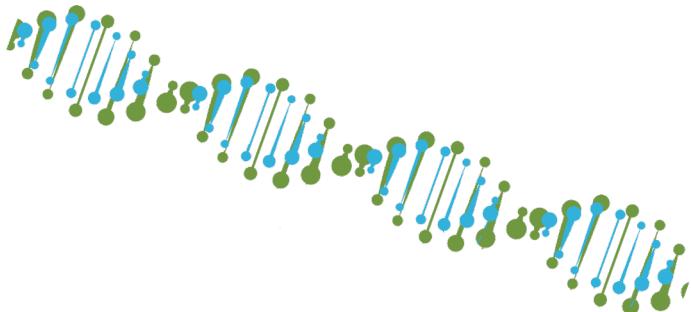


Hypertrichosis

“Werewolf Disease”

Nicole Roberts
Samantha Catbagan
David Contreras
Jade Garcia
Fall 2018 CSUDH



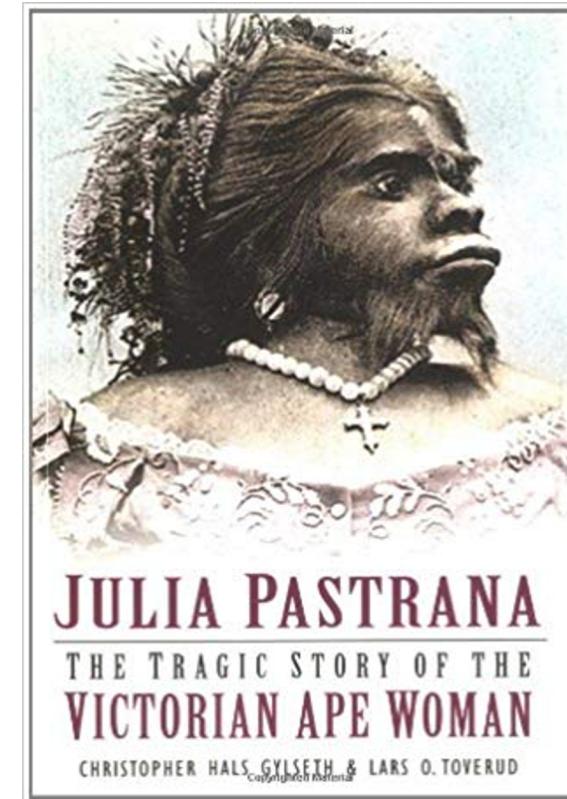
What is the Story and Genetic Concept?

- “These Diseases May Have Inspired Halloween Monsters” by Adam Barsouk (Forbes 2018)
- Hypertrichosis = “Werewolf Disease”
 - Condition of body-wide excessive hair growth
- First recorded case: Petrus Gonsalvus, 1537
- Werewolves become a concern in France because of Gonsalvus
- Likely a fault in SOX3 gene on X chromosome

Does the Media Report Accurately Represent the Scientific Information?

NO. Much more to it:

- Very rare congenital condition (~one in one billion)
- Excessive hair growth only one subset of abnormalities--Hypertrichosis also associated with craniofacial and skeletal defects
- Different types of Hypertrichosis, with different phenotypes and genetic causes



Types of Hypertrichosis

- **Congenital hypertrichosis lanuginosa:** When the fine lanugo hair found on a baby at birth does not disappear.
- **Congenital hypertrichosis terminalis:** Body-wide terminal hair growth beginning at birth and continuing throughout a person's life.
- **Nevoid hypertrichosis:** Excessive terminal, vellus, or lanugo hair growth of any kind appearing in a defined area.
- **Hirsutism:** Women only affliction; Terminal or vellus hair growing in places women normally don't have hair, such as their face, chest, and back.
- **Acquired hypertrichosis:** Food, drugs, cancer, other mutagens. Vellus hair or terminal hair growing in patches or all over.

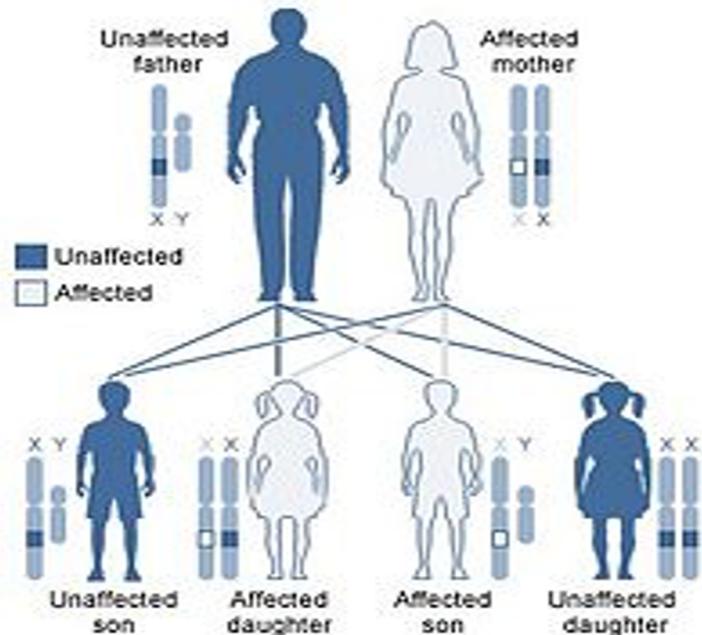
(Healthline, 2017)

SOX3 gene linked to Hypertrichosis

- Methods of Analysis
 - Genome-wide association studies
 - Genetic Variance in two families (Chinese and Mexican family)
 - SNP arrays
 - Linkage Analysis
- Why do the males express additional phenotypes such as scoliosis?

Generalized hypertrichosis associated with X-linked

X-linked dominant, affected mother



X-linked dominant, affected father

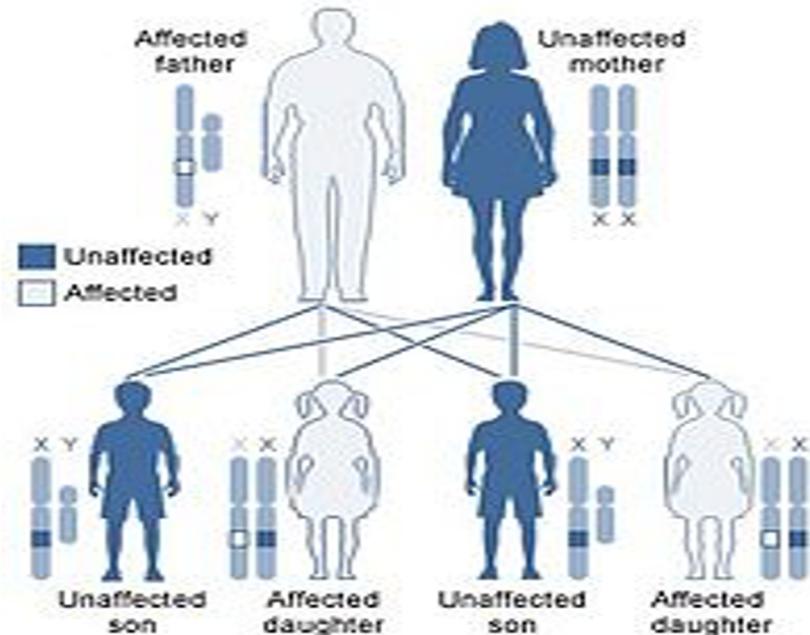


Figure 1. Phenotypes/Genetic Locus of Chinese Family

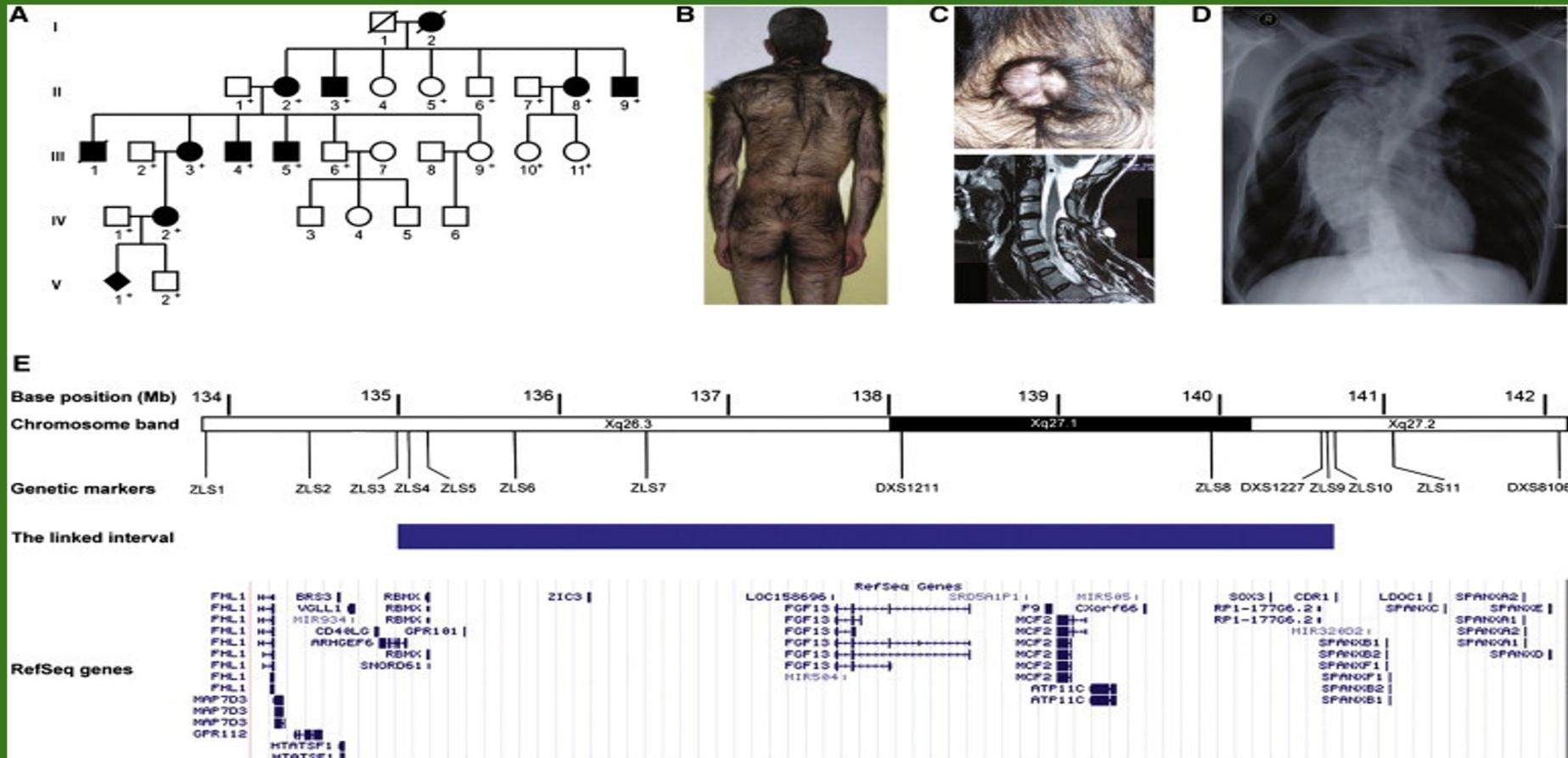


Figure 2. Identification of an Inherited Interchromosomal Insertion at Xq27.1 in the Chinese Family

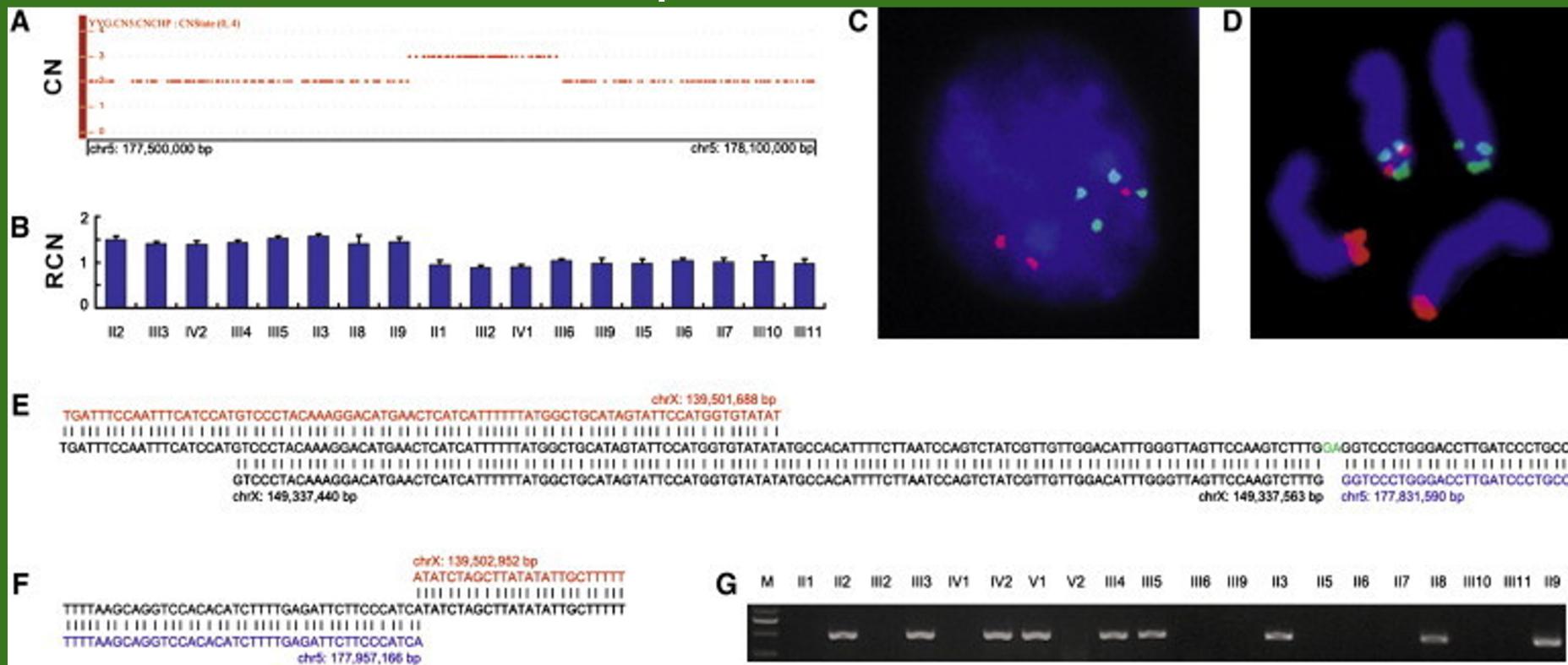
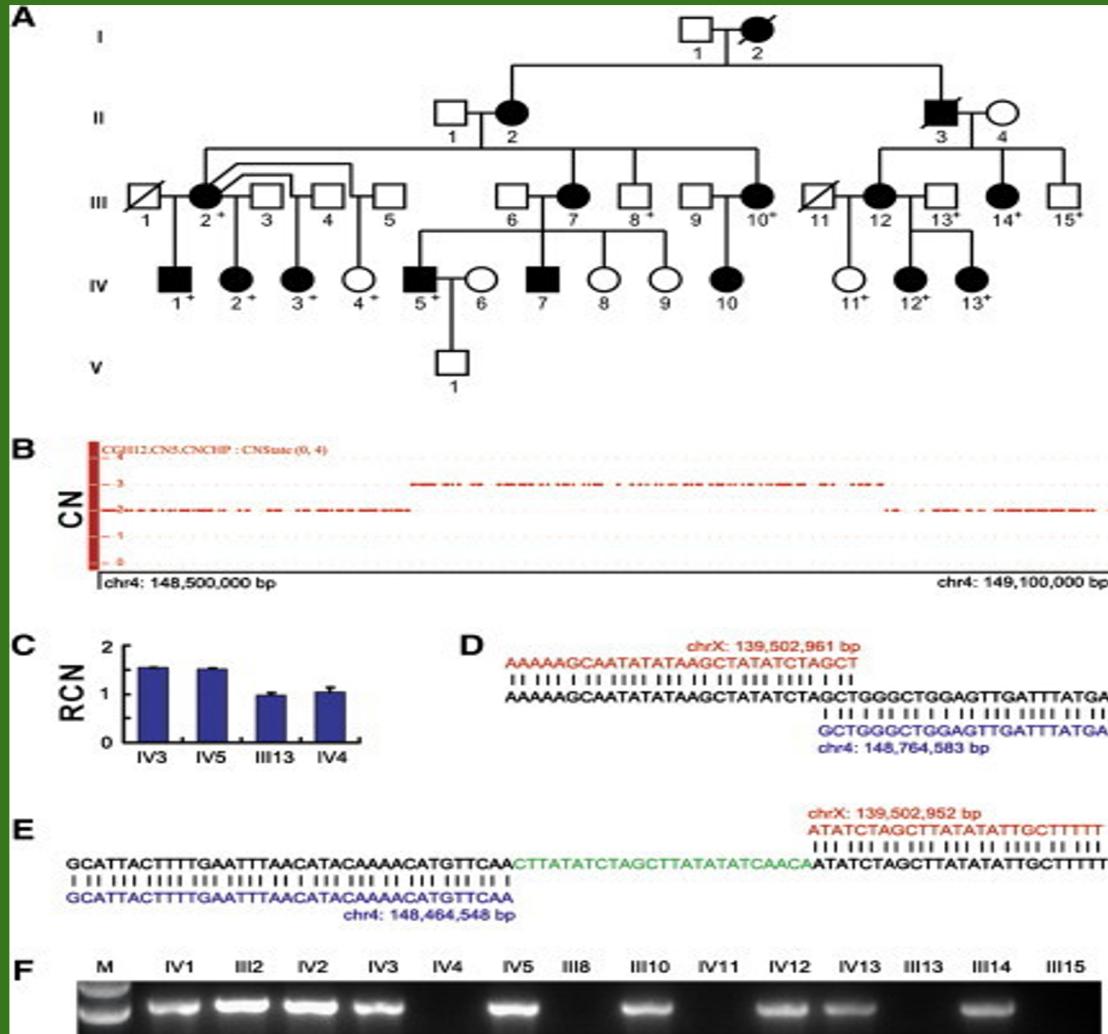


Figure 3. Identification of an Inherited Interchromosomal Insertion at Xq27.1 in the Mexican Family with X-Linked CGH



SOX3 gene linked to Hypertrichosis

- What do the results show?
 - Results suggest that the palindrome-mediated insertions are the underlying cause x-linked CGH
- What is the link between the identified interchromosomal insertion at Xq27.1 in the Mexican and Chinese family to the SOX3 gene (overall resulting in the cause of x-linked CGH)?
 - *SOX3* gene - its 3' end lies 82 kb telomeric to the palindrome sequence (containing the insertions/breakpoints)
 - the SOX family of transcription factors is among the most important groups of developmental regulators
 - Interchromosomal insertion found at the same Xq27.1 site located downstream from SOX3

Cholesterol Transporter Gene ABCA5

- Congenital hypertrichosis terminalis (auto recessive)
- Loss of function, substitution mutation (G-->C) in 5' donor splice site of intron 32 in *lipid transporting* ABC gene
- Decreased transcription of ABCA5 protein due to aberrant splicing
- Leads to failed clearance of autophagosomes resulting in accumulation of lysosomal cholesterol in keratinocytes
- Reduction/loss of lysosomal protein ABCA5 in hair/skin linked to excessive hair growth

(PLOS Genetics, 2014)



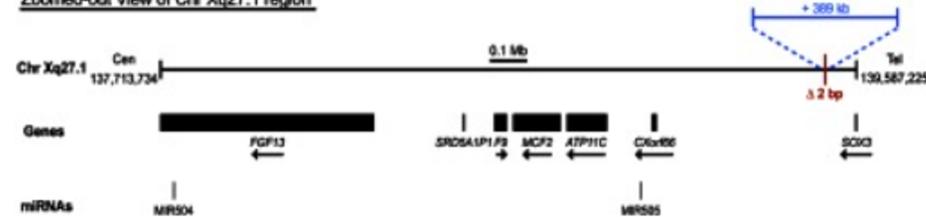
Position effect FGF13 and X-linked

- Position effect - effect on expression of a gene when its location in a chromosome is changed
- Fibroblast Growth Factor 13 (FGF13) is expressed in the hair follicle
 - Possible evidence of X-linked hypertrichosis
- X-linked congenital generalized hypertrichosis (X-linked CGH)
 - Extremely rare condition of hair overgrowth on different parts of the body
 - Affected males have 3x the number of normal hairs on the scalp, back, chest, arms, legs, and face
- Report done on a large Mexican family with this condition
- Performed linkage analysis
- Chromosome Xq24-27 (cosegregates with disease)

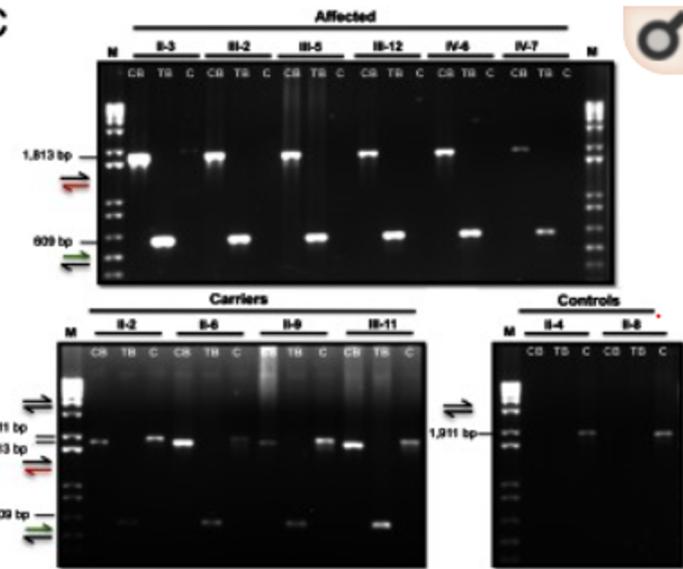
389-kb interchromosomal insertion at Chromosome Xq27.1

A

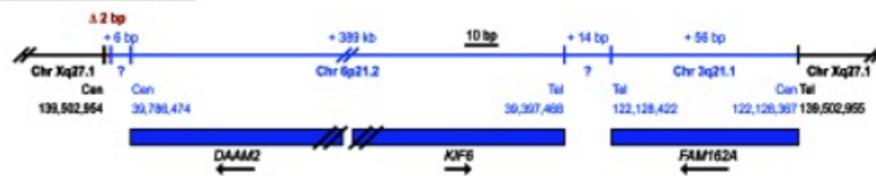
Zoomed-out View of Chr Xq27.1 region



C

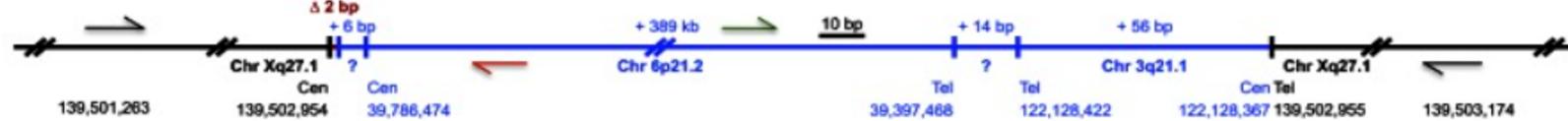


Close-up View of Insertion



D

PCR junction primers



Trps1 and target gene SOX 9 regulate epithelial proliferation

- **Position Effect Variegation (PEV)** = *Epigenetic regulation mediated by translocation of euchromatin to a heterochromatic region that alters gene expression*
- **SOX9** is a **TRANSCRIPTION FACTOR** located on Chromosome 17
- **TRPS1** is also a transcription factor on Chromosome 8 that **represses SOX9 expression**

Fantauzzo KA, Kurban M, Levy B, Christiano AM (2012) *Trps1 and Its Target Gene Sox9 Regulate Epithelial Proliferation in the Developing Hair Follicle and Are Associated with Hypertrichosis*. PLoS Genet 8(11): e1003002. doi:10.1371/journal.pgen.1003002

Novel regions of DNA associated with dark blue boxes of Copy Number Variation (CRV)

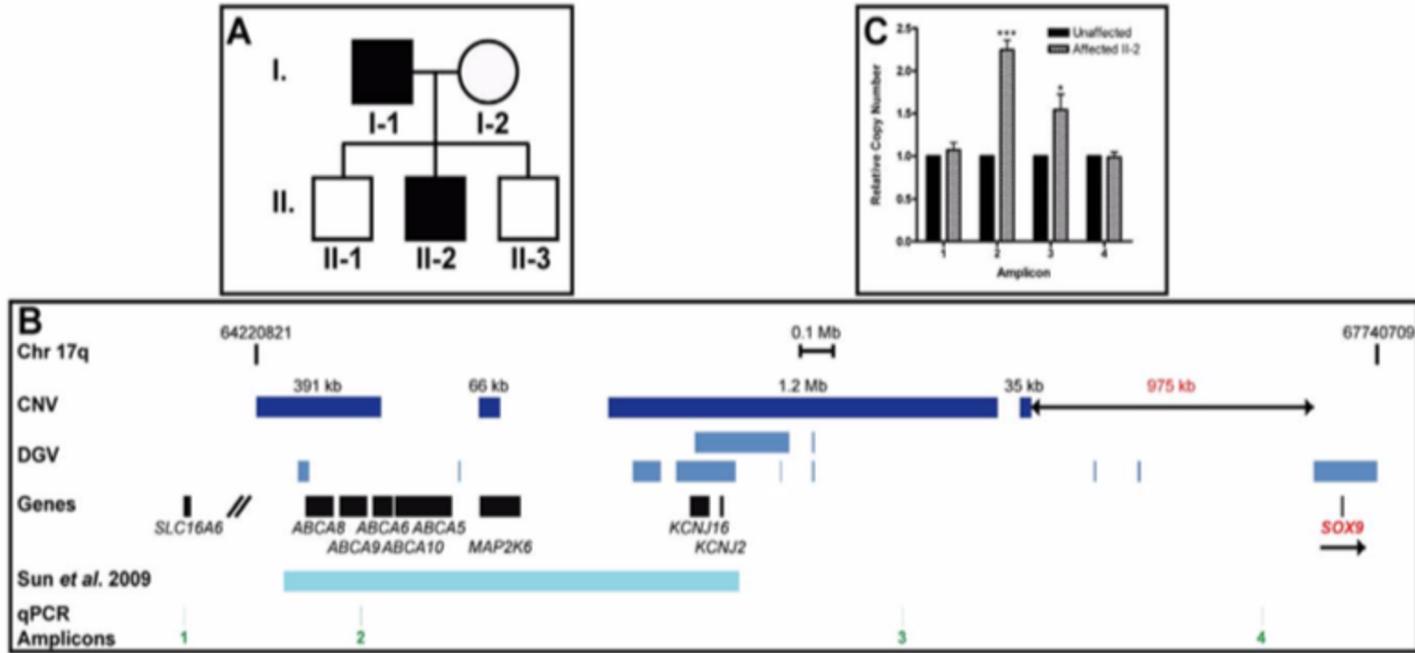


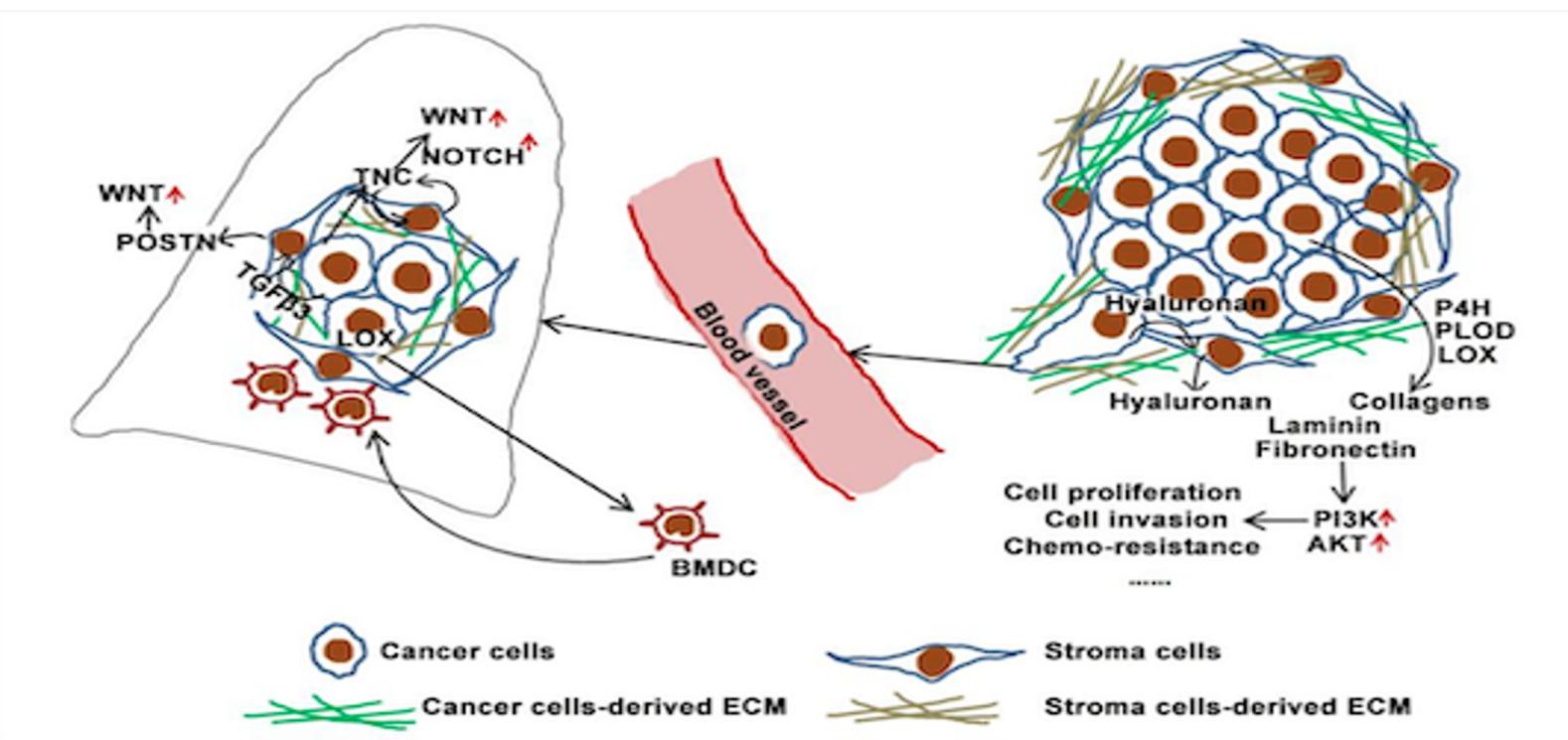
Figure 5. Copy number variations upstream of SOX9 associated with hypertrichosis. (A) Pedigree of family in which the father (patient I-1) and proband (patient II-2) exhibited CGHT. (B) Map of human chromosome 17q spanning base pairs 64,220,821–67,740,709 according to build hg18. Copy number variations (CNV) detected in our analyses are represented by dark blue boxes. The telomeric end of the duplication region identified here lies 975 kb upstream of SOX9. Duplications present in the Database of Genomic Variations (DGV) or previously identified by Sun *et al.* [15] are represented by lighter blue boxes. The locations of amplicons used in quantitative PCR analysis are represented by green lines. Scale bar, 0.1 Mb. (C) Bar graph depicting quantitative PCR values revealing significant increases in relative copy number of two amplicons in the proband within the duplication region identified here as compared to an unaffected control individual. Data are represented as mean \pm standard deviation. * = $p < 0.05$; *** = $p < 0.001$.

doi:10.1371/journal.pgen.1003002.g005

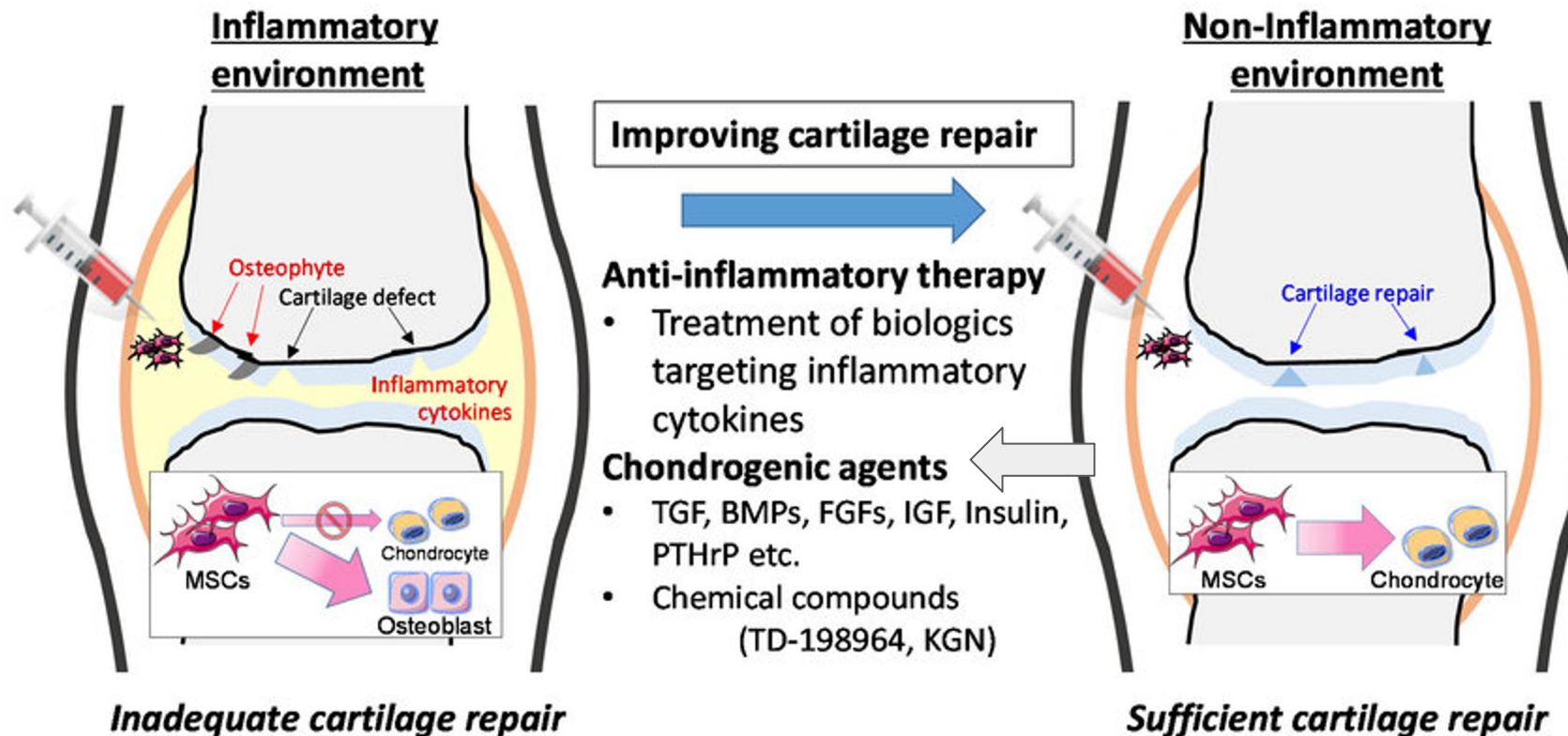
How can this Halloween disease help us understand cancer?

- The proliferation mechanism of SOX9 has been researched as a causative factor in diseases such as **ovarian tumors** and **basal cell carcinoma**
- It's role in **CHONDROGENESIS** = *embryonic differentiation of mesenchyme cells that GROW into cartilage and connective tissue*, can serve as an **important model** in understanding the network of cell invasion and proliferation of cancer cells

ECM = Endothelial Cell Morphogenesis



Pain control and inflammatory cytokines



How does this Hypertrichosis help us understand genetics more fully?

- The mechanism of somatic cell proliferation and chondrogenesis has important implications for **CANCER RESEARCH**
- Study of Hypertrichosis provides better understanding to the importance of genes involved in regulation of HF development (**SOX3 gene**)