Phenotypic presentation of Mendelian disease across the diagnostic trajectory in electronic health records

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15th September 2023

*Gregor Mendel: "**father** of modern **genetics**"*

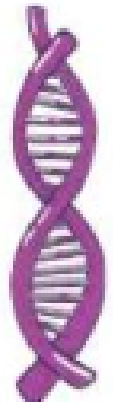
Genotype VS Phonotype

GENOTYPE

GENOTYPE refers to the genetic code of the individual. This is all the information that is found inside the individual's cells.

PHENOTYPE

PHENOTYPE is the expression of the genotype that is visible to other people and can be observed.



Dominant and Recessive (Tall = T, Short = t)

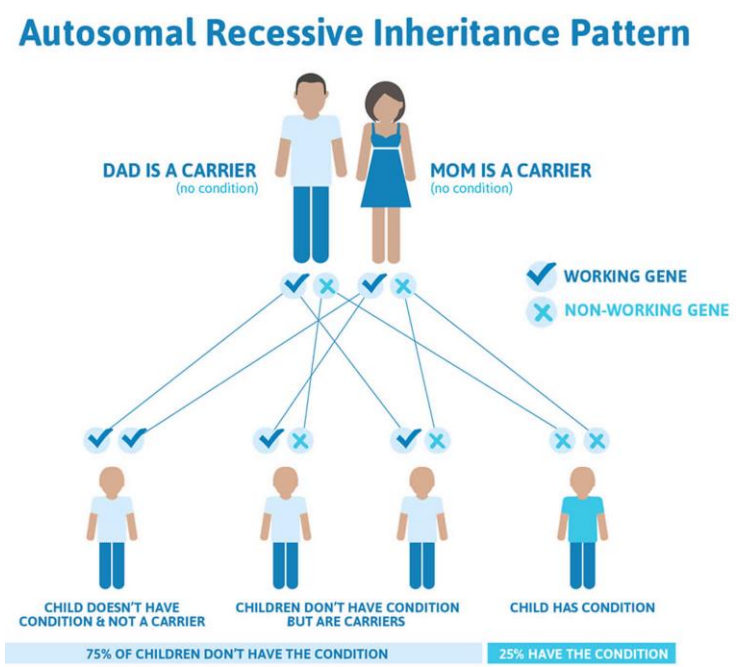
Cross between Tt xTt

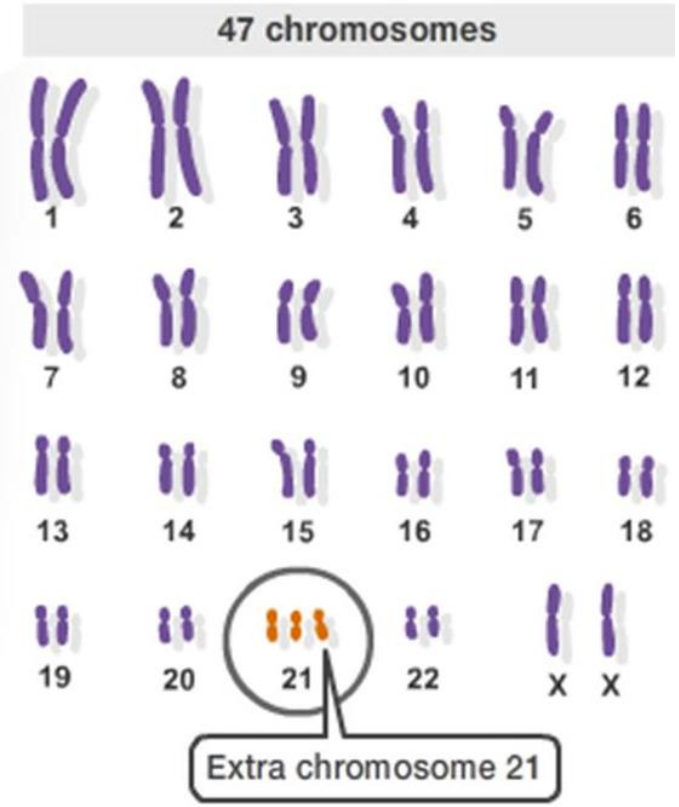
	T	t
T	TT	Tt
t	tT	tt

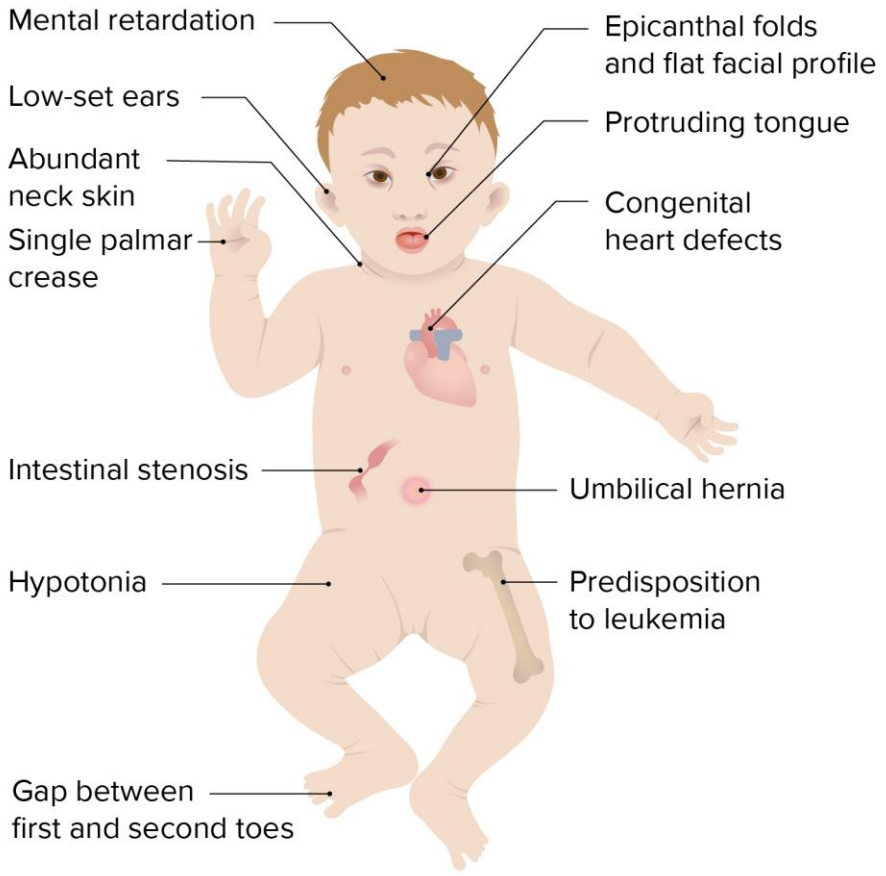
Hair colour

Blood group

Genotype to Phonotype







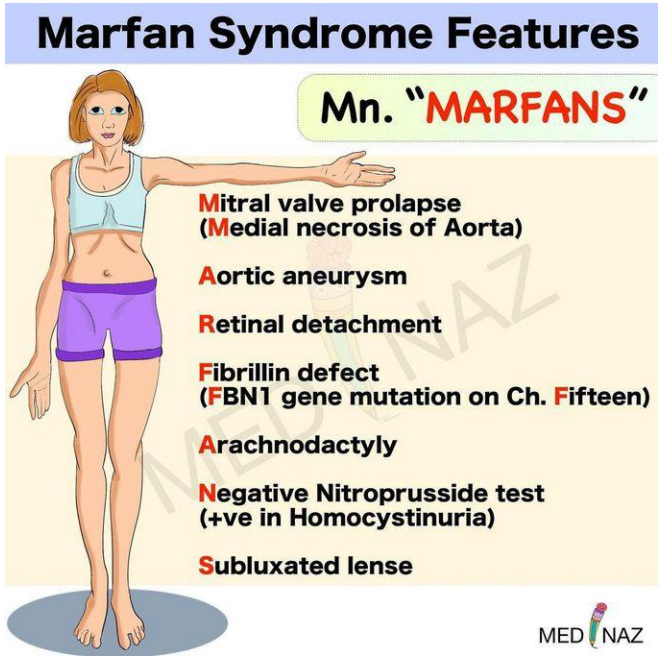
Down syndrome (Trisomy 21)'s Phenotype

https://healthjade.net/thalassemia-intermedia/

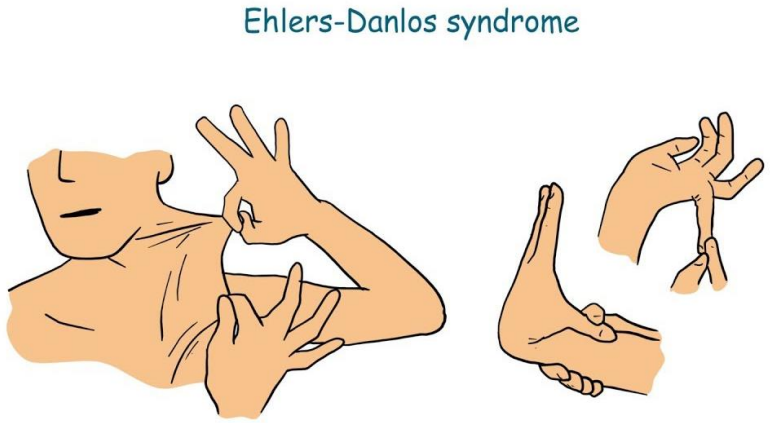
Lists of 9 Genetic Diseases (1)

Choose genetic diseases with (1) prominent multisystem phenotypes
that have reports of (2) diagnostic delay and vary by age of onset.

1. **Marfan syndrome (MFS):** a genetic disorder that causes people to have unusually long arms, legs and fingers.



2. **Ehlers-Danlos syndrome (cEDS):** a group of inherited disorders that affect connective tissues — skin, joints and blood vessel walls

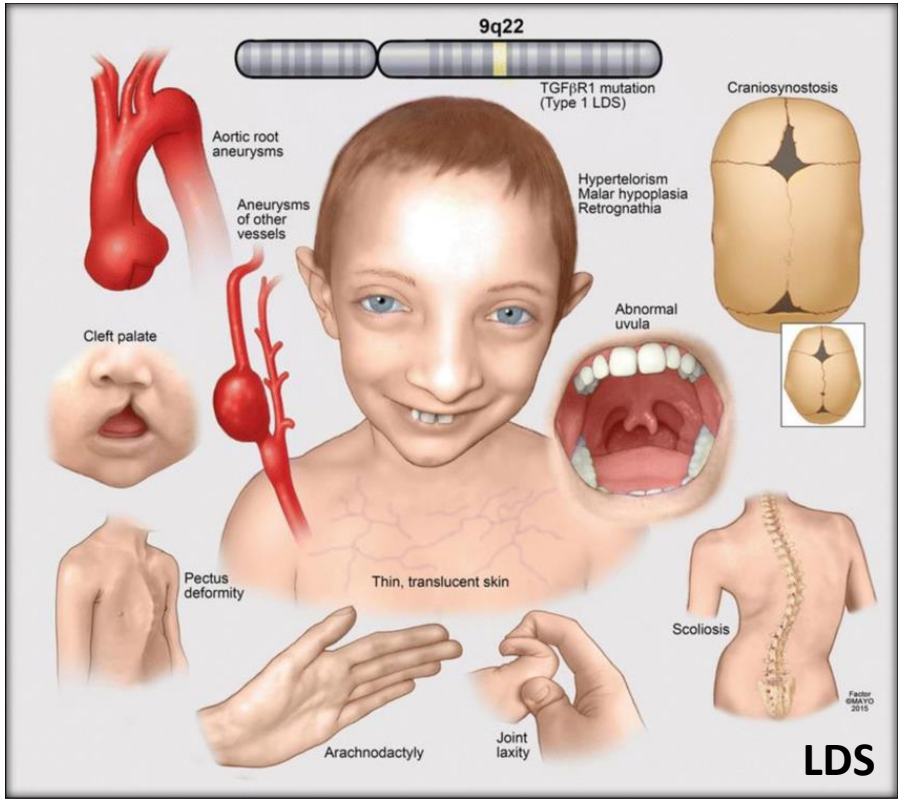


Lists of 9 Genetic Diseases (2)

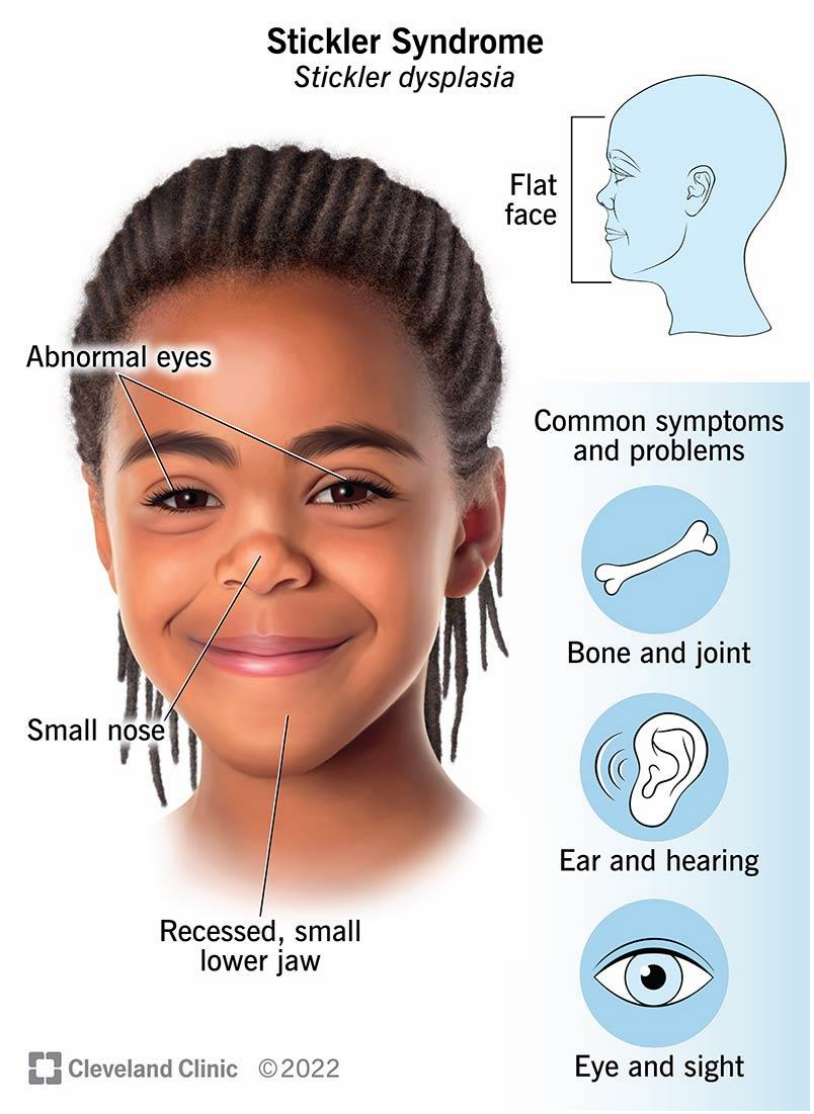
3. **Vascular Ehlers-Danlos syndrome (vEDS):** characterized by arterial, intestinal, and/or uterine fragility; thin, translucent skin; easy bruising; characteristic facial appearance (


vEDS

4. **Loeys-Dietz syndrome (LDS):** a disorder that affects the connective tissue in many parts of the body.



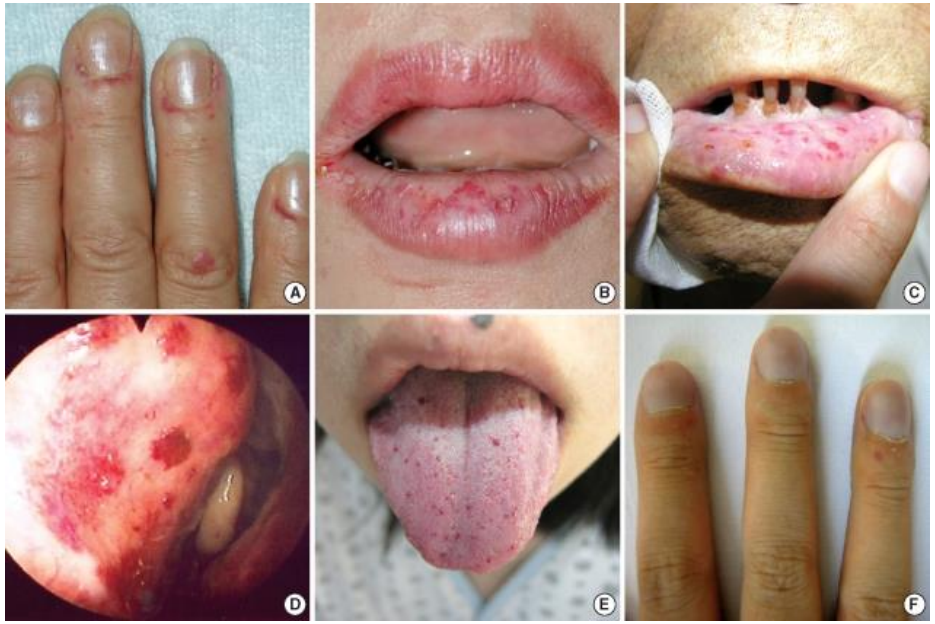
Lists of 9 Genetic Diseases (3)



5. **Stickler syndrome (STL):** a connective tissue disorder that can include ocular findings of myopia, cataract, and retinal detachment

6. **Hereditary Hemorrhagic Telangiectasia (HHT):**

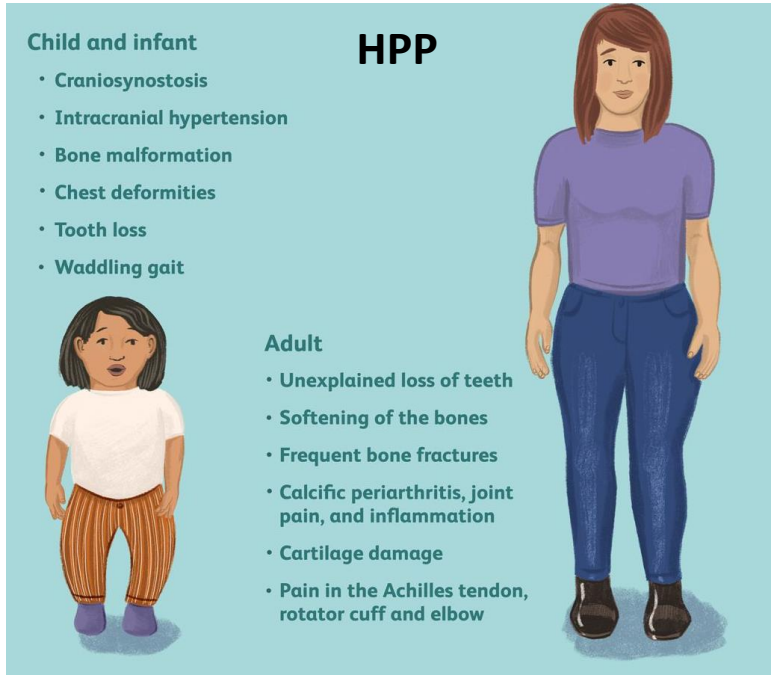
Lacy red vessels or tiny red spots, particularly on the lips, face, fingertips, tongue and inside surfaces of the mouth



Lists of 9 Genetic Diseases (4)

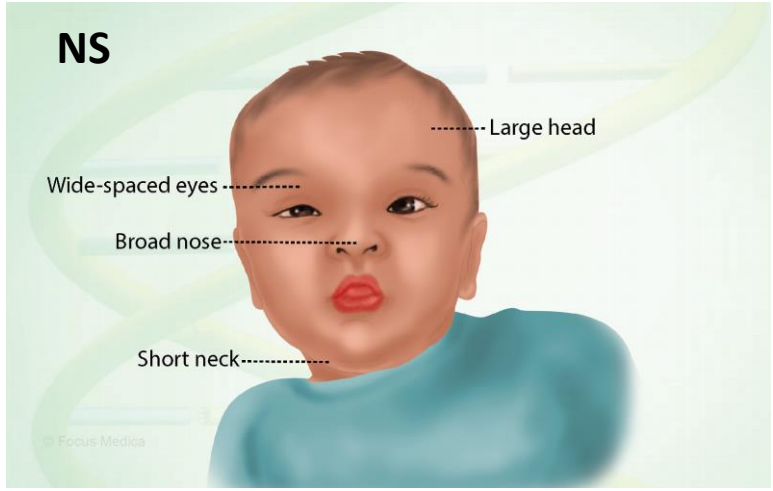
7. **Hypophosphatasia (HPP):**

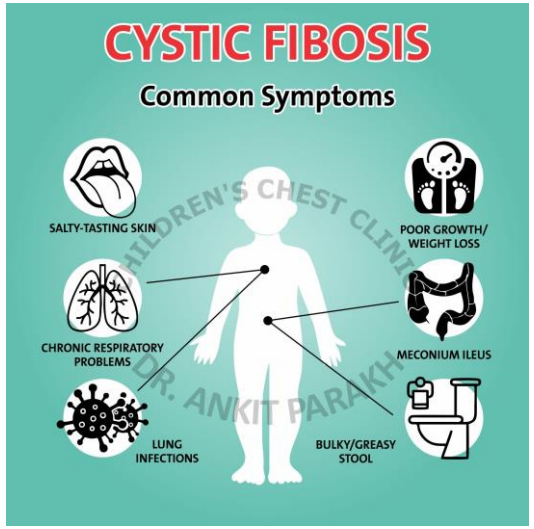
a rare genetic disorder characterized by impaired mineralization (“calcification”) of bones and teeth.



8. **Noonan syndrome (NS):**

a genetic condition that stops typical development in various parts of the body





9. **Cystic Fibrosis (CF):**

a disorder that damages your lungs, digestive tract and other organs.

Back to the Presenter

Dr. Cholatid!!

Limitation in this research (1):

1. Decision to only include individuals with a genetic and clinical confirmation of genetic disease means the cohort is rigorous and of high quality despite its size.

   However, some individuals in control population would have reached a clinical diagnosis without a positive genetic test.

   Given the size of our control cohort (1.8 million individuals used in our regression model), this likely would have had *minimal impact on our results*

2. The cohort of genetic diseases is small and based on a single tertiary medical center, which is based in a major metropolitan area with primary and secondary care inpatient and outpatient facilities.

   This prevents us being able to conclude if **diagnostic convergence** is a global phenomenon or one restricted to a particular medical context

   → key features of a Mendelian disease are ascertained in the EHR **only after** the disease is suspected.

Limitation in this research (2):

3. This analysis is on a subset of genetic diseases. Therefore, future work is needed to establish whether **diagnostic convergence** is a phenomenon seen in other genetic or nongenetic disease

4. This analysis was limited to only what was recorded in the EHR.

   As a result, it cannot be certain of the exact time a clinician became suspicious for a genetic disease or when a phenotype was noticed.

   This situation might happen because clinicians may not document all of their clinical assessments in the HER for various practical reasons

   - not wanting to stigmatize patients or affect their future insurability
   - a particular finding does not seem medically relevant

Applications that use AI to predict disease based on patient phenotype data

- Phenotypic Disease Prediction Platforms:

  Some companies and research institutions have developed AI-based platforms specifically designed to predict disease based on patient phenotype data. These platforms often incorporate machine learning algorithms that analyze a wide range of clinical and genetic information to make predictions.

  Examples include **FDNA's "Face2Gene"** and **GeneDx's "PhenomeCentral"**