STICKLER SYNDROME SUPPORT GROUP (SSSG)
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UNDERSTANDING GENETICS AND GENETIC TESTING FOR STICKLER SYNDROME

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1. UNDERSTANDING GENETICS WITHIN STICKLER SYNDROME

It is only in recent years that scientists have begun to understand and unravel the wonderful world of genetics. It must be stressed that the only conclusive diagnosis of Stickler Syndrome is through genetic testing.

2. WHAT WENT WRONG?

- Stickler Syndrome is caused by a defect in any one of three genes that hold the information for making the collagen present in vitreous and cartilage. There may also be another unknown gene that is defective in Stickler Syndrome.
- The genetic information passed on from parents to their children is contained in 22 chromosomes plus the sex chromosomes X and Y. Each person inherits a copy of all 22 chromosomes from each parent and either X and a Y chromosome in males or two X chromosomes in females. These sets of chromosomes contain around 30,000 genes which contain the information required for making the proteins which form the cells, tissue enzymes and other constituents from which our bodies are made. Genes are made of DNA which consists of four molecules abbreviated to A G C or T and each gene has its own distinct sequence of these 4 letters. Changes to the sequence can alter the information held in the gene and result in inherited disorders, because either the functional properties of the protein which they make, is either compromised or the protein may not be made at all.
- Stickler Syndrome is a dominantly inherited disorder, which means that only one copy of a gene needs to be defective to result in a genetic disorder. This is in contrast to recessive disorders, where both copies of a gene must be defective. This means an individual with

Stickler Syndrome has a 50% chance of passing the defective gene to their children.

- The genes that are defective in Stickler Syndrome are called COL2A1, COL11A1 and COL11A2. Only one of these genes needs to be defective to result in Stickler Syndrome.
- Although Stickler Syndrome is usually inherited, changes to the DNA sequence can occur sporadically during the process of copying DNA as cells grow and divide. This means children with Stickler syndrome can be born to clinically normal parents as the change may have arisen in the egg or sperm cells from which they developed. In some instances the change to the DNA sequence may be present in only a percentage of cells in one of the parents. These individuals are called "mosaic". This may mean that a 'mosaic' parent appears clinically normal even though they are capable of passing on the defective gene to their children. This may give the appearance of a recessive disorder, but affected children still have a 50% chance of passing the disorder to the next generation.
- As mentioned above, in Stickler Syndrome the defective genes are ones which make collagen. There are many different types of collagen in the human body. These have been numbered with roman numerals in the order in which they were discovered. To date there are 27 different types I-XXVII which have specific functions and can be found in various tissues. The collagens that are defective in Stickler Syndrome are types II and XI. These two collagens make the collagen fibrils that are present in both the vitreous of the eye and cartilage. Whereas one gene (COL2A1) holds all the information for making type II collagen, type XI collagen consists of proteins made from two different genes (COL11A1 and COL11A2). In addition to this the make up of this type XI collagen differs between cartilage and the eye. The type XI collagen in the

eye consists only of protein made from the COL11A1 gene, whereas type XI collagen in cartilage consists of protein made from both genes. This means patients with a defect in COL11A2 do not have eye problems in contrast to patients with a defect in COL11A1 that have eye, joint and hearing problems.

- Most families have DNA sequence changes unique to themselves and require lengthy and complex gene analysis to be performed on one affected family member to identify their specific DNA alteration. Once this is known it is a relatively simple matter to test other family members. The majority of patients with Stickler Syndrome have defects of COL2A1 and most of these result in only half the normal amount of type II collagen being produced. Changes to type XI collagen affect its function, which is to regulate how the more abundant type II collagen assembles into the fibrils which help to hold the cartilage and vitreous tissues together.
- Stickler Syndrome is a clinically variable disorder even within families and it is not possible to predict the severity of the disorder from one generation to another. It is not clear yet what causes this variation but other factors, some of which may also be genetic clearly modify the clinical outcome.

3. GENETIC TESTING FOR STICKLER SYNDROME

- The three genes known to be involved in Stickler Syndrome are all large and complex. As stated earlier most families have changes to the DNA sequence unique to themselves so that identification of the specific change involves a sometimes long, labour intensive and expensive process. Once the change has been found other family members can be tested to determine who is and is not affected.

- The first problem is deciding which gene to screen for the abnormal sequence. If a family is large it may be possible to perform linkage analysis to exclude two of the three genes. **Linkage analysis** involves identifying the different copies (alleles) of a candidate gene in the parents (there are four, two in each parent) and seeing which if any is co-inherited with the disorder in the children. This is done by using regions of DNA (sometimes called markers) that vary greatly between individuals. These markers are spread throughout the 22 and X and Y chromosomes, so ones that are close to the gene under test are selected. Because parts of chromosomes are shuffled before being passed to the next generation, the closer a marker is to the gene of interest the greater the likelihood is that it will be co-inherited with it, and therefore specifically identify the different gene alleles. In practise three or four different markers in and around the gene are used to identify or "tag" the four different versions of a gene it is possible to inherit from the parents. If all affected children inherit the same allele from an affected parent then this is consistent with the gene being linked to the disorder. If the affected children inherit different alleles then the gene is not linked to the disorder. The larger the family is then the greater the significance that positive linkage becomes. So the more family members that can take part in the analysis the more significant the results can be. It is not possible to perform linkage analysis in sporadic cases, and in small families statistically significant linkage may not be possible.
- It may be possible to identify the abnormal gene by specific **clinical features.** The majority of patients with Stickler Syndrome have defects in the COL2A1 gene, so this might be the first to choose in any case. However differences in the vitreous may also point the geneticist in the right direction. Most patients with defects in COL2A1 have a distinct membrane present in

their vitreous gel and this seems to be specific for this gene. Patients with defects in COL11A1 have a vitreous structure, with thickened strands that have a beaded appearance, but it is not yet clear how specific this appearance is with regards to the COL11A1 gene. Patients with defects in COL11A2 have normal eyesight and vitreous gel structure.

4. IDENTIFYING DNA CHANGES

- There are many methods that can be employed to identify the specific DNA changes that result in Stickler Syndrome. There are advantages and disadvantages to all, but none are capable of detecting all the different types of alterations to the DNA sequence that can cause the disorder. Some methods can be relatively quick and cheap but do not necessarily have an efficient pick up rate. The most reliable are usually more expensive and time consuming. The "gold standard" is to sequence the complete genes. But as they are large, COL2A1 contains over 31,000 letters (or nucleotides) and COL11A1 is even larger at over 250,000 nucleotides, this would prove too expensive. In practice small pieces of the gene called exons, that contain the protein coding regions are amplified (copied many time over to produce enough material to analyse) and then sequenced. This still involves over 5,000 nucleotides each for all three genes.
- Patients may be required to give a blood sample for DNA analysis or alternatively a skin biopsy. The skin biopsy is used to analyse the RNA sequence which is the intermediate molecule that is copied from the gene before being translated into collagen protein. DNA can be prepared immediately from blood samples, but skin biopsies have to be grown in culture dishes and this can take up to 3 months before RNA can be prepared from the cells.

- Whatever the strategy that is employed to identify these disease causing DNA alterations, it is not a quick, easy or indeed cheap process. Doctors and their patients should not expect an answer within weeks. The testing process is not suitable as a tool to confirm a suspicion of Stickler Syndrome. Instead patients should be thoroughly assessed clinically before testing is carried out on those that match the correct criteria.

5. HOW YOU CAN REACH US

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