**The benefits of genetic research on Systemic Lupus Erythematosus**

In most cases, despite the fear that genetic information will be misused in ways that harm individuals, the benefits of genetic research outweigh the risks. This is especially true in the case of Systemic Lupus Erythematosus (SLE), a complicated autoimmune disease that affects .05% of the western population.[1] Presently, prevention of the disease is non-existent; meanwhile diagnosis and treatment often lack precision and efficiency. One of the major challenges is that SLE is caused by a number of factors that affect each individual differently. With the biotechnology that exists today, a feasible way to overcome this challenge is to identify a gene(s) that is directly associated to SLE. Although up until recently genetic studies were for the most part inconclusive, the complex nature of SLE suggests that improvements in its diagnosis, prevention, and treatment will result from further genetic research.

Lupus is a chronic autoimmune disease where the immune system, instead of fighting harmful tissues, such as viruses, becomes hyperactive and attacks normal tissue.[2] When the immune system goes wrong, it produces auto-antibodies that circulate in the blood and can enter some of the body's cells (namely in the skin, joints, and kidneys) that have walls permeable enough to let them in. These antibodies can then attack the DNA in the cell's nucleus and cause painful and debilitating inflammation.[3] There are three different kinds of lupus: Discoid lupus (also known as Cutaneous lupus) affects the skin; Systemic lupus attacks multiple systems in the body which may include the skin, joints,

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[1] Prokunina, L. *et al*. A regulatory polymorphism in *PDCD1* is associated with susceptibility to systemic lupus erythematosus inhumans. *Nature Genet.* 28 October 2002

[2] OMIM #152700

[3] Http://www.uklupus.co.uk

blood, lungs, kidneys, heart, brain and nervous system; and finally drug-induced lupus which may develop after taking certain prescription medications[4].

The complexity of the disease's etiology poses one of the greatest challenges to improving its diagnosis and treatment. The definite origin of lupus is not presently known; it is likely to be a combination of factors including genetics, the environment, and drugs.[5] For most people, lupus is not simply an inherited disease; it develops because a person carries a genetic predisposition to lupus. This does not necessarily mean that the person will contract the disease, however, the risk that their hormonal make-up and/or certain environmental factors will elicit the disease is greater (ultraviolet light is one of the major factors that exacerbate the development of the disease). Finally, dozens of medications have been reported to trigger lupus in patients whether or not they have the predisposition gene[6]. The etiological uncertainties of this disease pose two challenges for medical practitioners: first of all, diagnosis becomes difficult because one single test may not identify all cases, and secondly, the same treatment may not be effective for every patient if their case of lupus comes from a different source.

Currently, the methods utilized to diagnose SLE are neither timely nor efficient. A survey of Lupus Foundation of America members suggests that more than half of those afflicted with lupus saw three or more doctors before obtaining a correct diagnosis.[7] One of the problems is that there is no one definitive diagnostic test for SLE, the doctor has to do a full examination of the patient and do various tests before looking at all the evidence and coming to a conclusion. Since SLE is a multi-system disease, there have to be

[4] OMIM #152700
[5] OMIM #152700
[6] OMIM #152700
[7] www.lupus.org

symptoms in many parts of the body and blood tests that support its presence. However, it can take time for the disease to show up in blood tests, which then often give inconsistent results, switching from positive to negative each time.[8] Thus, there is a high probability that a diagnosis based on blood tests is inaccurate. Another criteria for the diagnosis is that a person exhibit four of the eleven symptoms, ranging from skin rashes to joint pain.[9] The problem with this method is that it can take months or even years for enough symptoms to show up for the doctor to be able to make an accurate diagnosis;[10] a further flaw is that since many of the symptoms are also indicators of other diseases, there is no guarantee that SLE is the underlying cause. One final challenge for SLE diagnosis is that the disease can attack different organ systems of the body, and thus each diagnosis must be tailored to a specific case.

The use of molecular diagnostics, the ability to identify or predict a disease based on an individual's genetic profile, would significantly improve the accuracy and timeliness of SLE diagnosis, as well as give way to a form of preventive medicine. Once researchers find a definite gene(s) predisposing SLE, patients will be able to take genetic tests giving accurate results regarding their predisposition to the disease. Although predisposition does not equal infection, diagnosis based on symptoms will be more accurate if the doctor knows whether the patient has tested positively or negatively for the gene; symptoms in a predisposed patient will gain more significance. Furthermore, since doctors could identify patients that are more susceptible to the disease even before

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[8] http://www.uklupus.co.uk

[9] The symptoms can include- Arthritis, muscle pain and weakness, fatigue, sun-sensitivity, hair loss, "Butterfly" or malar rash, fever, anemia, headaches, recurrent miscarriages. Some people will have only a few symptoms, others may have them all. http://www.uklupus.co.uk

[10] http://www.uklupus.co.uk

symptoms began, they would be able to prevent the disease by advising those patients to avoid environmental factors that could elicit or exacerbate the disease, such as ultraviolet light or certain medications. Here, genetic research leads to a form of preventive medicine, which has the benefit of sparing the patient the painful inflammations that result from the disease.

In addition to improving diagnosis, genetic findings can aid in the development of better treatment. According to the Lupus Foundation of America, four of ten lupus patients are treated by three or more doctors, and take six or more medications to treat symptoms of the disease.[11] This evidence implies two problems: patients are not receiving adequate treatment from their physicians, and many of the prescribed medications are not very effective. The first problem may result from the lack of knowledge that doctors have about the effects of SLE on different people. Since lupus affects individuals in unique ways, each may need a different treatment or medication that treats their specific symptoms. In addition, since genes have been shown to influence the progression of a medical condition, it is possible that specific genes may influence the responses to different treatments.[12] Thus, better genetic information could explain why some drugs work better in some people than others. Using genetic testing, doctors could prescribe treatments based on the individual's specific genetic idiosyncrasies and thus make treatments less hit-and-miss than in the past.

Yet, another challenge to treating SLE is that as of now the majority of treatments target the symptoms of the disease ineffectively, while the ones that target the root cause have terrible side effects. There are four families of medications used in the treatment of

[11] www.lupus.org

[12] http://www.uklupus.co.uk

lupus: Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antimalarials, and cytotoxic drugs. Medications in the first three families target SLE symptoms such as inflammation and fever[13]; the problem with these drugs is that they only temporarily control the symptoms, rather than providing a permanent cure. Cytotoxic drugs, on the other hand, aim to stop the course of the disease; the trouble is that they often cause deleterious side effects. Ciclosporin, for example, suppresses the functioning of the body's immune system and can make patients more sensitive to sunlight[14] (a condition that actually exacerbates SLE). Another drug, an antibody to CD40, works towards blocking the communications between the T cell protein (CD40L) and the B cell protein (CD40), in order to help correct the hyper-activity of the immune system that is characteristic of lupus. However, these drugs are not being actively developed for lupus anymore, because there was a significant risk of blood clotting problems in previous trials.[15] Overall, the problem seems to be that these medications are not geared specifically towards curing SLE.

Biotechnology paired with further genetic research on SLE has the potential to overcome this problem by making it possible to develop treatment that will target the gene(s) responsible for lupus. Recently, Swedish scientists discovered a gene mutation that's partially to blame for the genetic underpinnings of lupus; they estimate it could account for as much as 20 percent based on statistical analysis.[16] The gene PDCD1, found on chromosome 2, plays a role in helping the immune system distinguish itself from foreign invaders; however, when the gene is mutated, it contributes to the

[13] http://www.uklupus.co.uk
[14] http://www.uklupus.co.uk
[15] www.lupus.org
[16] http://www.uklupus.co.uk

malfunctioning of the immune system by refusing to bind with the protein in charge of regulating the gene's production of antibodies to fight invaders.[17] This finding is a significant step towards developing new SLE treatments because it identifies a distinct root for the disease. The treatments would be more effective because they would be targeted at a specific malfunction in the individual's body rather than at the potential causes of certain symptoms.

Genetic research in the field of Systemic Lupus Erythematosus has come a long way and will continue to expand. The greatest benefit to the patient will be the availability of more accurate and individualized medical care that is based largely on the strengths and weaknesses found in their genes. For physicians, the advantage will be the ability to make more accurate diagnosis and treat the underlying causes of disease rather than just the symptoms. In this way, genetics leads to a win-win situation for both parties.

[17] Prokunina, L. *et al*. A regulatory polymorphism in *PDCD1* is associated with susceptibility to systemic lupus erythematosus inhumans. *Nature Genet.* 28 October 2002