

Topologically Associating Domains (TADs) and related syndromes

Gunnar Douzgos Houge MD PhD
Department of Medical Genetics
Haukeland University Hospital
Bergen, Norway

1

Introduction to genome structure

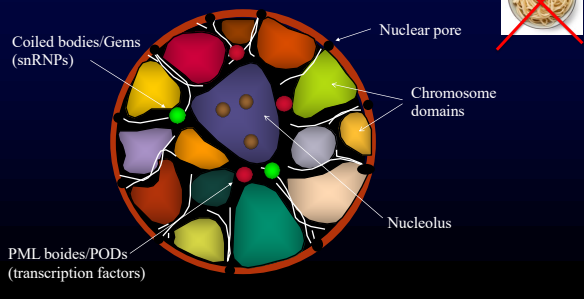


27 000 genes...

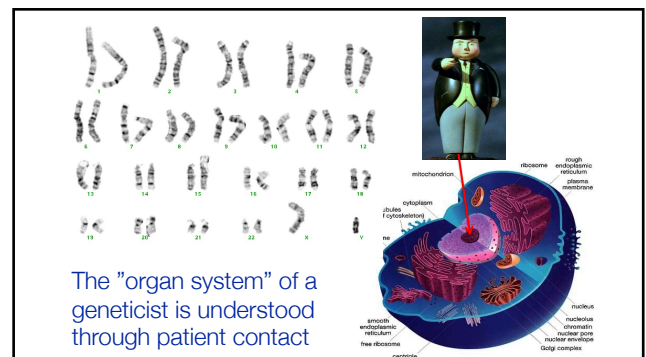
- A 2 m long thread of DNA
- 1,5% («3 cm») is protein-coding genes; $n \approx 20\,000$
- The rest of the genome is for regulation and structure
- For genome structure long-read sequencing (PacBio/ONT) or conformation capture techniques (ChIA-PET, 4C, HiC) are needed
- We are all full of variation:
~1 SNP (single nucleotide polymorphisms) per kb
~20 000 SVs (structural variants) affecting ~11 Mb of the genome

2

The nucleus is an organised structure



3



4

The 3 causes of genetic disease

1) Genomic imbalance

copy number aberrations
disruptive gene variants (LoFs)

1 – 2 – 3

2) Changed gene function

activating mutations (GoFs)
dominant-negative mutations

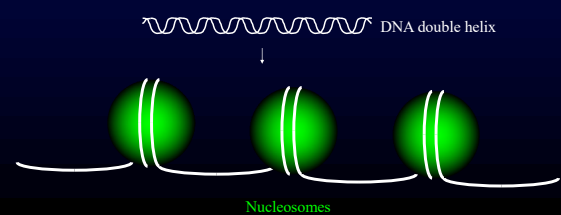


3) Gene regulation disturbances

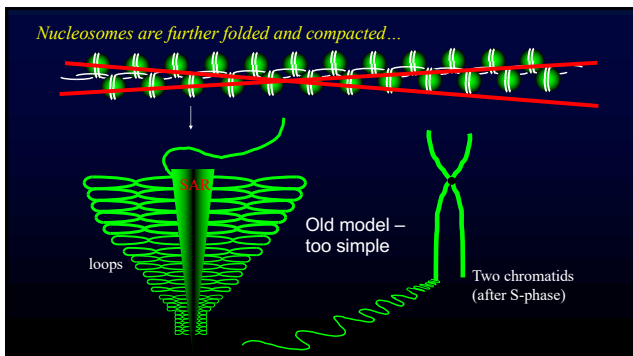
epigenetics and structural errors

5

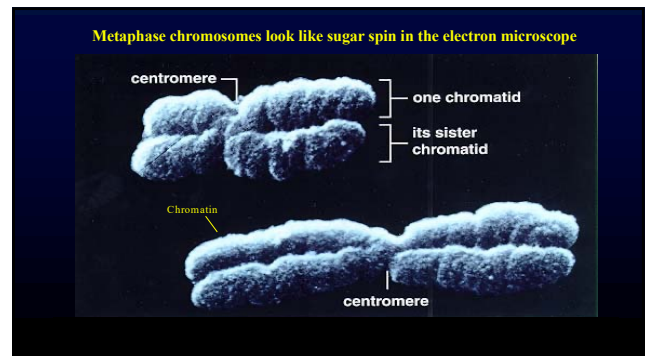
Classical model: Chromosomes are condensed DNA wrapped around nucleosomes



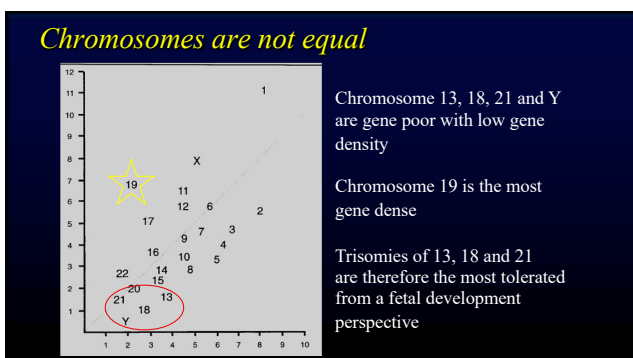
6



7



8



9

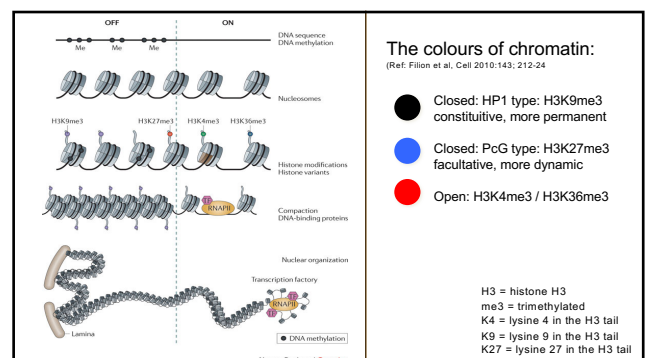
Genetics	Genomics
~ 20 000 protein-coding genes - Types of pathogenic variants: - nonsense - missense - frameshift - indels (insertion/deletions) - repeat expansions - Classical mechanisms: - loss-of-function (LoF) - gain-of-function (GoF) - dominant-negative	- Balanced structural variants - translocations, inversions and insertions - Imbalanced structural variants - deletions (del) - duplications (dup) and triplications (trp) - Gene regulation - promoters - enhancers - chromatin structure (open/closed) > 20 000 RNA genes - Topologically associated domains (TADs)

10

Hetero-chromatin (B compartment, closed)

- Constitutive** – permanent (e.g. centromeric)
- Facultative** – dynamic (e.g. inactive X)
- DNA modification:** C-methylation and hydroxymethylation, especially at CpG positions (and CpG islands in promoters)
- Histone modification:** Most important is histone (H) lysin (K) methylation (me), e.g. H3K9me3 and H3K27me3 on the histone 3 tail

11



12

3D genomics

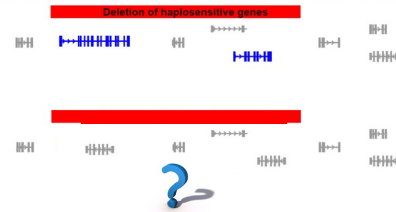


modified and expanded after Malte Spielmann

13

Can structural variation cause disease if the region contain no dosage-sensitive genes?

Only some (15-20%?) of genes are dosage sensitive



14

Long Range Control of Gene Expression

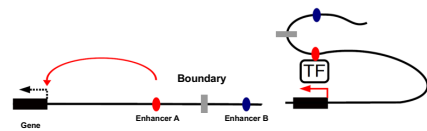


Spielmann & Kitzmann 2013 Current Opinion in Genetics & Development

15

Tissue specific gene expression

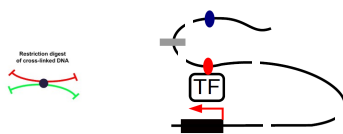
Many enhancer-promoter loops are preformed – also in cells not normally expressing the actual gene. The primed complex waits for "dormant" RNApol-II to be kicked off.



Spielmann & Kitzmann 2013 Current Opinion in Genetics & Development

16

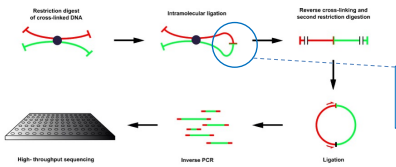
4C: Circular Chromosome Confirmation Capture



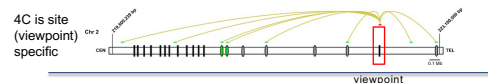
Mild paraformaldehyde crosslinking of intact nuclei

17

Circular Chromosome Confirmation Capture (4C)

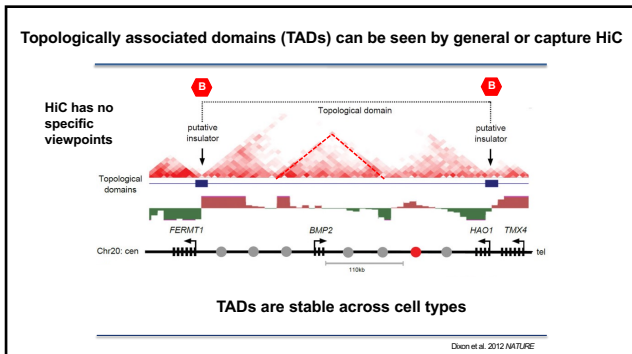


Such hybrid DNA fragments reveal the contact points

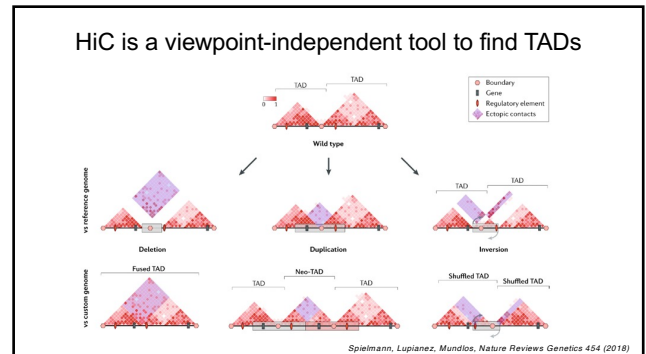


4C is site (viewpoint) specific

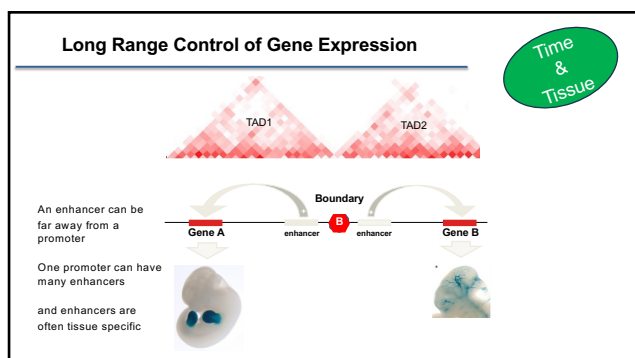
18



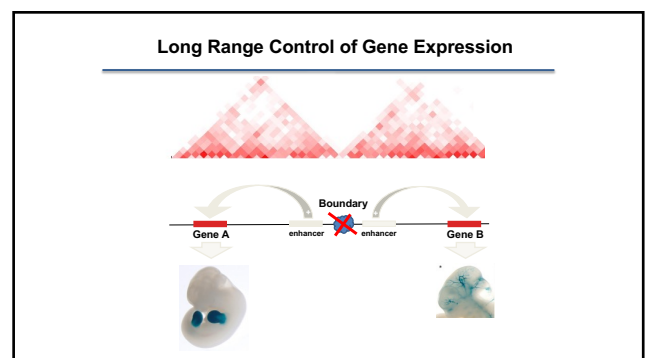
19



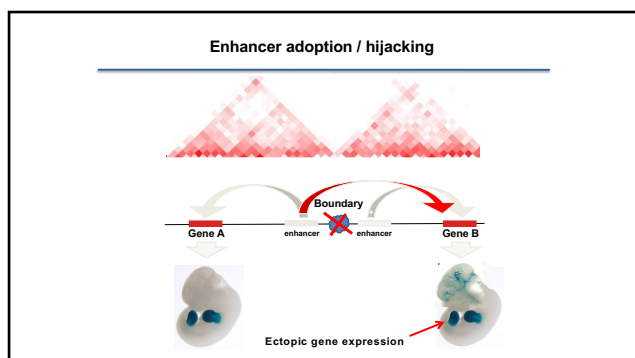
20



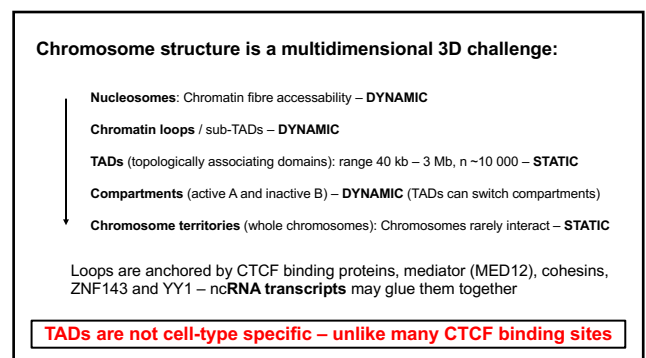
21



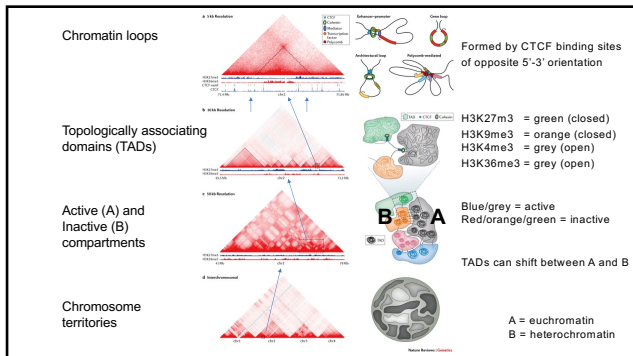
22



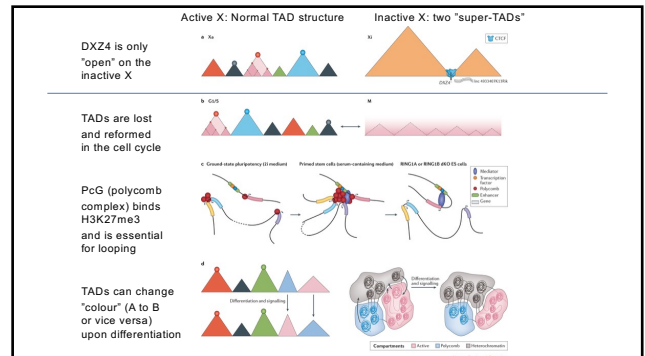
23



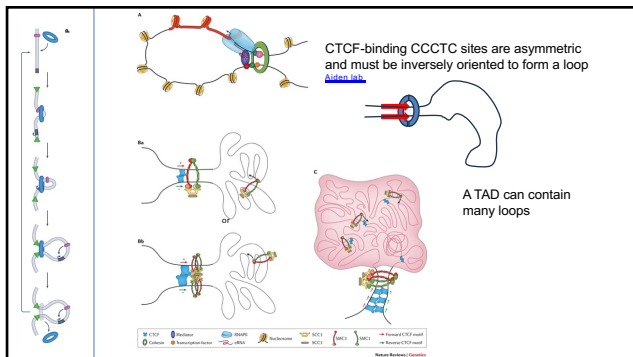
24



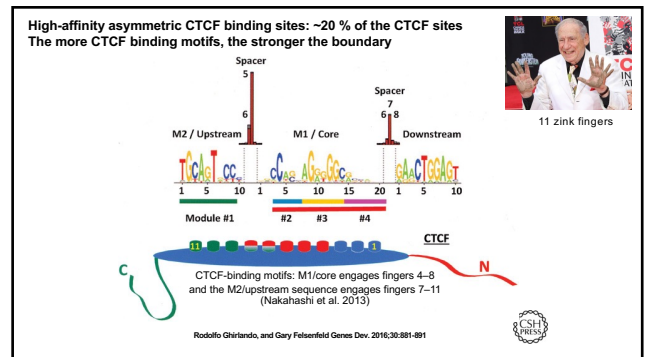
25



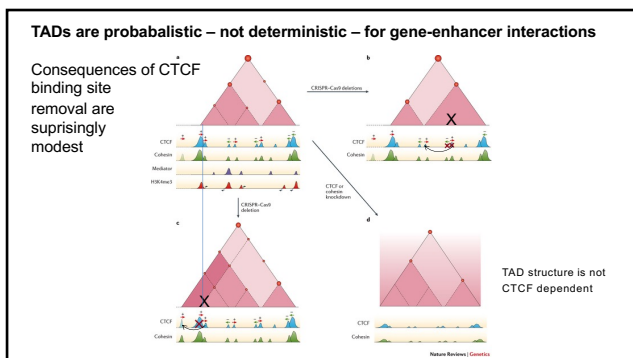
26



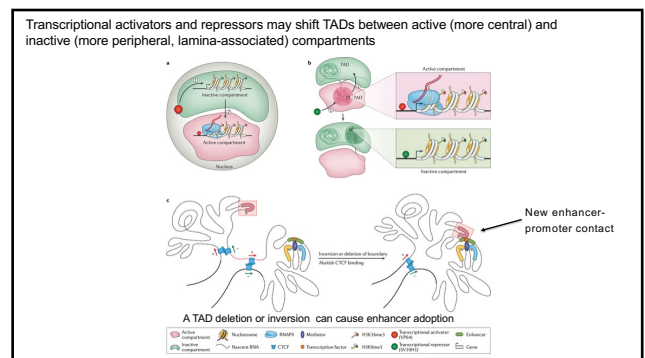
27



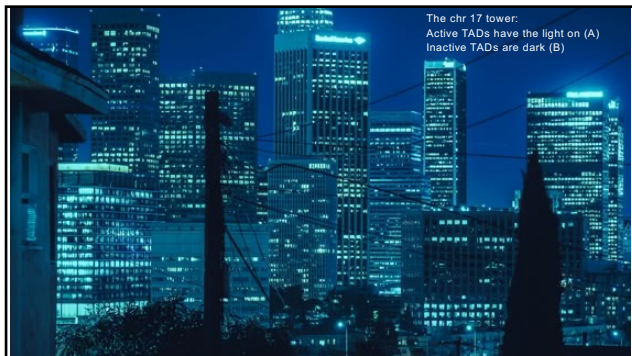
28



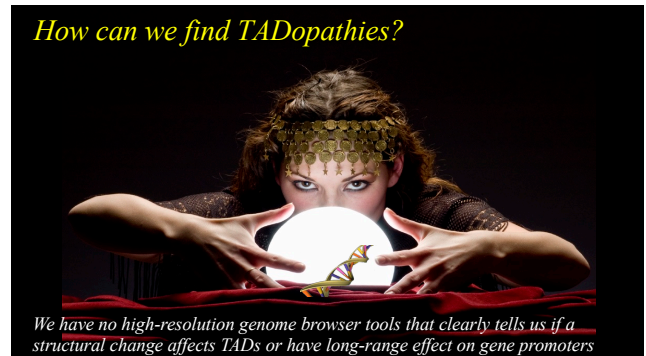
29



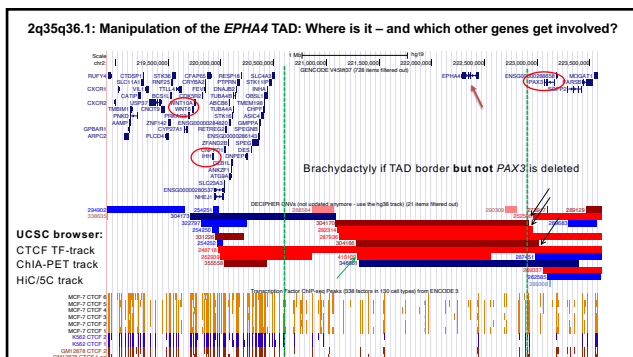
30



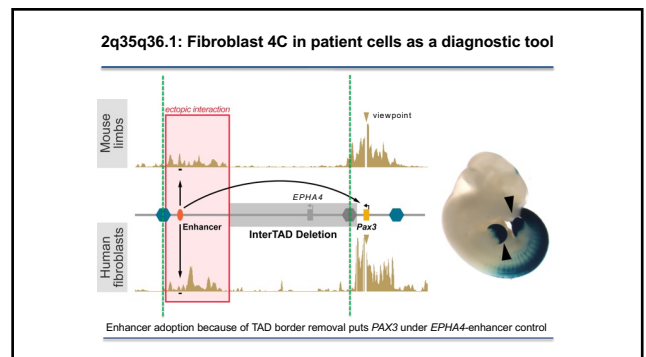
31



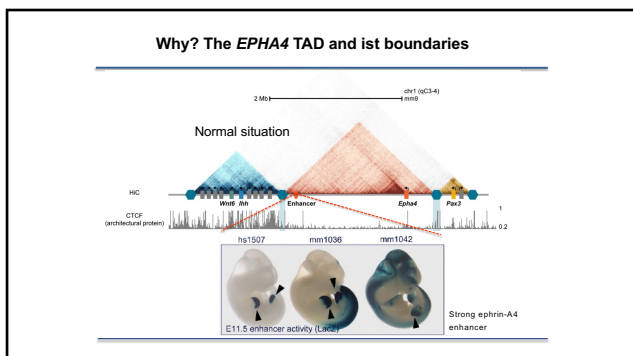
32



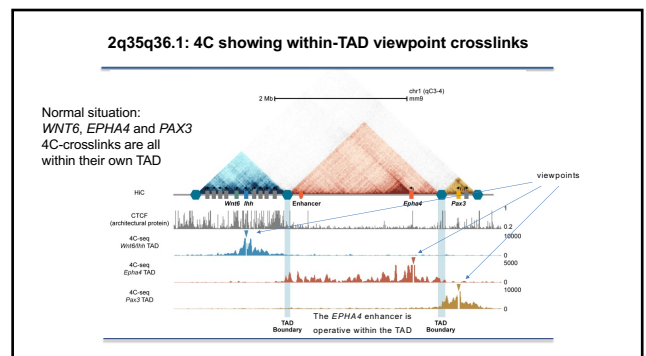
33



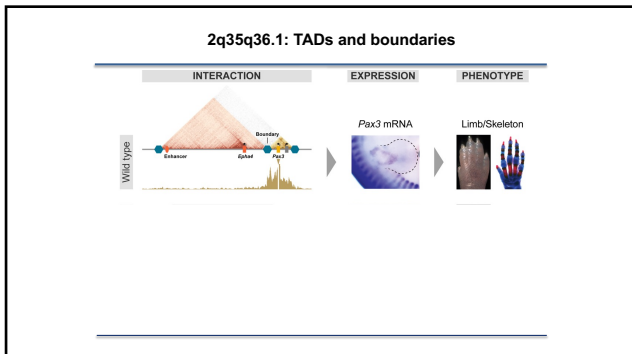
34



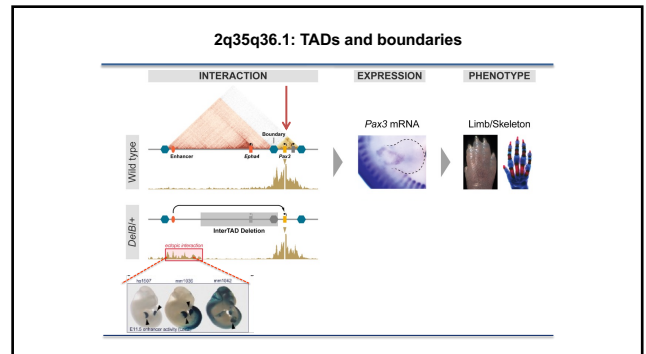
35



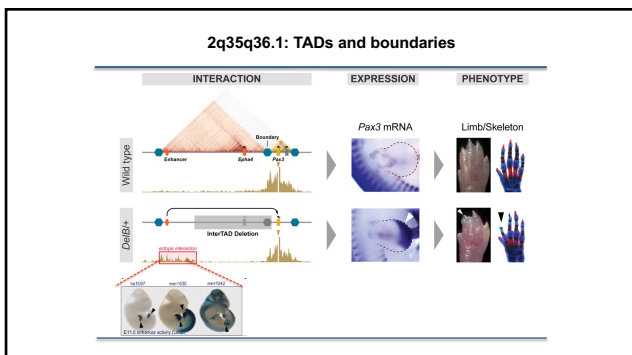
36



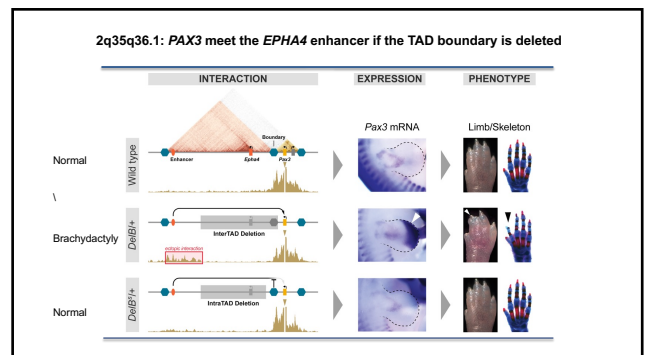
37



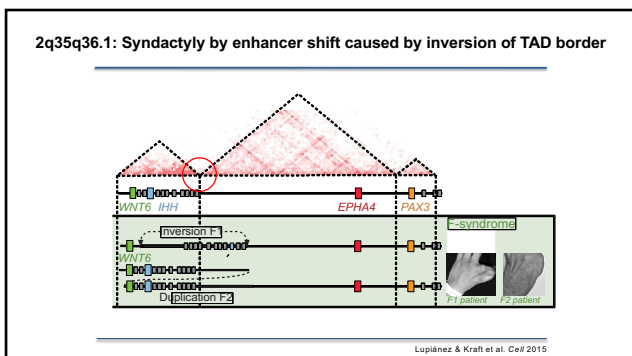
38



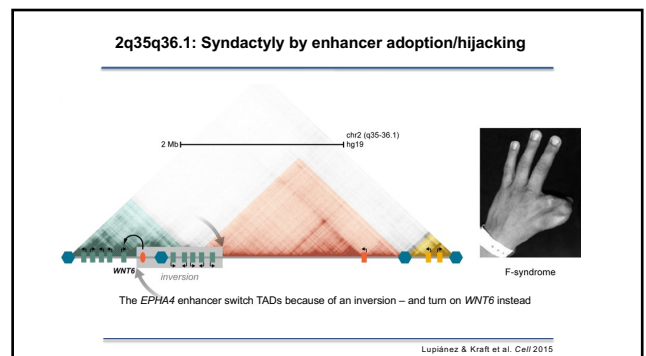
39



40

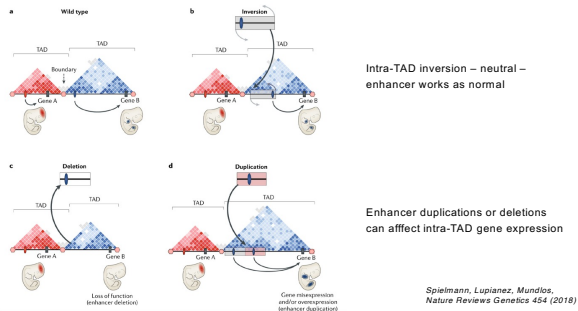


41



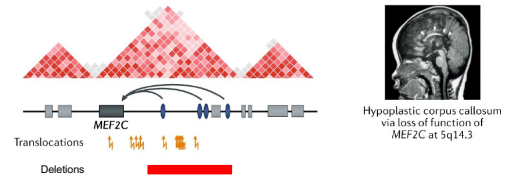
42

Within-TAD structural variation can affect gene expression



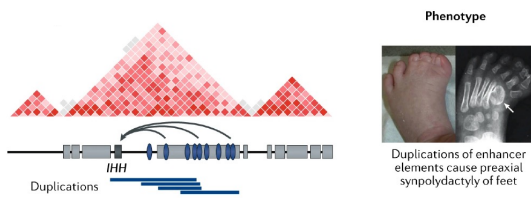
43

LoF by intra-TAD enhancer removal by deletions or translocations



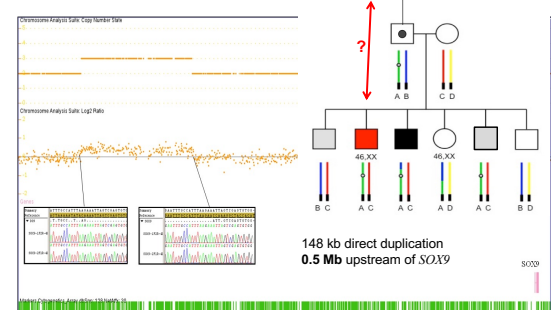
44

GoF by intra-TAD enhancer duplications



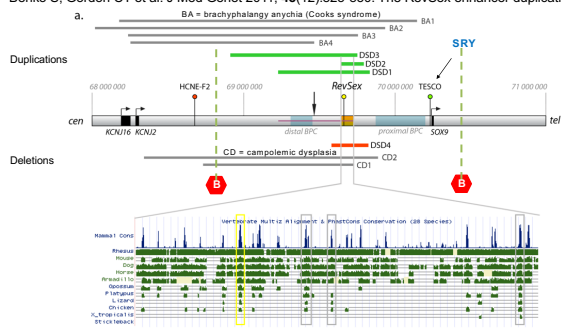
45

A family with a *SOX9* enhancer duplication



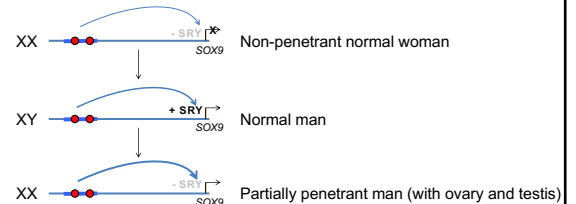
46

Benko S, Gordon CT et al: J Med Genet 2011, 48(12):825-830: The RevSex enhancer duplication

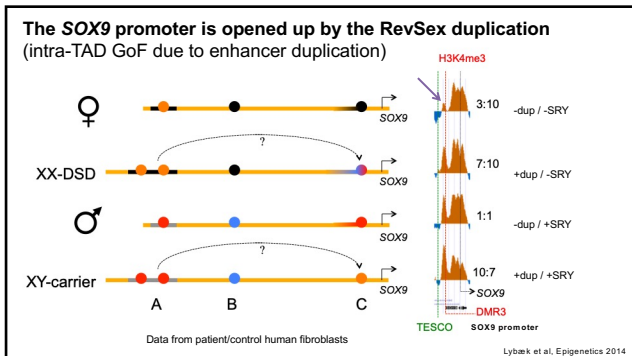


47

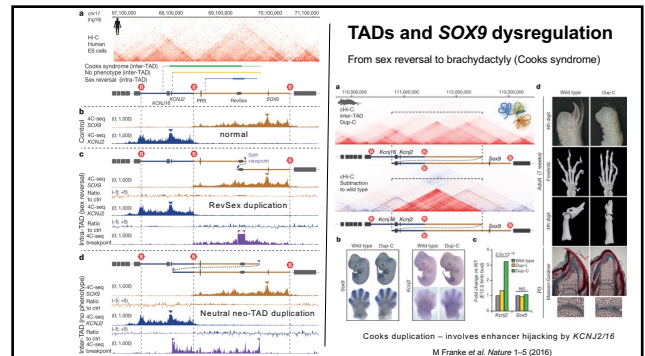
Why was the grandmother normal?



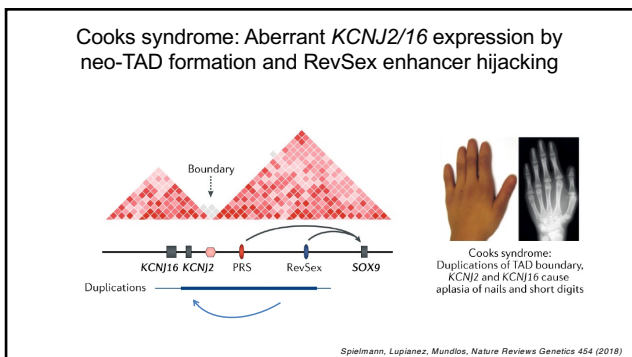
48



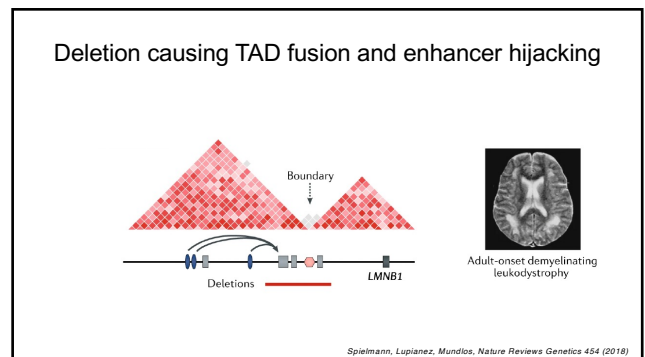
49



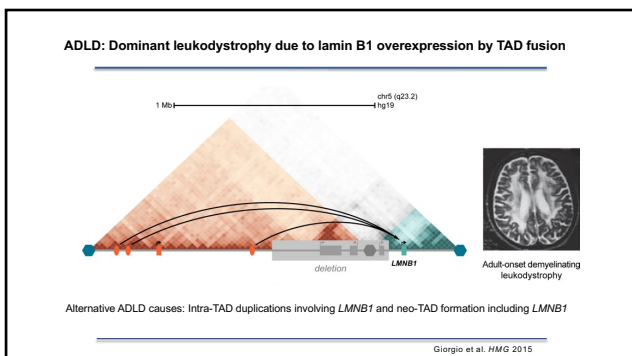
50



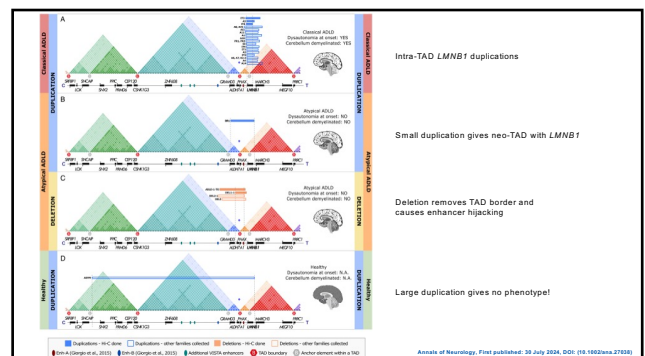
51



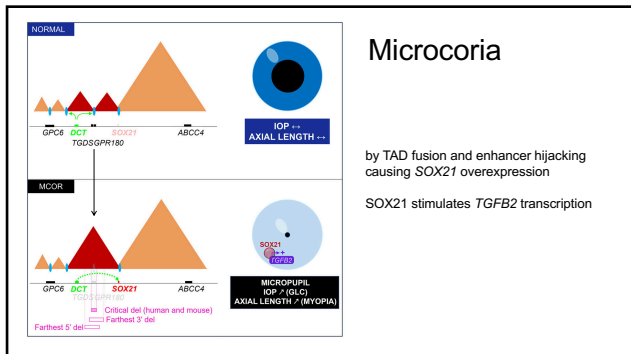
52



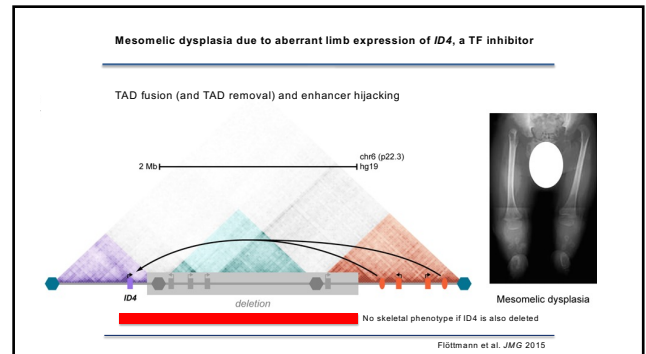
53



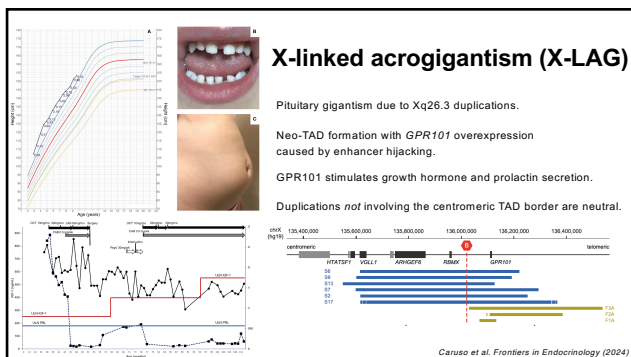
54



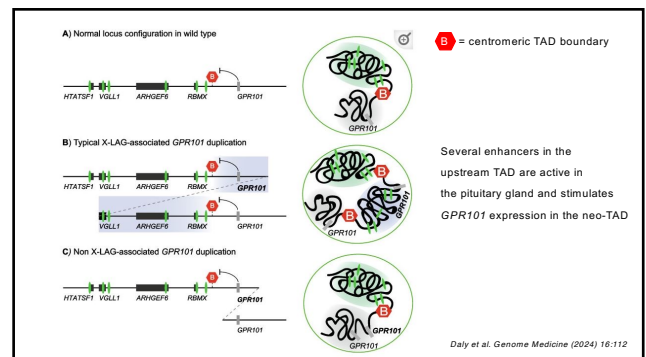
55



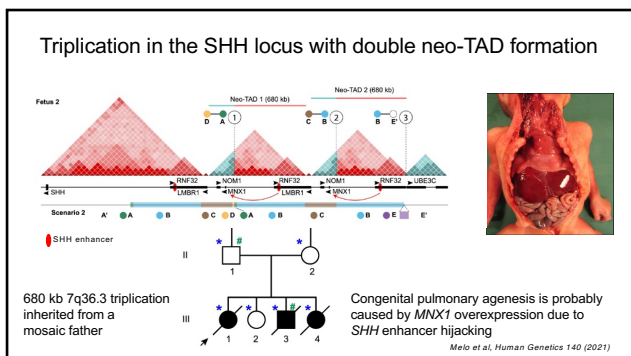
56



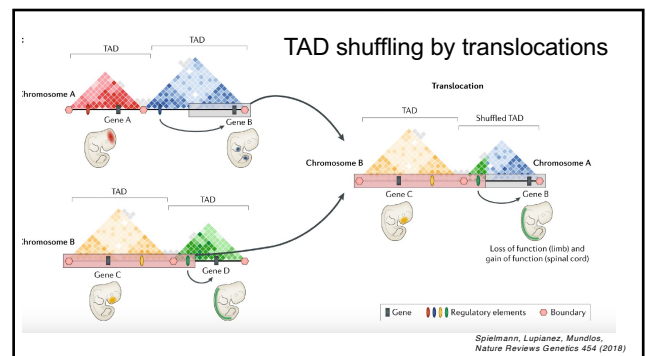
57



58



59



60

