or sons.
Pathogenic		This variant directly contributes to the development of disease. Some pathogenic variants may not be fully penetrant. In the case of recessive or X-linked conditions, a single pathogenic variant may not be sufficient to cause disease on its own. Additional evidence is not expected to alter the classification of this variant.
Likely Pathogenic		There is a high likelihood (greater than 90% certainty) that this variant is disease-causing. Additional evidence is expected to confirm this assertion of pathogenicity, but there is a small chance that new evidence may demonstrate that this variant does not have clinical significance.
VUS	Variant Uncertain significance	There is not enough information at this time to support a more definitive classification of this variant.
Phenotype Name		Phenotype represents the observable characteristics or traits of an organism that are produced by the interaction of the genotype and the environment : the physical expression of one or more genes.

Symbol		Description
Zygosity		Zygosity refers to the similarity of alleles for a trait in an organism. If both alleles are the same, the organism is homozygous for the trait. If both alleles are different, the organism is heterozygous for that trait. If one allele is missing, it is hemizygous, and, if both alleles are missing, it is nullizygous
Allele Frequency		Allele frequency is a measure of the relative frequency of an allele on a genetic locus in a specific position and it is expressed as a proportion or a percentage. Population genetics studies the different "forces" that might lead to changes in the distribution and frequencies of alleles - in other words, to evolution. Besides selection, these forces include genetic drift, mutation, and migration. Based on their frequency, the variants can be classified in rare variants and common genetic variants. Rare variants are alternative forms of a gene that are present with a minor allele frequency (MAF) of less than 1%. As a general principle, rare variants are more likely to cause rare diseases while common variants are more likely to increase the risks of genetic and complex diseases.
Significance		Significance refers to the standard term used by ClinVar, the internationally recognized database on which this report is based, to classify the types of variants. As the database is a clinical database, the information is clinical and based on an authoritative source when available. The Significance section includes the following standard terms to classify the variants: • **Pathogenic**: A Pathogenic is classified as such if this variant directly contributes to the development of disease. Some pathogenic variants may not be fully penetrant. In the case of recessive or X-linked conditions, a single pathogenic variant may not be sufficient to cause disease on its own. Additional evidence is not expected to alter the classification of this variant. • **Likely Pathogenic**: A Likely Pathogenic variant is classified as such if there is a high likelihood (greater than 90% certainty) that this variant is disease-causing. Additional evidence is expected to confirm this assertion of pathogenicity, but there is a small chance that new evidence may demonstrate that this variant does not have clinical significance. • **Conflicting Interpretations of Pathogenicity**: A Conflicting Interpretations of Pathogenecitity variant is classified as such if it is submitted from a scientific consortium, where groups within the consortium have conflicting interpretations of a variant but provide a single submission to ClinVar. • **Variant of Unknown Significance**: A Variant of Unknown Significance is classified as such if it is there is not enough information at this time to support a more definitive classification of this variant. • **Drug response**: A Drug response variant is classified as such if it represents a complex phenotype that emerges from the interplay of drug-specific genetics, human body, and environmental factors. • **Association**: An association variant is classified as such if there are one or more genotypes within a population co-occur with a phenotypic trait more often than would be expected by chance occurrence.
Review Status		ClinVar reports the level of review supporting the assertion of clinical significance for the variation as review status. Stars provide a graphical representation of the aggregate review status on web pages. Table 1 provides definitions of each review status and the corresponding number of stars. Review status is reported in text format in ClinVar's products available by FTP. A higher number of gold stars corresponds to higher review status. If you wish to get more information about that, please visit ClinVar at the following link: https://www.ncbi.nlm.nih.gov/clinvar/docs/review_status/

Methods

Versions

VCF Version: X3BQ7yQ93_nsurbKmnH1fjV4KcjuySFw
Clinvar Database Version: QoqCB67VTISXJBo0M_5ZtdenJ9F4gGG0

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.