Ulcerative Colitis Report

Introduction

The Ulcerative colitis test is based on Whole Genome Sequencing Test. As such, it analyzes all Common and Rare Variants associated with Ulcerative colitis instead of a limited set of genes. Ulcerative colitis is an inflammatory bowel disease (IBD) that causes long-lasting inflammation and ulcers (sores) in your digestive tract. Ulcerative colitis affects the innermost lining of your large intestine (colon) and rectum. Symptoms usually develop over time, rather than suddenly. Ulcerative colitis can be debilitating and can sometimes lead to life-threatening complications. Depending on the severity of the inflammation and where it occurs, symptoms may vary. Some of these include, diarrhea, often with blood or pus, abdominal pain and cramping, rectal pain, urgency to defecate, fever. Previously, diet and stress were suspected. One possible cause is an immune system malfunction. Heredity also seems to play a role in that ulcerative colitis is more common in people who have family members with the disease.

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

- Rheumatoid arthritis

Genes/Locations included in report:

IRF5 (2)	ABCB1 (2)	IL23R (0)	PTPN2 (0)	IL10RA (0)	IL10RB (1)

Variants Found:

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
IRF5	chr7:128578301	rs2004640	Rheumatoid arthritis	HET	G>T	0.41354	pathogenic	
ABCB1	chr7:87160618	rs2032582	Inflammatory bowel disease 13	HOM	A>C	0.61701	drug response	□□□
ABCB1	chr7:87138645	rs1045642	MDR1 POLYMORPHISM	HOM	A>G	0.60483	drug response	□□□
IL10RB Rare	chr21:34669478	rs118117891	Inflammatory bowel disease	HET	T>C	0.0016	uncertain significance	□
IRF5	chr7:128589427	rs10954213	Systemic lupus erythematosus 10	HET	G>A	0.53594	risk factor	

Individual Variant Interpretations:

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

rs2488457 - NM_015967.6(PTPN22):c.-1123C>G

By sequencing both strands of genomic DNA from 35 healthy Japanese individuals, Kawasaki et al. (2006) identified a -1123C-G promoter SNP (rs2488457) in the PTPN22 gene. In a study of 484 Japanese patients with type I diabetes (IDDM; 222100), 317 of whom had acute-onset diabetes, and 492 healthy controls, the authors found that the heterozygous C/G genotype was associated with susceptibility to acute-onset but not slow-onset type I diabetes (OR = 1.42, p = 0.015). A similar tendency was observed in 69 Korean patients with acute-onset type I diabetes (p = 0.0105, combined OR = 1.41).

PubMed PMID: 16470599

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

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.