

The Genetics of Williams syndrome: An Update

Williams syndrome is due to an accidental mis-pairing of the #7 chromosomes leading to a deletion of 26-28 genes. This occurs because the genomic structure of chromosome 7 in that area has many repeats, and it takes place during conception at the time that the chromosomes match up. The reason it occurs is not because of anything you did, but because of the genomic structure of chromosome 7. It happens because the human chromosome is built that way. This is the reason that the incidence of WS is the same in any part of the country or anywhere in the world.

Approximately 6% of the general population has an inversion of the Williams syndrome region and approximately 25% of “transmitting” parents of children with Williams syndrome have an inversion. Interestingly, this inversion is considered a normal variant as it is more than 4% of the general population. However, there is absolutely no way that a transmitting parent would have known they had this inversion. A parent with an inversion has a 50% chance of transmitting that inversion to their children which is why a sibling of someone with WS has a higher chance of having a child with Williams syndrome (although still rare). It has only been reported three times that a parent has more than one child with Williams syndrome. A person with Williams syndrome has a 50% chance of having a child with Williams syndrome while a parent with an inversion of the WS region has a 1 in 9500 chance (the same as for those without an inversion) of having a child with Williams syndrome. There is no such thing as being a “carrier” of Williams syndrome.

Where there is a deletion, there can be a duplication. In fact, a duplication of the WS region has been found. “Dup7” is not as common as Williams syndrome. Individuals with the duplication have developmental delay, significant feeding and speech problems and anxiety (especially separation anxiety) but do not have WS. In WS, you have one normal chromosome and then you are missing those genes in the WS region on the other. With the duplication, individuals actually have 3 copies of the genes.

Scientists are currently studying which genes in the region cause the various problems found in Williams syndrome. In order to do so, they are looking at individuals with smaller or different deletions and comparing symptoms to people with Williams syndrome who have typical deletions. Additionally, mice with a deletion of individual genes are being studied to determine what problems they have, and we are beginning to get some answers. We now know that the elastin-deficiency results in SVAS, hernias, hoarse voice and diverticuli of bowel and bladder. Everyone with Williams syndrome has thicker

The size of the deletion plays a role in the symptoms of WS. Individuals who have a deletion of 28 instead of 26 genes are less likely to have hypertension. Deletions longer than 28 genes are associated with more severe intellectual disability, and seizures (infantile spasms). Deletions shorter than 26 genes are associated with fewer symptoms which vary depending on what genes are deleted.

arteries because of the elastin-deficiency, but not everyone has SVAS or symptoms. The LimK1 deficiency (the gene just next door) contributes to visual spatial deficits and the GTF21- deficiency is associated with lowered cognitive ability.

The symptoms of Williams syndrome are modified by several factors. First, the size of the deletion plays a role. Individuals with WS who have a deletion of 28 instead of 26 genes have the deletion of the NCF1 gene and are less likely to have hypertension. Deletions longer than 28 genes (up to 40 or even 50 genes) are associated with more severe intellectual disability, and seizures (infantile spasms) which are associated with the deletion of the MAG12 gene. Deletions shorter than 26 genes are associated with fewer symptoms which vary depending on what genes are deleted.

A person’s gender also affects the symptoms of Williams syndrome. It appears that males with WS are more likely to have severe cardiovascular disease than females. The specific genes involved also play a role. For example, individuals with a common variant of the alpha1 antitrypsin gene are more likely to have scoliosis and joint dislocation.

If an individual with WS has another genetic abnormality, they would be expected to have additional symptoms, such as lower IQ than is typical.

If an individual with WS has a lower IQ than is typical, or has Autism, one may want to do additional studies, such as microarray, to look for other deletions or duplications.

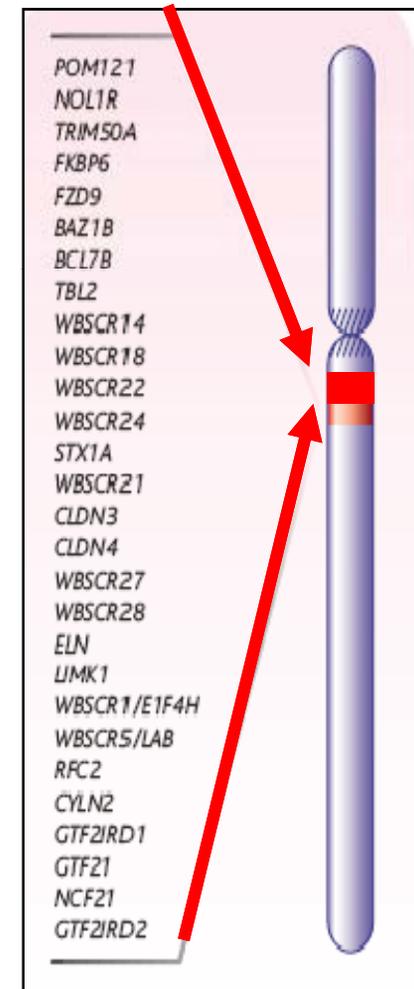
Microarray vs. FISH

A microarray gives us a lot more detail than a FISH test. About 20% of individuals with mental retardation show an abnormality on microarray. On a standard chromosome study, only 2% would show an abnormality. If a psychologist says that a child appears to have WS, but is functioning at a lower level than expected, that is the child for whom you should get a microarray (which looks at every chromosome). If the child has WS and Autism, a microarray is also recommended. If we find an additional problem then there might be a different treatment available which can impact the child’s outcome. The FISH test is still perfectly accurate for diagnosis, but it does not tell you how many genes are missing. If a diagnosis was done via a FISH test, there is no need to get a microarray done unless there is an additional issue present.

The Genetic Basis of Williams Syndrome

Cause of Williams syndrome :

- Deletion (missing piece) of chromosome 7q11.23
- Approximately 28 genes live in that piece of deleted material
- **WS is a "Contiguous Gene Deletion" syndrome (all the genes "line up" in one area)**
- Each gene has one or more jobs (function)
 - Some are performed while the baby is in the womb
 - Some are performed after birth
- We now know the functions of some genes in the missing piece but not all the functions of every gene



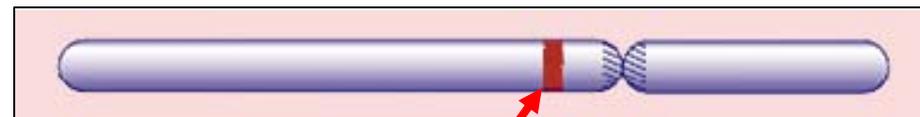
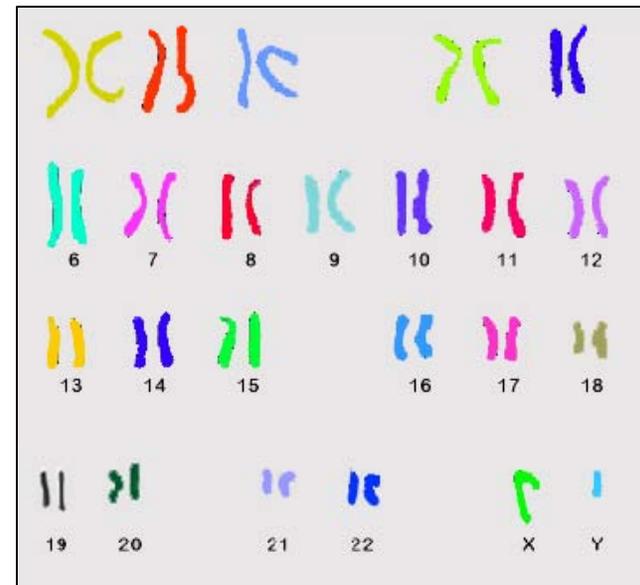
The Cause of Williams syndrome

Deletion of chromosome 7q11.23:
Missing piece of chromosome

- Every human has 46 chromosomes
- 23 pairs – one from mother
one from father
- Each chromosome is like a specific street,
with specific houses at each address.
- each room (gene) in a house, has a specific
job or role

p = short arm

q = long arm



• 7q11.23