The Achondroplasia Gene

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As some of you may know, exciting new discoveries have taken place in the study of achondroplasia and its etiology. The discoveries relate to the gene for achondroplasia. A gene is a unit of heredity - information that is passed on from one generation to the next. Genes are present on the chromosomes in the nucleus of most of the cells of the body. In order to locate the achondroplasia gene it was necessary to study many families in which achondroplasia was transmitted from a parent to an offspring. This allowed comparison between families to determine what chromosome was associated with the presence of achondroplasia. Through this study the gene for achondroplasia was located on the short arm of chromosome 4. After pinpointing the location of the gene, the next step was to isolate the gene itself. This was done by obtaining blood from individuals with and without achondroplasia, extracting the DNA from the white cells and examining the genes on the end of the short arm of chromosome 4. The gene for achondroplasia was found to be fibroblast growth factor receptor 3 (FGFR3) which is one of four fibroblast growth factor receptor genes.

"What is a growth factor receptor?" you might ask. There are many different growth factors (like growth hormone) that are present in the human body and usually circulate around the body. Each of these growth factors has individual receptors which may be present on the surface of some cells. The receptors allow the growth factor to have an effect on the cell (such as making it grow or duplicate). A receptor is made up of 3 parts: a part outside the cell, a part crossing the cell membrane and a part inside the cell. Usually the extracellular part is the identifier - its structure fits or complements the structure of the specific hormone and recognizes it when it is circulating in the blood. When a molecule of growth factor comes by and attaches itself to the receptor a message is sent into the inside of the cell to "get busy and make a change". In the case of most growth factors the change is to grow, increase metabolism or divide. In the case of the fibroblast growth factor's effects on the fibroblast growth factor receptor 3, it is to make cartilage grow.

Genes are made up of a special chemical called DNA (desoxyribonucleic acid). The DNA is made up of tiny units (nucleotides) arranged into groups which are like the links of a chain. The nucleotides that make up the FGFR3 gene carry the instructions for making the protein that will be the receptor on cells. In the case of achondroplasia one of the parts of the gene has a change and one of the nucleotides has been substituted by a different one. This change or "mutation" leads to an abnormality in the receptor. It is important to remember that this gene for the receptor is present in all individuals and only when it has the abnormal change does it lead to achondroplasia. FGFR3 is normally present on cartilage, kidney, lung, and brain cells. There are three other fibroblast growth factor receptors which are present in specific tissues. There are also 13 different fibroblast growth factors known to circulate in the blood that can attach to those four receptors. Several abnormalities of the other three growth factor receptors have also recently been found to lead to abnormalities in bone growth (particularly in the bone of the skull).

The gene for achondroplasia is unusual because the mutations or changes in the gene are at the same spot. Most of the time "mutations" or change in the genes occur all over at many different places in genes in different people. Researchers believe that because of the high incidence of achondroplasia in the population this place or piece of the gene may be a "hot spot" for mutation. Research on achondroplasia will eventually provide useful information as to why mutations occur with a higher frequency in this spot or maybe even why mutations occur at all.

So far only a few families have been studied and so it is still necessary to study the DNA from a lot more affected individuals in order to see if this change in the gene is constant in all people with achondroplasia or if there are a number of different changes that lead to the same disorder. Presently more than 200 people with achondroplasia have been tested and 98% of them have exactly the same mutation. In cases of sporadic achondroplasia (cases with no family history), which makes up 80% of all cases of achondroplasia, the mutation is just the same as in the familial cases.

What does this new discovery mean for individuals with achondroplasia? Firstly, the location of the achondroplasia gene to a specific chromosome allows people with achondroplasia to utilize prenatal testing to detect whether achondroplasia is present (in single or double dose) in the developing fetus. Secondly it will allow researchers to try to find ways to make up for what is missing in achondroplasia and either fool the cells by using another receptor or by using a different growth factor or increased amounts of fibroblast growth factor to stimulate increased growth of cartilage cells. It also means that it may be possible to synthetically produce the missing protein.

In achondroplasia the mutation or change is at one very specific place in the transmembrane part of the gene (nucleotide 1138). This suggests the part of the gene crossing the membrane is very important to get cartilage cells to turn on and grow normally. The possibility of providing the normal protein to individuals with achondroplasia in a way that is helpful is still a long way away but needless to say, the discovery of the gene is a definite step forward for understanding and providing appropriate care to affected individuals.

References:

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Acknowledgements

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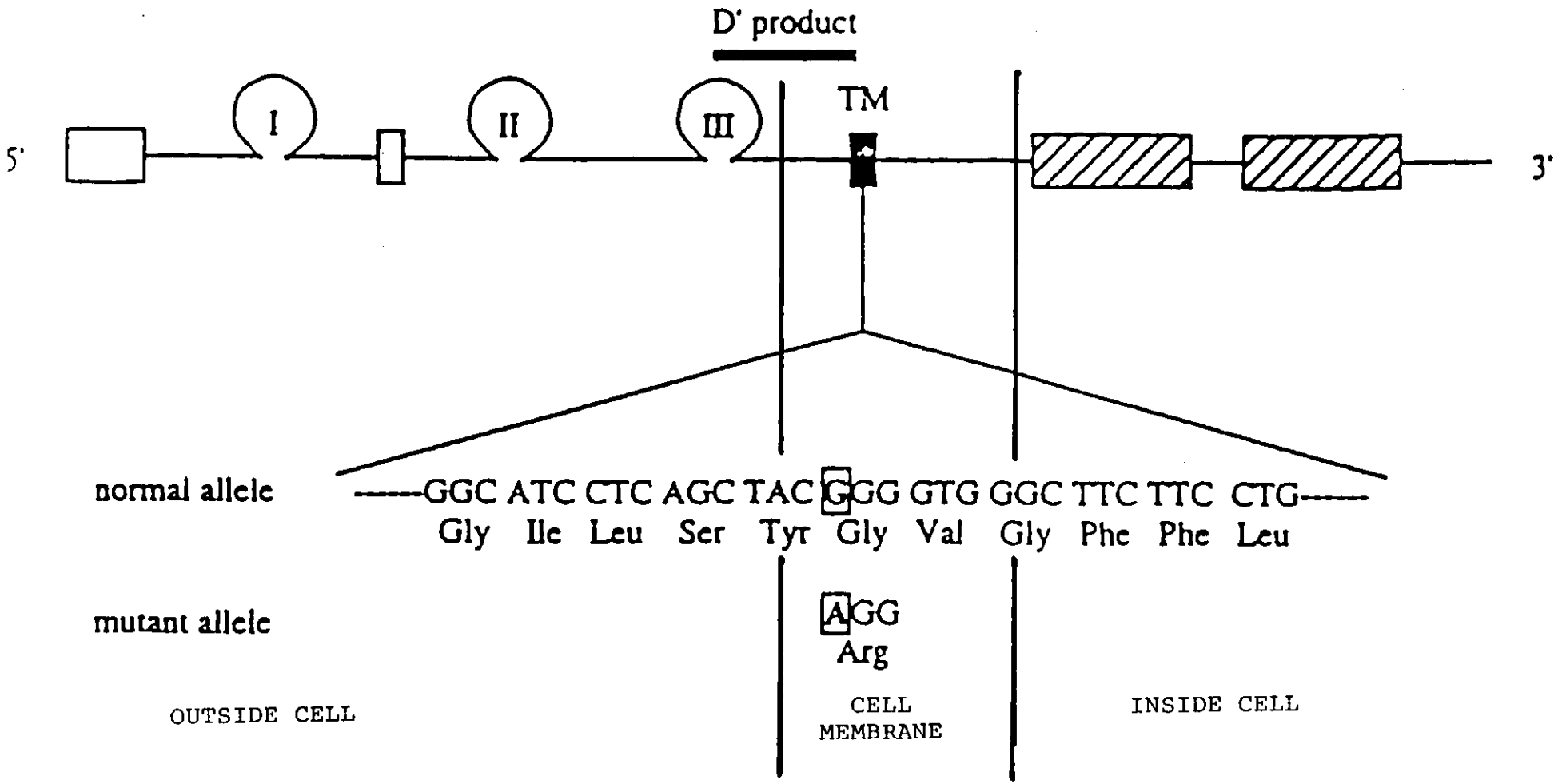
[editor: Dr. Hall is Professor and Head, Department of Paediatrics at the University of British Columbia and British Columbia's Children's Hospital; and Professor, Medical Genetics, at the University of British Columbia.]



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