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## **One Size Fits All: Can the Cure for Severe Combined Immunodeficiency X-linked Also Work for SCID due to Adenosine Deaminase Deficiency?**

### **Introduction**

There are several types of Severe Combined Immunodeficiency (SCID), and Adenosine deaminase (ADA) deficiency is the cause of only portion of all SCID cases. The most common form is SCID X-linked, which is caused by a mutation on the X chromosome, and affects only males. SCID-ADA is an autosomal recessive gene and is caused by the inheritance of two defective ADA genes, one from each parent. The defective ADA gene is the cause of about one-half of autosomal recessive cases of SCID. There are three separate phenotypes coded by the ADA gene, dubbed ADA 1, ADA 2-1, and ADA2. The location of the gene was found to be on chromosome 20, after mouse-man somatic cell hybrids were studied. Its exact locus is on 20q, next to the gene for S-Adenosylhomocysteine Hydrolase, or SAHH, and they are separated by 20q13.1. ADA deficiency is coded by an unusual type of genetic mutation, because most mutations cause polymorphisms, coding for a different protein that doesn't have the same effects, but the defective ADA gene causes a deficiency of the protein, which in turn causes a rare form of Severe Combined Immunodeficiency. The symptoms are similar to SCID X-linked, which are dysfunctional T and B-lymphocytes, and a decreased production of immunoglobulins. However, the reasons for the dysfunction are different. A deficiency in Adenosine deaminase causes an increase in dATP, which in turn inhibits the production of S- Adenosylhomocysteine Hydrolase, increasing S-adenosylhomocysteine.

Both S-adenosylhomocysteine and dATP have toxic effects on T and B-lymphocytes, depleting their dNTP pools and rendering the lymphocytes effectively useless.

### **Possible Solutions**

Many possible cures for SCID-ADA have been investigated, and some have been semi-successful. One attempt at reducing the symptoms of the disease involved transfusing ADA positive blood, but that presented problems because ADA degrades in a few minutes in human blood, and the procedure would have to be constantly repeated. Doing so would raise the level of iron in the blood to toxic levels, and the treatment is thus not a viable option. Changing the genotype of the patient would be a much more desirable treatment, and one way of doing this would be to undergo a complete bone-marrow transplant from an unaffected person, but the marrow would have to be an exact match, and one is hard to find. Another method would be to use avirulent retroviruses to deliver the fixed gene to the T and B-lymphocytes, but this treatment must be repeated frequently, because it only affects existing mature lymphocytes. Another method that affects immature lymphocytes is effective for a longer period of time, but since it only affects the phenotype, it also must be repeated. Both of these methods help to alleviate the symptoms of SCID-ADA for periods of time, and are an inexpensive way to sustain life until a more effective treatment can be implemented, but they are obviously not perfect solutions and are far from curing the disease, which is why a way to change patients' genotypes would be the best course.

Gene therapy is the most viable option to cure SCID, and a successful application of gene therapy to a child with SCID X-linked has been documented. Because a good match for a bone marrow transplant could not be found for the patient, his own marrow

was sampled, cultured, and a viral vector was used to implant the fixed gene, then the marrow was reimplanted. The subject then had normal T and B-lymphocyte production. Although this procedure has been used to cure SCID X-linked, it is a promising option for patients afflicted with SCID-ADA because both are caused by a single gene mutation.

### **Protein Comparison**

Using E-Matrix, the proteins of SCID X-linked, SCID-ADA, and SAHH (which may be related to SCID-ADA) can be compared, and their correlation evaluated. The Adenosine deaminase protein only brings up hits which are other species' forms of ADA, but SAHH is related to the interleukin 2 receptor gamma chain, which is the protein coded for by Xq13, is also the site where the mutation affecting SCID X-linked is located. The correlation coefficient was  $4.95e-08$ , indicating that there was a very low chance the hit was bogus. This suggests that the proteins coded for by the genes affecting SCID X-linked and SCID ADA are related in a structural way. If this is true, then the same method that was used to cure SCID X-linked might only have to be manipulated slightly in order to provide a permanent cure for the ADA caused form of Severe Combined Immunodeficiency.

### **Conclusion**

Up until very recent time, Gene Therapy was not a very viable option for patients because of the many complications with the new technology. However, we have now seen that it can provide an extremely effective treatment now that the technology for delivering the cure has been thoroughly tested and perfected. Culturing an individual's cells and reimplanting them with altered genes has been used to cure a child of a fatal disease, SCID X-linked, and the time is right for expanding that treatment to other

diseases. The first obvious choice is SCID-ADA, which is another form of the same disease, and is also caused by a single gene mutation. The afflicted protein in each disease has been structurally related using E-matrix, making the treatment an even more viable option. With the application of Gene Therapy to afflicted patients, the hope of using Genomics to cure many diseases caused by single nucleotide polymorphisms is brought one step closer to a reality.

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'Bubble boy' saved by gene therapy

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