

WHAT IS THE FISH TEST?

In 1993 it was shown that a person having a tiny piece missing from one of the number 7 chromosomes causes Williams Syndrome. Because the piece is too small to be seen under a microscope this is called a chromosomal micro deletion. The missing piece contains a number of genes including the elastin gene, which is roughly in the middle of the deletion. Since the deletion cannot be seen on a routine chromosome test a special test called the FISH test (short for Fluorescent in-situ Hybridisation) is used. In this test a 'gene probe' tagged with fluorescent paint sticks to the elastin gene if it is present and the glow can be seen down a special microscope. In WS the fluorescent signal is missing from one chromosome 7 because the elastin gene is missing. The FISH test does not tell you how big the deletion is, it just tells you whether or not the elastin gene is missing. We think there are about 40 genes in the 'micro deletion' so people with WS are functioning on half the normal amount of genes from this piece (i.e. only from their normal chromosome 7). For many genes we can function on just one copy quite happily so it is possible that not all of these contribute to the characteristics of WS.

WHAT GENES ARE IN THE 'MICRODELETION'?

The first one to be discovered was the elastin gene. We know this is important for the strength and elasticity of the arteries. If a person only makes half the normal amount the arteries can narrow. This is what causes the characteristic heart problem of WS which is SVAS (supravalvular aortic stenosis).

Our work has shown that people with SVAS (and not WS) also have errors in one of their elastin genes. This proves that having only one working copy of elastin causes the heart problem but not the other feature of WS.

There are about eighteen other genes that we know about but we do not yet understand exactly what most of these do. It has been suggested that a gene called **LIMK1** is involved in the unusual pattern of abilities and difficulties of WS but our joint work with Professor Annette Karmiloff-Smith on people with small pieces missing showed this was unlikely.

Another gene we have found is called **GTF3**, this works in muscles and we wonder whether the muscle weakness and tiredness people with WS complain of is due to half amounts of this gene.

WHY DOES THE PIECE GO MISSING IN THE FIRST PLACE?

On either end of the missing piece there are stretches of the DNA with a very similar genetic code to each other. When an egg is forming the two chromosome 7s from the mum line up with each other and swap DNA before one of the pair goes into the egg (the same happens when dad makes his sperm). Sometimes the pair of chromosomes 7s line up a bit skewed (like doing up a zip out of line) and then the piece between the similar stretches of DNA gets pinched out.

IS THE FISH TEST ALWAYS ABNORMAL?

Probably 100% of people with 'classic' WS have a deletion on the FISH test. Theoretically it would be possible for a person to have a smaller deletion and a normal FISH test result but as yet there is no-one described in the medical literature for whom this is the case.

CAN YOU HAVE AN ABNORMAL FISH TEST AND NOT HAVE WS?

Yes, an abnormal FISH test does not necessarily mean that someone has Williams Syndrome. Lack of elastin causes the heart and blood vessel problems in WS and may also contribute to the increase in hernias in WS – it does not cause the learning problems, hypercalcaemia or unusual facial features of WS individuals, which must be caused by other missing genes. We know this because there are families who have the elastin gene missing and they only have supravalvular aortic stenosis. (we also know that in WS not everyone with the elastin gene missing has heart problems).

SHOULD ALL PEOPLE WITH WS HAVE THE FISH TEST?

Many people with WS were diagnosed on their pattern of characteristics long before the cause was known. Having the FISH test will not change anything for these people. However, when researchers are doing studies (like Dr Neil Martin's growth study) and since there is now a test, it makes the study more scientifically valuable if all the participants are proven to have a positive test. By doing the tests on everyone we may also identify a few WS people whose tests give slightly different results, such people are also very valuable for our research in matching genes in the missing piece to WS characteristics.

WHAT DOES THE FISH TEST INVOLVE?

Just a small blood test. It is usually taken from a vein in the arm or hand through a fine needle. It feels like a small pinch, but if someone is very anxious, they can have some 'magic cream' on the spot to numb it.

WHAT ABOUT TESTS IN PREGNANCY?

The risks for a normal parent having a second child with WS are extremely low. Apart from identical twins there are no reported cases of siblings both with WS. Although the FISH test could be done at an amniocentesis or a chorionic villus biopsy in pregnancy, the risk of the test causing a miscarriage would far outweigh the chances of having another WS child. The exception to this would be for WS adults who have a 1 in 2 chance in a pregnancy of having a WS baby themselves.

SHOULD PARENTS AND SIBLINGS OF A WS INDIVIDUAL HAVE THE FISH TEST?

No, this is not necessary. The deletion occurs as a 'one off' in an egg or sperm and parents of a WS child are not 'carriers'. Nor do brothers and sisters who are normal themselves have any increased chance of having a child with WS.

Finally, can we thank everyone who has participated in our research to date. Our work is going well and we are continuing to attract grant funding from various sources. As well as blood samples we are also looking at other tissue to see how genes from the missing piece work. If you know of a WS person who is going to have an operation we would really appreciate knowing about it so that we might request that some tiny samples of skin and other tissue are collected at the same time. The size of pieces we are talking about are something like the diameter of a drinking straw. Our contact telephone number is 0161 276 6002/6264 and we appreciate as much warning as possible.

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