The Genetics of SLE

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What is Genetics?
Genetics is the study of genes and how they behave and function. Consequently it is one of the fastest growing fields in science today. Many branches of science and medicine believe that the future of medical care and treatment for numerous diseases is encoded in our genes: crack the code, and a world of improved healthcare and quality of life may follow.

Lupus Geneticists (scientists who study genetics) believe this may be true of systemic lupus erythematosus, aka SLE or lupus. By studying families with SLE patients, the genes predisposing to lupus may be found.

The Human Genome
Within the nucleus of each cell in the human body is a microscopic set of chromosomes. Chromosomes are composed of genes, which are the genetic material of the cell and made of deoxyribonucleic acid, or DNA. Genes act as the cell's instruction guide for all life-supporting functions. This process in turn determines an individual's traits and features, such as eye-color or height, as well as day-to-day cellular activities.

Humans have an estimated 27,000 genes, over 23 chromosomal pairs: 22 matched pairs (or autosomes) and 1 pair determining a person's gender (sex chromosomes). Each chromosomal pair contains two inherited chromosomes: one from the father and one from the mother. These 23 chromosomal pairs compose the Human Genome. Chromosomes, which resemble "X"s when viewed under a light microscope, vary in length. They have been assigned numbers by scientists according to these relative lengths, chromosome 1 being the longest and chromosome Y the shortest, so that the scientific community may refer to them consistently.

Chromosomes contain thousands of genes, as well as "blank" spots. Each gene on a chromosome occupies a specific location (a locus) and usually appears as a pair. For example, a gene appearing at a specific locus on chromosome 1 will appear at the same locus whether we are studying the chromosome 1 inherited from the individual's father or the chromosome 1 inherited from the individual's mother. If their genes are different at the level of their DNA sequence, then the two genes are referred to as alleles. While individual genes are responsible for specific traits, an allele is one of at least two of the possible expressions of a specific gene, such as eye color.

Heredity, Dominance & Genetic Change
Eye color is easy to consider as it is determined by one gene and easily observed. Eye color is designated by two gene alleles: one inherited from the mother and one from the father. There are several allelic combinations that may occur to get the resulting color, most commonly blue, brown or green/hazel. An allele's dominant or recessive nature can affect the gene's expression, or how it is visible in the person. The allele for brown eye color is dominant and will "hide"

blue alleles that a person may have. However, it is still possible for two brown-eyed parents to produce a blue-eyed child if only the blue alleles are passed on.

When the genes that produce eye color do not function properly, the resulting lack of color appears pink. This particular genetic mutation is not physically harmful, and mutations may happen frequently without obvious or ill-effect. Other types of mutations may lead to diseases, such as cystic fibrosis (caused by one gene), cancer (usually a cellular mutation) or lupus (caused by several genes).

Genetics and Lupus

Systemic lupus erythematosus, aka SLE or lupus, is thought to be a genetically complex disease, meaning that several different genes are involved in its development. Scientists suspect that tens, or even hundreds, of genes may be involved in the disease. These genes, according to recent genome-wide genetic scans, may vary depending on a patient's ethnicity or the disease symptoms from which the patient suffers. While several genomic "hot spots" (areas where scientists believe it is extremely likely lupus genes exist) are currently being explored, some of the genes have clearly been identified (e.g. FcγRIIA; FcγRIIIA; complement components C2, C4 and C1q; PDCD-2; and HLA-DR).

The Heredity of Lupus

Many researchers think that lupus is hereditary, meaning it is passed on genetically from one generation to another. The pattern of inheritance is, however, unclear. It is known that not everyone who has the lupus genes develops the disease, as demonstrated in numerous identical twin studies (concordance, or the rate at which both identical twins are affected with lupus, varies from 15-69%).

This information indicates, first, that people who have lupus genes have a genetic predisposition to the disease, or a higher likelihood of developing it, than the general population. Merely having lupus-linked genes is not enough to cause a person to develop lupus. This in turn indicates that an external or environmental trigger is also involved in lupus disease onset in people with genetic predisposition. (Known triggers include stress, hormonal changes, illness, certain viruses including Epstein-Barr virus and chemical exposure.)

LUPUS GENES

How They are Studied

Lupus Geneticists have been conducting familial studies of lupus for a decade. They study families that are both multiplex (families with 2 or more patients) and simplex (families with one patient) for lupus. These two kinds of families are useful in different ways for finding the lupus genes. Multiplex family research allows for the study of inheritable lupus, or lupus that is passed on genetically. These studies use DNA samples (usually blood) from the lupus patients and other unaffected family members whose relationships may prove useful for genetic linkage, usually parents, siblings, grandparents, etc. Simplex family research allows for the study of randomly-occurring lupus, or cases in which the lupus-associated genes come together arbitrarily to create a predisposition to disease. These studies use DNA samples (usually blood) from nuclear families, typically a lupus patient, 1-2 siblings and their parents.

By examining the genes of multiplex lupus families (comparing the genes of those affected by lupus and the genes of their unaffected family members) scientists are locating "hot spots" within the human genome worthy of more specific study. Multiplex lupus studies have also benefited from the sub grouping of families, or grouping families according to certain characteristics that they share in common (i.e. ethnicity, lupus patients' symptoms, patient gender) in order to find genes that may be specific to these ethnic groups or symptomologies.

More recently, geneticists have been able to capitalize upon the information available from SNPs (pronounced "snips," the abbreviation for single nucleotide polymorphism). A SNP is a single genetic variation that can occur within an individual's DNA. These differences are what make each person's genetic code unique. SNPs are pretty rare, occurring in just under 1% of the DNA bases in the human species. If they occur in the part of a person's DNA that codes for protein production, then SNPs may alter the biological function of the protein. In order to use SNP technology effectively, lupus "hot spots," often discovered via multiplex family studies, are used as candidate areas for SNP study.

Some lupus "hot spots" currently under analysis include the following:
1q22-23
2q34 Associated with African-American patients with renal disease
4p15
5p15 Associated with rheumatoid arthritis
5q12 Associated with thyroid disease
10q22 Associated with Caucasian patients with renal disease
11p13 Associated with African-American patients with thrombocytopenia
11q14 Associated with African-American patients with specific ANA pattern or with hemolytic anemia
12q24 Associated with Hispanic patients
16a13
And others

Why look for Lupus Genes?
There are several reasons researchers wish to discover the lupus genes. As we already know from work done on breast cancer, early screening for disease may benefit individuals with lupus in their families or with other lupus-risk factors. Early screening may help an individual genetically predisposed to lupus adopt a lifestyle with fewer risk factors, like stress, that may contribute to disease onset, or perhaps avoid complications with a potentially life-threatening lupus symptom. If scientists can relate genes to certain symptoms, they might be able to discern how each gene is contributing to the disease and develop treatments that specifically target these genes and/or the proteins they produce. This may lead to more effective treatments with the possibility of fewer side-effects. And ultimately, if we know what genes are contributing to lupus, we may be able to develop therapies that could prevent patients from becoming ill with lupus before they are diagnosed. Having a method of disease prevention or a cure is a great motivation for researchers. Here at the beginning of the 21st century it is at least possible to dream of the arrival of such a day.

The Future of Lupus Genetics

Discoveries in lupus genetics are highly dependent not only on the physicians and researchers conducting lupus research, but also on the willingness of families and healthy individuals to participate in such studies. By enlarging the pool of families available for genetic analysis, confirmation of findings and locating the genes that predispose to lupus may contribute to the treatment, diagnosis, and possible prevention of the disease for future generations.

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