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Genomics of Autoimmune Diseases

One set of diseases that have a particularly interesting genome and epigenome relationship are autoimmune diseases. Autoimmune diseases are generally described as the resulting effects of when your immune system attacks healthy cells. This causes tissue damage and actually decreases the body's ability to fight off various infections. Usually some sort of event triggers the production these antibodies that attack the bodies own cells, but also there are genetic predispositions to these diseases. The combination of the two is what almost always leads to the expression of the disease. As this is a very generalized description, there are many diseases that fall under this umbrella. This includes psoriasis, hepatitis B, osteoarthritis, thyroidism and approximately 80 more.

Description	Chromosome	Gene	SNP	Risk alleles	Tested by*
Allergies (general)	A	FCER1A	rs2427837	AA, AG, GG	A3
			rs2251746	CC, CT, TT	A
Ankylosing Spondylitis	5	ARTS-1	rs27044	CC, CG, GG	A
			rs17482078	CC, CT, TT	A3
			rs10050860	CC, CT, TT	**A**
			rs30187	CC, CT, TT	**A**
			rs2287987	CC, CT, TT	A3
	A	IL23R	rs11209026	AA, AG, GG	**A**
			rs1004819	CC, CT, TT	A
			rs10489629	AA, AG, GG	A2*
			rs11465804	GG, GT, TT	A
			rs1343151	CC, CT, TT	A
			rs10889677	AA, AC, CC	A
	5	LNPEP	rs2303138	AA, AG, GG	**A**
	6	-	rs7743761	AA, AC, CC	**A**
	12	CLSTN3	rs7302230	AA, AG, GG	**A**
Asthma	A	intergenic	rs4950928	CC, CG, GG	**A**
	6	PLA2G7	rs1805018		A, B
			rs1051931		A, B
	6	TNF	rs1800629	AA, AG, GG	A
	7	AAA1	rs324981		A
	11	GSTP1	rs1695	AA, AG, GG	A, B
	17	GSDML	rs7216389	CC, CT, TT	**A, B**
Celiac Disease	A	RGS1	rs2816316		**A, B**
	B	intergenic	rs917997	CC, CT, TT	**A, B**
	3	intergenic	rs6441961		**A, B**
	3	intergenic	rs17810546	AA, AG, GG	**A, B**
	3	LPP	rs1464510		**A, B**
	4	KIAA1109	rs13119723		A
	4	intergenic	rs6822844	GG, GT, TT	**A, B**
	6	HLA-DQA1	rs2187668	CC, CT, TT	**A, B**
	6	TAGAP	rs1738074	AA, AG, GG	**A, B**
	12	SH2B3	rs3184504	CC, CT, TT	**A, B**
	19	MYO9B	rs2305764	AA, AG, GG	A
			rs2305767	CC, CT, TT	**A**
Crohn's Disease	A	IL23R	rs11209026	AA, AG, GG	**A, B**
			rs11805303	CC, CT, TT	**A**
	B	ATG16L1	rs2241880	AA, AG, GG	**A, B**
			rs10210302	CC, CT, TT	**A**
	3	BSN	rs9858542	AA, AG, GG	A, B
	3	MST	rs3197999	AA, AG, GG	**A**
	5	5p13 region	rs17234657	GG, GT, TT	**A, B**
	5	IBD5	rs12521868		A, B
	5	IRGM	rs4958847	AA, AG, GG	A, B
			rs7714584	AA, AG, GG	**A**
	6	TNF	rs1800629	AA, AG, GG	A

Along with including a large number of diseases, there are also a large number of genes implicated in studies surrounding causation of autoimmune diseases. For example, the picture

above is a chart of various autoimmune diseases and the respective gene and SNP correlations. The data was gathered by 23andMe and DeCODme. I retrieved it from Eupedia. This is also an interesting detail in that most of the data comes from personal genomics as opposed to medical databases, meaning that these studies would likely have not been possible before genome sequencing became so inexpensive and restrictions on sequencing freed up with the new paradigm of genetic thinking. This is most likely because autoimmune diseases are generally not life threatening but still have many negative symptoms that can affect the quality of life for those that suffer from them. (Genes and Mutations Associated with Autoimmune Diseases)

Each autoimmune disease has not only multiple genes associated with it, but also multiple SNP's associated with each gene, also depicted in the photo above. This means that genetic testing for these diseases and also work towards any cure for all autoimmune diseases, or even a few is very challenging and requires a great deal of research before any experimentation. The group of genes most commonly associated with autoimmune diseases is the HLA gene family. The HLA gene family on chromosome 6 is frequently correlated with autoimmune diseases as it is comparable to the MHC gene, major histocompatibility complex, in many other organisms. For example, HLA-DQA1 exists in bovines and is listed under MHC class II DQA2. The HLA family includes genes that code for human leukocyte antigen complex proteins. Its role is to help the body's immune system tell the difference between invaders to the cell and its own proteins and cells. Naturally, when this malfunctions the body has a much higher likelihood of damaging its own tissues, causing a large array of problems. The HLA gene family includes over 200 genes, but they can be split into three classes. Class I genes code for proteins that sit on the surface of the cell and bind to proteins that have been exported from the cell. They then display them to the immune system which can determine whether or not it is foreign and instruct

the cell to self-destruct if it is foreign with the use of killer T-cells. This is very useful for protecting the cell from viral infections. Class II HLA genes instruct proteins that are only on immune system cells and similar to Class I, they display these peptides to the immune system, T-lymphocytes in particular. The difference is that they bond to and display antigens from the outside of the cell, then the antigens can stimulate the production of T-helper cells, then B-cells that produce antibodies. Regulatory T cells stop self-antigens from doing this. Class III codes for proteins involved in other immune system activities. Some of these activities include cancer defense, or general disease defense. (HLA Gene Family) Additional functions of the HLA genes are perceptions of body odor by different people, and potentially in mate selection. In mice, in an experiment done by Brown, mice tended to choose mates that had drastically different MHC complexes than their primary caregiver. This effect has not been tested in humans. However, it is important to note that the MHC complex can have effects not only on autoimmunity, but also on behavior, signifying how diverse of a gene family it is, and therefore how diverse the diseases it's mutations cause must be. (NCBI)

HLA-C belongs to Class I of human MHC genes. It is a heterodimer molecule that consists of both a heavy and a light chain of beta-2 hemoglobin, as seen in the picture above. It is attached to the cell membrane by the heavy chain. There are over 100 known alleles for this gene. (NCBI Entry 3107)

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Associations

SNP	RAF	p-value	OR	Beta	CI	Region	Location	Functional class	Reported gene(s)	Mapped gene(s)	Reported trait	Study
rs13191343-T	0.13	2 x10^{-72}	2.37		[2.16-2.61]	6p21.33	chr6:31273332	nearGene-5	HLA-C	HLA-C	Psoriatic arthritis	Huffmeier U (PMID: 20953186), 2010
HLA-C*07:01	0.16	1 x10^{-18}		0.054 unit increase	[0.042-0.066]		chr?:?		HLA-C		Beta-2 microglubulin plasma levels	Tin A (PMID: 23417110), 2013
HLA-C*03:04	0.08	8 x10^{-8}		0.043 unit decrease	[0.027-0.059]		chr?:?		HLA-C		Beta-2 microglubulin plasma levels	Tin A (PMID: 23417110), 2013
HLA-C*03:03	0.05	1 x10^{-6}		0.05 unit decrease	[0.030-0.070]		chr?:?		HLA-C		Beta-2 microglubulin plasma levels	Tin A (PMID: 23417110), 2013
rs9264638-A	0.58	2 x10^{-23}		0.04 unit decrease	[0.032-0.048]	6p21.33	chr6:31270541	intron	HLA-C	HLA-C	Beta-2 microglubulin plasma levels	Tin A (PMID: 23417110), 2013

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Catalog traits

Reported trait	Mapped ontology traits	Ontology traits synonyms	Study

One disease in particular that it is associated with is Psoriasis. Psoriasis is a chronic autoimmune condition causing red, patchy skin rashes. It is described as the immune system attacking skin cells. The allele ID associated with psoriasis is 29945 at 6p21.3. (Relating Variation to Medicine) The association with HLA-C is listed as a risk

Search results for *rs13191343*

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Studies

Author	Date	Journal	Title	Reported trait	Association count
Huffmeier U (PMID: 20953186)	2010-10-16	Nat Genet	Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis.	Psoriatic arthritis	3

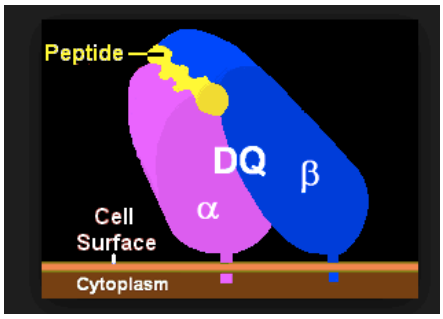
Initial sample description	572 European ancestry cases, 888 European ancestry controls
Replication sample description	Up to 1,761 European ancestry cases, 3,727 European ancestry controls
Platform [SNPs passing QC]	Affymetrix [1,585,307] (imputed)

Associations

SNP	RAF	p-value	OR	Beta	CI	Region	Location	Functional class	Reported gene(s)	Mapped gene(s)	Reported trait	Study
rs13191343-T	0.13	2 x10^{-72}	2.37		[2.16-2.61]	6p21.33	chr6:31273332	nearGene-5	HLA-C	HLA-C	Psoriatic arthritis	Huffmeier U (PMID: 20953186), 2010

factor. Because HLA-C has such a large number of alleles it is expressed differently in various cells in order to code for the specific peptide binders to display the correct protein to the immune system. This means it is possible that the 29945 allele codes for the wrong peptide binding sequence, causing the immune system to react poorly to the host's own skin cells. Psoriasis patients usually control their symptoms with a topical gel. However, the current creams often have negative long term side effects. Scientist are working on a new cream made using Dual-F-NALP, which is a gene regulating nanoparticle that will suppress inflammation and psoriasis flare-ups. (Novel Combination Anti-psoriasis Therapy Targets Genetic Abnormalities in Deeper Layers of the Skin.) There are also other labs working on more specialized genetic treatments. One such lab is the BioBank, which used to be the National Psoriasis Tissue Bank, which was started in 1994, so this collection of data is relatively new and samples were only released to researchers starting in 2010. (Genes and Psoriasis)

HLA-DQA1 is another member of the human MHC family and is also believed to cause predispositions to some autoimmune diseases. The two it is most strongly correlated with are systemic lupus, rheumatoid arthritis, along with others like allergies and celiacs. It is a Class II human MHC gene, so that means it has a function very similar to that of the previously described HLA-C gene. The difference in the two classes is that the peptides it presents are antigens from outside of the cell and these attract T-lymphocytes, which spurs the production of B-cells that produce specified antibodies. HLA-DQA1 is one of eight variations of HLA-D as there are two alpha and two beta sheets options to create this gene. It is located on Chromosome 6 and has a structure of two molecules- one alpha helix and one beta sheet, as seen in the picture



to the right.

Systemic lupus is a diseases causing skin rashes, joint swelling, headaches, hair loss, blood-clotting problems, Raynaud's syndrome and anemia. It is not curable, but there are some treatments to alleviate symptoms. Current alleviators include steroid creams, anti-inflammatory medications and antimalarial drugs. (Systemic Lupus Erythematosus) It is associated with

HLA-DQA1*05:01-?	NR	3×10^{-9}	1.89	[1.534-2.335]		chr?:?	HLA-DQA1		Systemic lupus erythematosus	Armstrong DL (PMID: 24871463), 2014
HLA-DQB1*02:01, rs558702	NR	5×10^{-6}	1.755	[1.381-2.238]		chr?:?	HLA-DQB1		Systemic lupus erythematosus	Armstrong DL (PMID: 24871463), 2014
HLA-DRB1*03:01, rs9275572	NR	3×10^{-7}	1.934	[1.507-2.494]		chr?:?	HLA-DRB1		Systemic lupus erythematosus	Armstrong DL (PMID: 24871463), 2014
rs2002842-A	0.49	6×10^{-6}	1.61	[NR]	18q23	chr18:78649597	SALL3	LINC01029 - SALL3	Rheumatoid arthritis	Julia A (PMID: 18668548), 2008
rs6457617-?	NR	1×10^{-9}			6p21.32	chr6:32696074	HLA-DQA2, HLA-DQA1	HLA-DQB1 - MTCO3P1	Rheumatoid arthritis	Julia A (PMID: 18668548), 2008

the HLA-DQA*05:01 SNP of HLA-DQA1, as seen in the picture above. Along with HLA-DQA1, it is also correlated with many other genes and even different SNP's within this HLA gene, including rs11243676-A which is an intron, rs979233-T and rs2187668-A. This means that noncoding sequences, likely enhancers, have an effect on its expression, so this disease would require more than just a genetic cure as epigenetics also affect the expression of systemic lupus. There are some genetic factors, such as HLA-DQA1 SNP's that increase the risk of it, but they are not the only factors, making treatment very difficult. The pharmacoepigenetics involved with potential treatment of systemic lupus will involve changing the chromatin structure of DNA, likely in the HLA gene. This affects the actual expression of the DNA by making the genes more or less accessible for transcription. Also, miRNA's can alter drug targets when a disease or new drug is introduced, so manipulation of the miRNA's through therapeutic drugs

could also be very beneficial. These methods could potentially also work for other autoimmune diseases as the HLA complex is involved with many immune response functions. However, it is important to note that we are still far from knowing each SNP or miRNA action involved with the expression of these diseases, so while pharmocoepigentic treatment is possible, it is still far away. (NCBI entry 25218424)

Rheumatoid arthritis is an inflammatory disorder that affects the lining of small joints in your hand or feet and causing swelling that can lead to bone damage. (Rheumatoid Arthritis) It similarly does not have a cure, but researchers do believe that it would be possible to find one and are working towards it. (NCBI Entry 25415526) Current treatment includes surgeries, anti-inflammatories and general pain relievers. As with most autoimmune diseases, epigenetics play a large role in effective treatment. A separate type of DNA modification occurs to trigger rheumatoid arthritis. The two mechanisms that generally play a role alter the histones in the chromatin by acetylation or methylation. Negative environmental factors, such as smoking, deacetylases histones in cells with Rheumatoid arthritis. Synovial fibroblasts also play a role in the disease by mutations in cell signaling, cell apoptosis and adhesion to various molecules. Methylation is also usually altered in cells with Rheumatoid arthritis, so one potential cure suggestion is reversal of hypomethylation. This process would be done with a drug that inhibits the polyamine recycling pathway. The polyamine recycling pathway is the return of polyamines to the cell membrane following endocytosis of the molecules.

Autoimmunity is a very complex process, with numerous factors contributing to one set of fairly similar responses, an overactive immune system. Overactive immune systems lead to diseases such as psoriasis and rheumatoid arthritis. One causal gene group, the HLA gene family, consists of three separate classes of genes all to determine whether or not substances are

harmful to the cell and initiate a response. Within these classes, there are even more genes and a numerous amount of allele variations within each gene. In addition, to the actual genetics there is the effect of epigenetics, with miRNA's, environmental factors, and chromatin modifications. Epigenetics are a fairly new field, and pharmacoepigenetics is even more recent. This means there is still a great deal of uncertainty in what exactly triggers these harmful immune responses. However, the future is bright as the field is progressing quickly with the increased prevalence of convenient personal genetic testing, and specific research for autoimmune diseases, such as is done by the biobank. Ideally, in the future autoimmune diseases will have a successful cure as opposed to temporary relief providing treatments.

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