The cause of WS

- The missing segment of genes are “lost” when the duplicated (homologous) chromosomes cross-over during egg or sperm formation.

Williams syndrome is classified as a microdeletion genetic disorder caused during crossing-over or autosomal recombination.
Diagnosing WS

- Prior to 1993, the genetic region affected by Williams syndrome was not yet discovered.
- Studies of SVAS lead geneticists to identifying ELN as an affected gene.
- With research they learned that over 90% of those with WS were missing this sequence which lead to a progression of new discoveries about WS.
Prior to the early 1990’s, little was known about the structural reason behind SVAS. Scientists were unsuccessfully looking for the protein that caused it.

- The field of molecular genetics has increased our understanding of disorders.
  - Traditionally, scientists had to identify the protein and then work backwards to figure out the gene that creates the abnormality.
  - Today’s research takes a forward approach. We can test for many genetic anomalies and compare several subjects who are missing common sequences to pinpoint the cause of disorders.
Genes affected by WS

- ELN is missing in 95-99% of individuals with WS
  - Reason why this gene was chosen for FISH testing
  - Now many families are tested using microarray.

Elastin is most likely the most famous of the genes affected by WS because it was the first gene discovered in WS testing and it is used for diagnosis in the FISH test.
A FISH test (A) and microarray (B) indicating WS.

WBSCR deletion
ELN is made up of roughly 42,118 base pairs that code for 14,000 amino acids or protein building blocks. These amino acids create tropoelastin.

- You have a gene sequence on the 7th chromosome called ELN. This sequence codes for the protein tropoelastin.

- Several tropoelastin proteins fold together to create elastin— a stretchy fiber used to give flexibility to tissues while maintaining the tissue’s integrity.
How do you make tropoelastin?

Genes are transcribed inside the nucleus to create RNA.

Then, RNA travels out to ribosomes and is used to assemble proteins during translation.
Structure of tropoelastin

- Top of molecule provides it’s “spring” and is called the coil region (NC).
- The base acts like an anchor, attaching the protein to neighboring molecules (CF).
- In between there is a bridge that acts like a shock absorber, helping the molecule maintain its integrity (BR).

(source: Yeo et al)
Building elastin

- Tropoelastin is used to make elastic fibers in connective tissue.
- As the tropoelastin accumulates at the cell surface, an enzyme creates cross links and binds it to microfibrils or a net made of protein.
Building elastin

Diagram on left represents the elastin fiber of an individual with WS, notice reduced amount of tropoelastin in comparison to a typical elastin fiber.

- Less tropoelastin created = thinner elastin
- Thinner elastin means some tissues will look and perform differently than expected.
Where is elastin in the body?

- It is a protein found in connective tissue.
- Connective tissues are for support throughout the body. They have several functions:
  - Connecting tissues and organs
  - Storing nutrients
  - Creating support and flexibility for an organ
  - Transport
How is elastin used in connective tissue?

Elastin fibers fill in spaces around the cells in the connective tissue. This area is called the extracellular matrix. The cells are called fibroblasts because they build fibers.
What is elastin?

- Elastin is a protein that gives connective tissue its elastic or stretchy properties—like a rubber band.
- Used in the skin in a layer of tissue that allow the skin to stretch and then spring back to shape.
- Also found in vessels and the heart—stretch to control blood pressure.
- In joints—allows spring in cartilage to absorb shock and avoid injury.
Elastin in arteries

- Elastin makes up much of the middle (media layer) of arteries (blood vessels that carry blood away from heart)
- Elastin and smooth muscle bundles are arranged in rings around the vessel
- Flexibility is an important characteristic of arteries:
  - Used to manipulate the size of the opening
  - Regulates blood pressure

Picture of an aorta section and increased magnification of the elastin found in the middle layer
How is it related to SVAS

- Narrowing of aorta in this location is directly related to decreased levels of tropoelastin production.
  - Less tropoelastin causes elastin fibers to have fewer structural components - thinner elastin
  - Body tries to compensate and increases production of smooth muscle, making aorta thicker and narrower
  - In WS, the tissue making up the aorta is disorganized compared to typical aortic tissue.
Issues associated with SVAS

- Thicker, less flexible
- Narrow opening can blood pressure issues and places stress on the heart
- Overtime can cause damage to aorta lining
- Heart tries to pump harder to get blood through, causes hypertrophy, blood pressure issues, shortness of breath, circulation issues, potential chest pain and congestive heart failure
Future research

- Scientists are now trying to pinpoint the mechanism of how the artery’s tissue structures change with WS.
  - Based on what they find, the future of treatment using medication may be feasible.
  - May find ways to decrease the degree of narrowing if SVAS is caught early in life.
Other symptoms related to ELN

- One puzzling aspect of WS is that the lack of ELN can cause many issues but not everyone with WS have them.
- Many scientists think this spectrum of variation in WS may be controlled by several genes that work with ELN.
- The expression of ELN and production of elastin is controlled by many genes that make the enzymes and microfibrils.

Although we know so much more over the past two decades about the relationship between ELN and the vessels, its relationship to skin and facial features is less understood.
Other symptoms related to ELN

- Different genotypes or varieties in these enzymes may have a hand in other WS connective tissue disorders that are less common than SVAS
Elastin has a life span

- As we age, elastin integrity is challenged by the environment.
  - Damage such as sun, smoking, stretching during pregnancy etc. makes elastin lose its structure
  - An enzyme called alpha 1 antitrypsin (AAT) inhibits the elastase enzyme from degrading elastin. Some evidence suggests that more severe SVAS and joint issues could be based on this enzyme phenotypes.

Some families have genotypes of AAT that accelerate the connective tissue degradation of elastin. This might explain why some have greater severity CT issues.
ELN and the skin

In the skin, the elastin works with collagen—a fiber designed for strength. It is arranged in sheets of tissue.

Elastin is suspected to influence the following WS traits due to its known presence in skin:
- Soft skin
- Pre-mature aging
- Unique WS facial features such as puffiness around eyes
Elastin is found in the dermis of the skin (shown in pink). It gives skin its characteristic “stretch”.
Anatomy of the vocal cords

- The vocal cords are made of a combination of cartilage, muscle and connective tissue
  - The vocal folds in the larynx vibrate or create a wave due to pressure changes in the structure.
  - Made up of layers of elastic dense tissue- called lamina propria.
  - Flexibility of the vocal folds is directly related to the tone of the voice.
  - A hoarse sound results from a vibrating epiglottis.
ELN and the Digestive system

ELN is arranged in nets in the abdomen.

- Connective tissue is found in the lining of the bowels to keep the organs organized and provide support.
- Weaknesses in this tissue can cause the tissue to bulge – called a hernia.
Inguinal hernias are found more often in males but can still occur in females.

- The most common hernias in WS are inguinal hernias
  - occur in 40% of individuals with WS during infancy
  - Occurs when the connective tissue becomes weak in the groin and the small intestine slips down into the area around the reproductive organs.
  - Requires surgery
Diverticulitis is usually an elderly issue but due to the lack of elastin it can occur in those with WS at ages as young as 17.

- Diverticulitis can become a problem in adults with WS
  - Typically a disorder for the elderly but due to the degradation of elastin earlier in life.
  - Diverticulitis is similar to a hernia but it occurs in the walls of the colon. Small pouches can bulge and fecal matter can get caught inside causing infection.
ELN and joints

- Elastin is an important component of the joints.
  - It is used to make ligaments that connect bone to bone.
  - It is found in the intravertebral discs that cushion the spine.
There is evidence that a lack of elastin coupled with some enzyme genotypes makes scoliosis more prevalent.

Scoliosis is caused by tissue damage during growth spurts. If the intervertebral disc in the spine has elastin damage, some enzymes may not be prompted to repair it and the body cannot support the weight.
ELN and joints

- The stability of a joint depends on ligament and tendon integrity.
- Joints are held together by tendons that pull tightly and stabilize the area.
- When the joint becomes loose (due to lack of elastin), the joint can dislocate or hyperextend and cause injury.
Sources

You can find a blog post on this topic and direct links to the primary sources used at www.understandingwilliamssyndrome.blogspot.com

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