

GENETIC DISORDER, HPO, OMIM and ClinVar

Nov 30 2024

Giảng viên: TS. Lưu Phúc Lợi

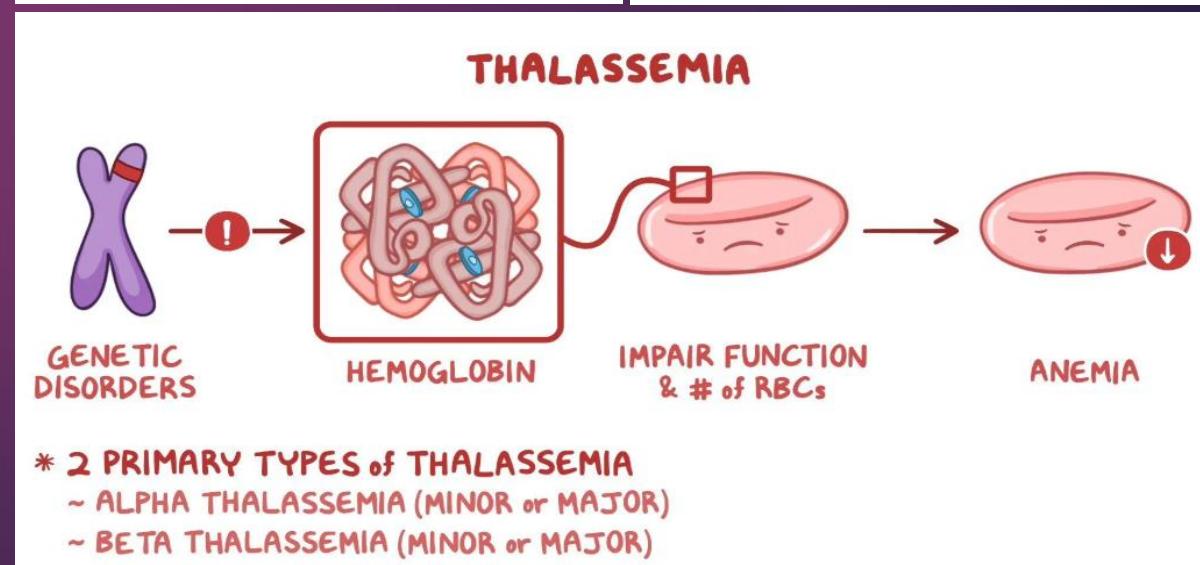
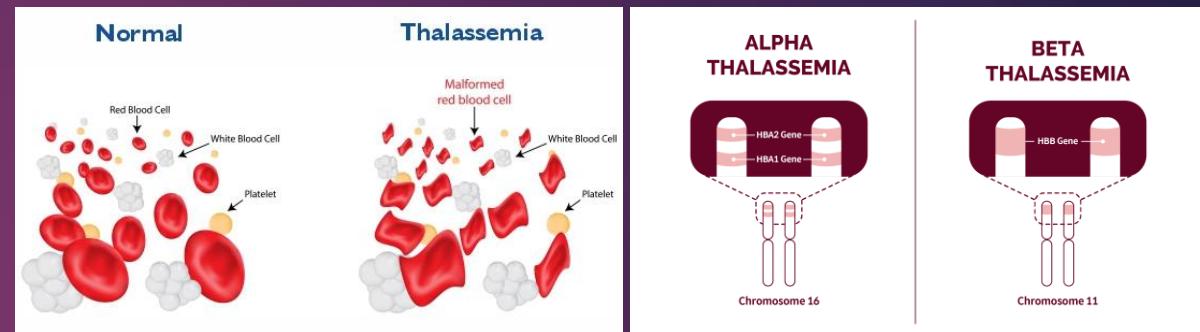
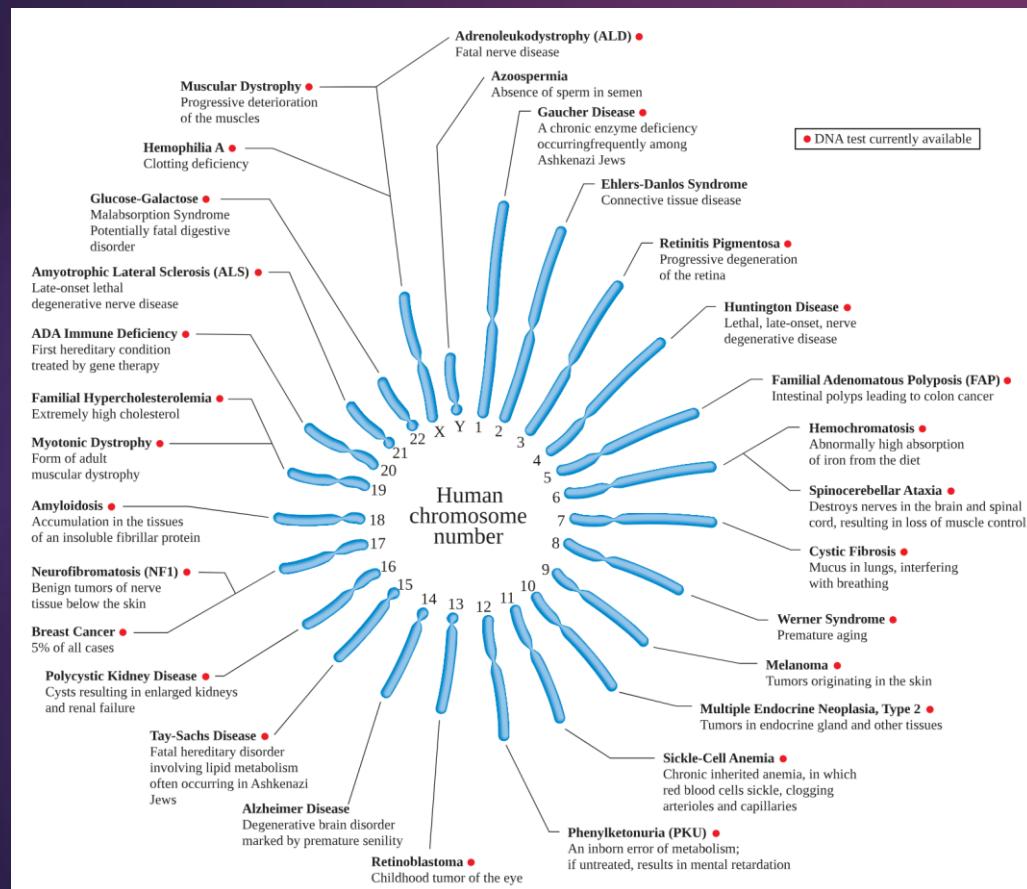
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Content of Lecture 3

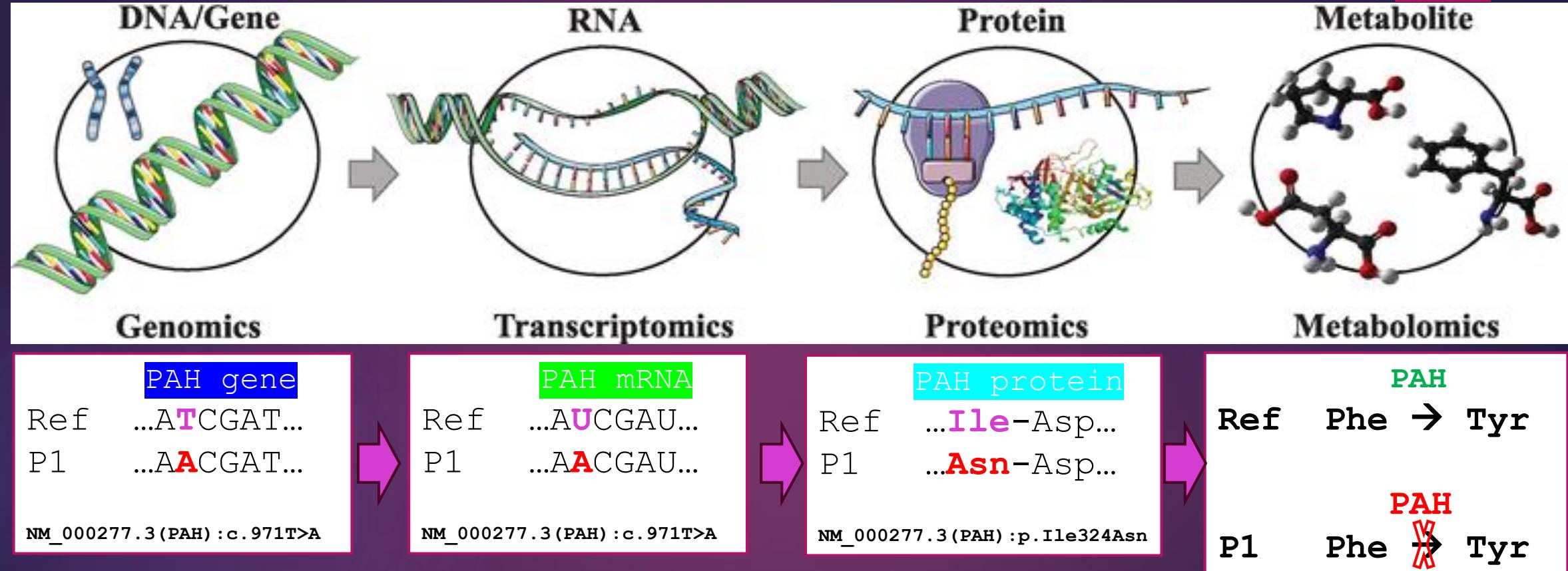
1. Genetic disorder
2. Introduction to HPO (The Human Phenotype Ontology)
3. Introduction to OMIM
4. Introduction to ClinVar

Genetic disorder

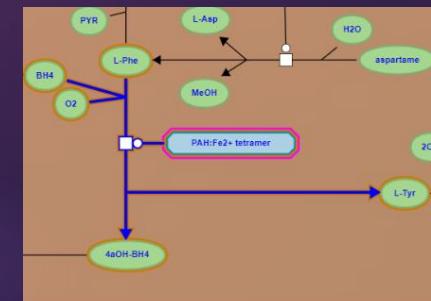
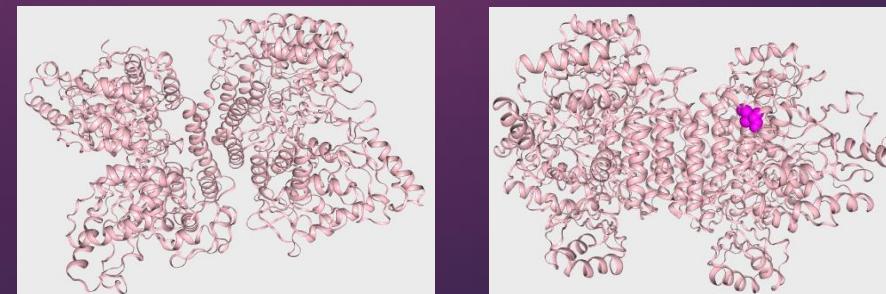
- A genetic disorder is a health problem caused by one or more abnormalities in the genome. It can be caused by a mutation in a single gene or multiple genes or by a chromosome abnormality.



Quan hệ nhân quả: Biến thể gen và bệnh di truyền



10.5772/intechopen.71769



Genetic classification of hereditary diseases

According to the type of mutation and character of gene – environment interaction genetic disorders can be classified into six categories

- 1) **Single gene inheritance, or gene disorders** (also called Mendelian or monogenic inheritance): autosomal dominant, autosomal recessive, and X-linked.
- 2) **Chromosome diseases** caused by chromosomal and genomic mutations, i.e., structural and numerical abnormalities of chromosomes, respectively.
- 3) **Multifactorial diseases** (also called complex or polygenic diseases) caused by a combination of environmental factors and mutations in multiple genes (i.e., both genetic and non-genetic or environmental factors are involved in determining the trait).
- 4) **Genetic diseases of somatic cells.** Examples are cancer, autoimmune diseases.
- 5) **Diseases due to incompatibility of genes.** Example is haemolytic disease of newborns, in which fetal red blood cells die earlier due to the action of antibodies formed by the mother against fetal Rh-antigen.
- 6) **Mitochondrial inheritance:** This type of genetic disorder is caused by mutations in the nonchromosomal DNA of mitochondria. Each mitochondrion may contain 5 to 10 circular pieces of DNA.

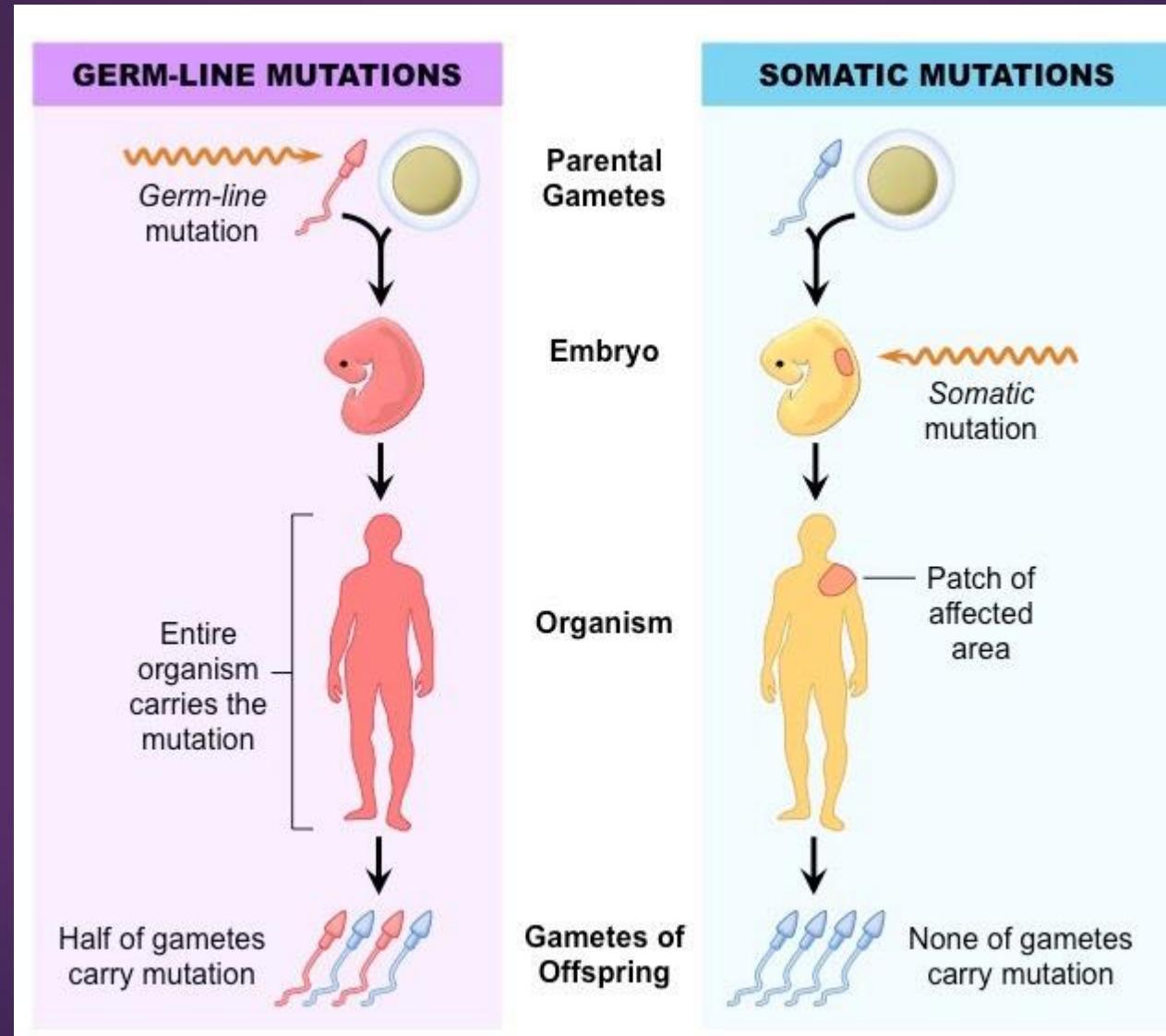
Single gene inheritance, examples

- ▶ Huntington's disease is a progressive neurodegenerative disorder that exhibits autosomal dominant inheritance. Other examples of autosomal dominant diseases include Marfan syndrome, neurofibromatosis, retinoblastoma and polydactyly.
- ▶ Phenylketonuria represents a prominent example of a single gene genetic disorder with an autosomal recessive inheritance pattern. Other examples of autosomal recessive diseases include cystic fibrosis, sickle cell anemia and Tay-Sachs disease.
- ▶ Hemophilia A is a disorder where the blood cannot clot properly due to a deficiency of a clotting factor called Factor VIII. It exhibits an X chromosome-linked recessive pattern of inheritance, so men with a mutant copy of the gene will always have the disease, whereas women are rarely affected by it. Other examples are Duchenne muscular dystrophy and glucose-6-phosphate dehydrogenase deficiency.
- ▶ X-linked dominant conditions are rare but do exist. Heterozygous mutations in the X-linked MECP2 gene result in Rett syndrome – a severe neurodevelopmental disorder of young females. A nonobstructive spermatogenic failure that leads to infertility problems in males is an example of a Y-linked disorder.

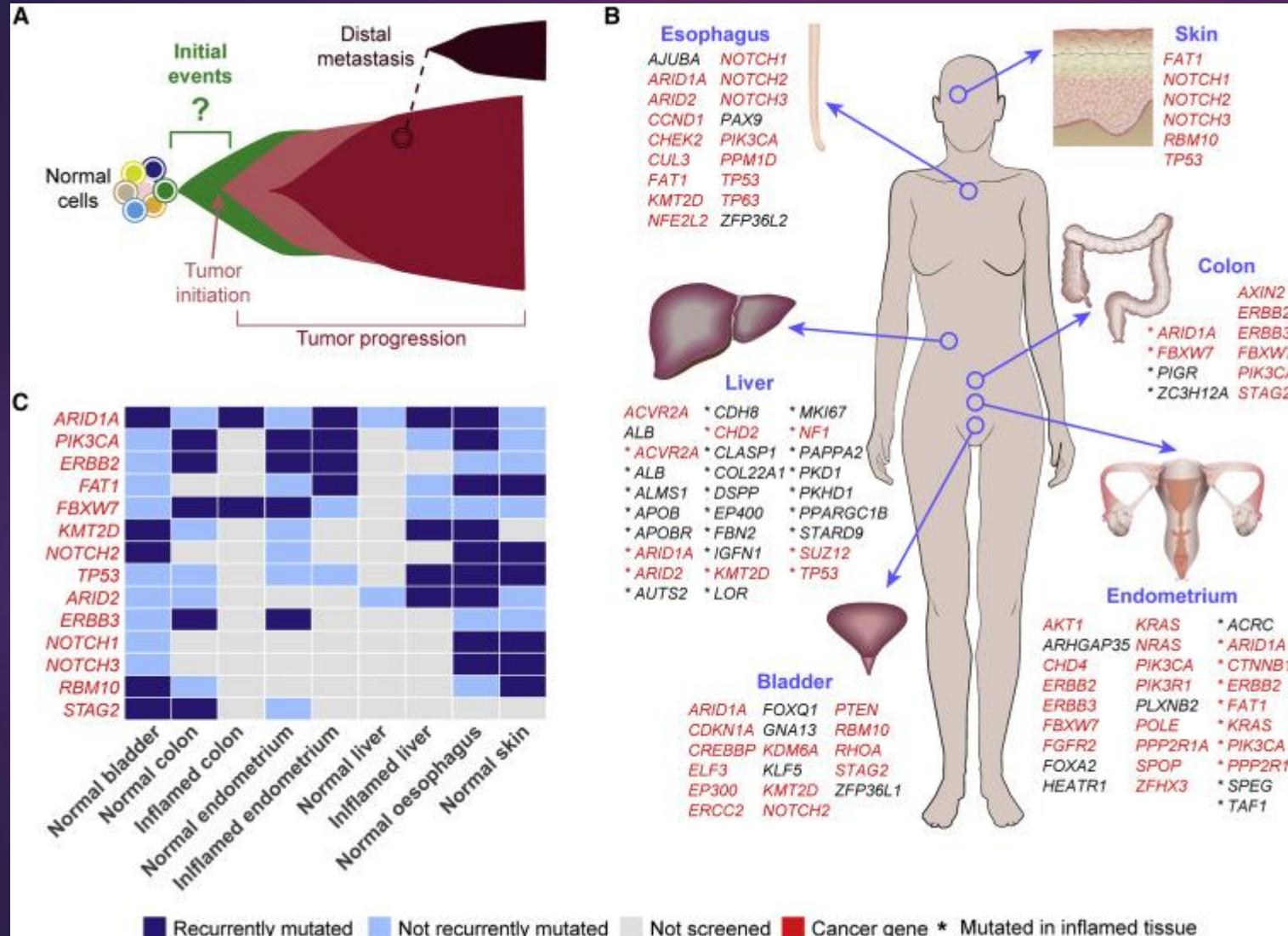
Chromosome diseases, examples

- ▶ Down syndrome: Also known as trisomy 21, this is the most common chromosomal disorder and occurs when a person has three copies of chromosome 21 instead of two
- ▶ Turner syndrome: A monosomy, or the absence of a chromosome, that occurs when a female is born with only one X chromosome
- ▶ Prader-Willi syndrome: A disease caused by uniparental disomy, which is when a person inherits two pairs of a homologous chromosome from one parent and no copy from the other
- ▶ Edward's syndrome: Also known as trisomy 18, this is the second most common trisomy after Down syndrome
- ▶ Patau Syndrome: Also known as trisomy 13, this is the third most common trisomy after Down syndrome and Edward's syndrome
- ▶ 13q deletion syndrome: A rare chromosomal disorder
- ▶ 18q deletion syndrome: A common syndrome that occurs in about 1 in 10,000 live births

Genetic diseases of somatic cells



Genetic diseases of somatic cells, examples



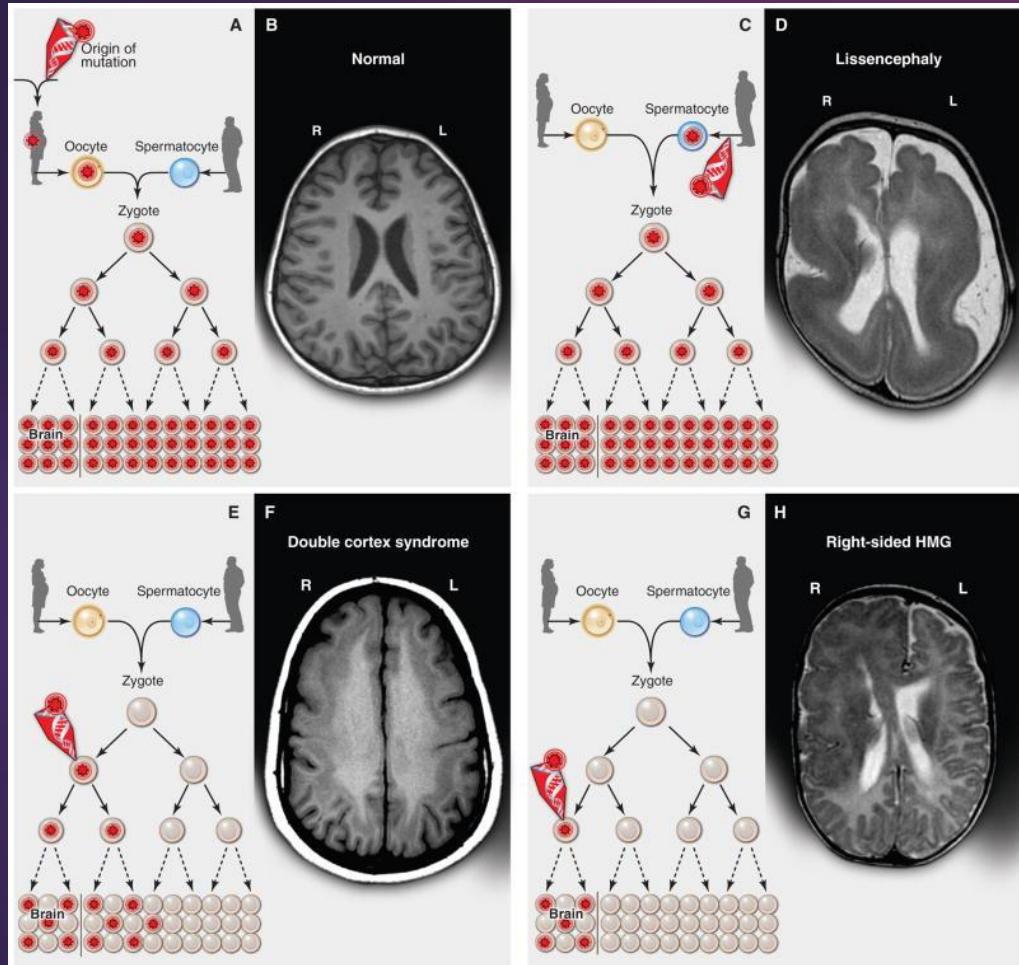
Landscape of Somatic Mutations in Human Adult Tissues

(A) Schematics of cancer initiation and progression. The initial driver events that lead to tumor formation starting from normal cells are currently mostly unknown.

(B) Mutated genes under positive selection (Brunner et al., 2019; Lawson et al., 2020; Lee-Six et al., 2019; Martincorena et al., 2015, 2018; Moore et al., 2020; Olafsson et al., 2020; Yokoyama et al., 2019) or frequently mutated (Anglesio et al., 2017; Lac et al., 2019a, 2019b; Lee-Six et al., 2019; Suda et al., 2018; Yokoyama et al., 2019; Zhu et al., 2019) in the human adult tissues that have been screened so far.

(C) List of genes under positive selection or frequently mutated in at least two tissues. Cancer genes were derived from the Network of Cancer Genes (<http://ncg.kcl.ac.uk/>) (Repana et al., 2019).

Genetic diseases of somatic cells, examples



(A) A heterozygous mutation is inherited from one parent. This mechanism is typical of autosomal dominant epilepsy. In this example, the mutation originally presented in the mother, whose oocytes in turn carry the mutation. (The mutation arose during gametogenesis in one of the parents of the mother, top left.) It is present in the zygote and thus all cells of the affected child. (B) This axial T1-weighted image from a MRI study of a patient with inherited epilepsy appears normal. Individuals with dominantly inherited epilepsies caused by mutations in genes encoding ion channels, for example, have normal neuroimaging studies despite every cell carrying a mutation. (C) A de novo mutation may arise sporadically during gametogenesis, in this case spermatogenesis. This mechanism of mutation would be typical of a de novo mutation in the gene SCN1A associated with severe myoclonic epilepsy of infancy or LIS1 associated with lissencephaly. Even though every cell in the individual carries the mutation, the predominant effects of the mutation depend on the distribution of gene expression; in these examples, the brain is primarily affected. (D) An axial T2-weighted MRI image shows the severe gyral simplification—more pronounced posteriorly (the bottom of the figure)—that is associated with mutations in the gene LIS1. (E) An early post-zygotic mutation results in a mutation present in most or all tissues of the organism (including the leukocytes, which are generally assayed for clinical genetic testing) but in a mosaic fashion, with only a portion of all cells in each tissue harboring the mutation. This pattern, illustrated by the axial T1-weighted image in (F), has been observed in mosaic cases of double cortex syndrome involving the gene DCX. Visible is the extra band of gray matter underlying the normal-appearing outer aspect of the cerebral cortex. Because DCX is required for normal migration of neurons from the ventricular region deep in the brain to the superficial cortex, the cells carrying the DCX mutation only migrate about halfway to the cortex and then arrest their migration. (G) A late post-zygotic mutation will be present in only certain tissues in a mosaic fashion, in this case apparently in half of the brain. This is the pattern observed in some cases of HMG with somatic mosaic point mutations in AKT3 and other related genes and somatic mosaic increase of copy number of chromosome 1q. (H) This axial T2-weighted MRI image shows right-sided HMG, characterized here by enlargement of the right hemisphere, abnormally thick and dark-appearing gray matter anteriorly, heterotopic periventricular gray matter, and abnormal white matter signal in the right hemisphere. (R, right; L, left).

Monogenic and polygenic concepts in Chronic Kidney Disease (CKD)

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Monogenic kidney disease

- Accounts for up to 50% of paediatric and 10% of adult kidney disease



- Factors which increase likelihood of genetic diagnosis



Family history

Young onset

Extra-renal features

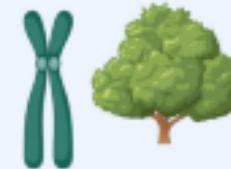
- Yields of genetic testing for diagnosis are between 50-66% in early onset kidney disease



- Common genes identified include *COL4A3-5*, *HNF1B*, *PKD1-2* and *PKHD1*

Polygenic factors in CKD

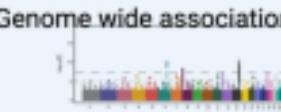
- Kidney function clusters within families which represents complex environmental and polygenic factors



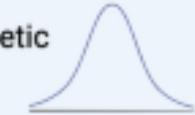
- Kidney function is a heritable trait

Family studies: 35-69%

Genome wide association: 7.1-20.3%



- Polygenic risk scores aggregate relevant genetic loci into a risk score for disease



- Hypertension, IgA nephropathy and membranous nephropathy have unique genetic associations

- Further research in polygenic factors in kidney disease will inform personalised medicine, pharmacogenomics and future research targets



Journal of Nephrology

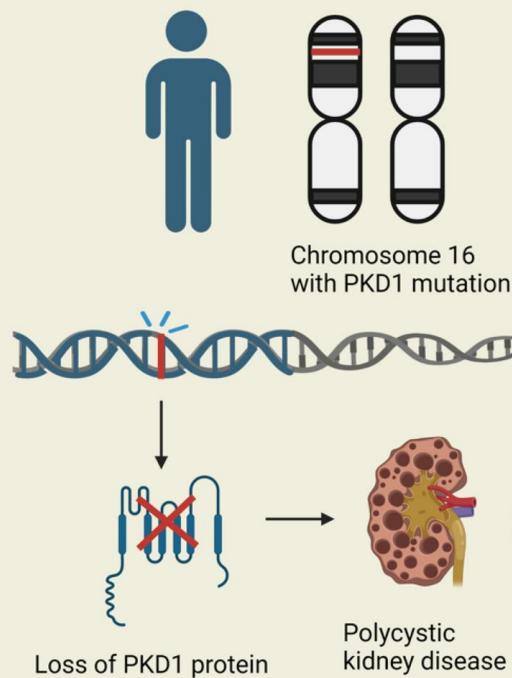


Clinical genomics is well established for monogenic kidney disease, with a developing understanding of polygenic factors in kidney disease. Research is underway to further understand polygenic factors in CKD through development of polygenic risk scores, pharmacogenomics and potential clinical applications.

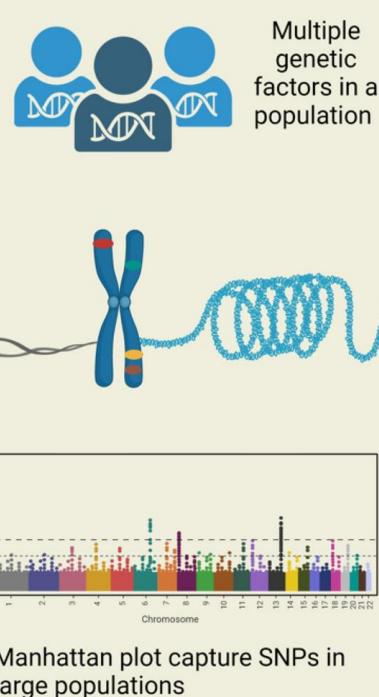
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Monogenic vs polygenic diseases

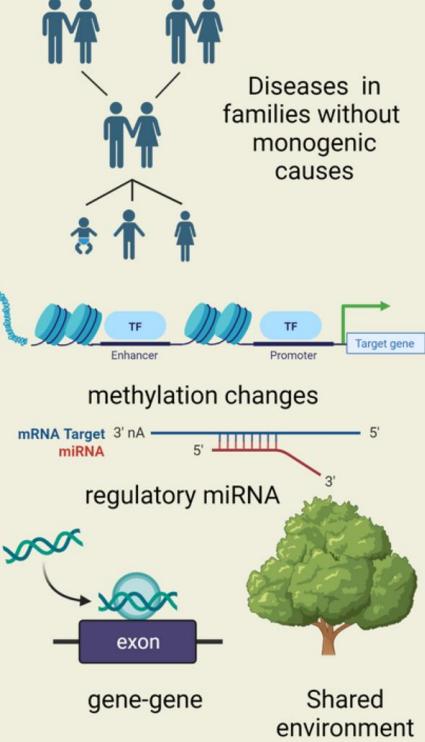
Single gene disorders



Polygenic risk



Familial risk



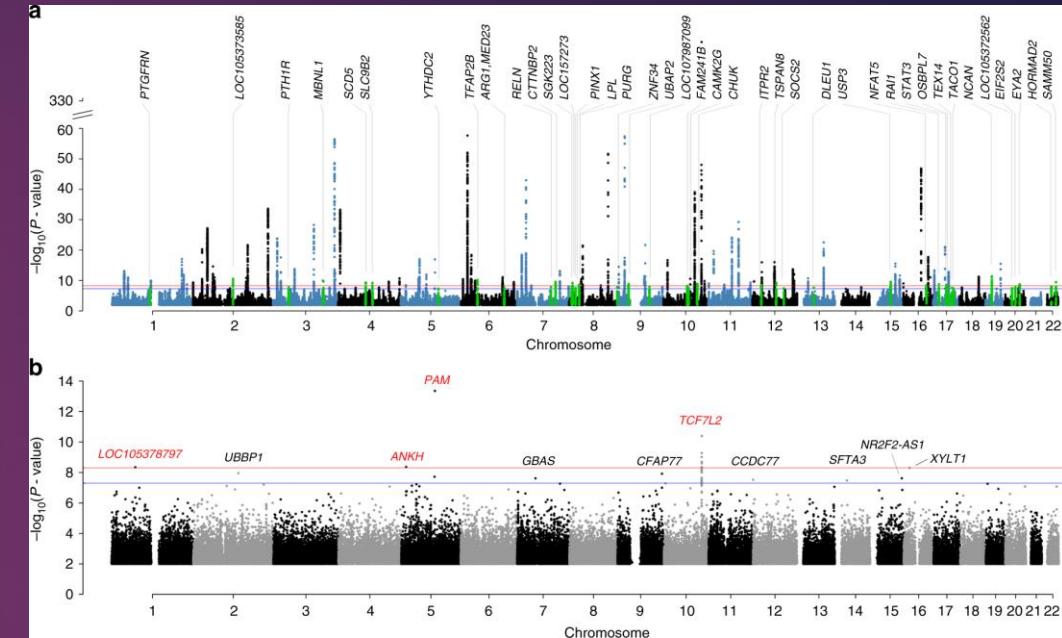
Classical mendelian inheritance patterns with clear genotype phenotype correlations and inheritance patterns in families account for 10% of adult onset kidney disease.

Polygenic risk scores capture SNP changes from GWAS studies to give a personalised risk score

Epigenetic modifications including methylation patterns, gene-gene interactions, miRNA and environmental factors.

GWAS = 7.1-20.3%

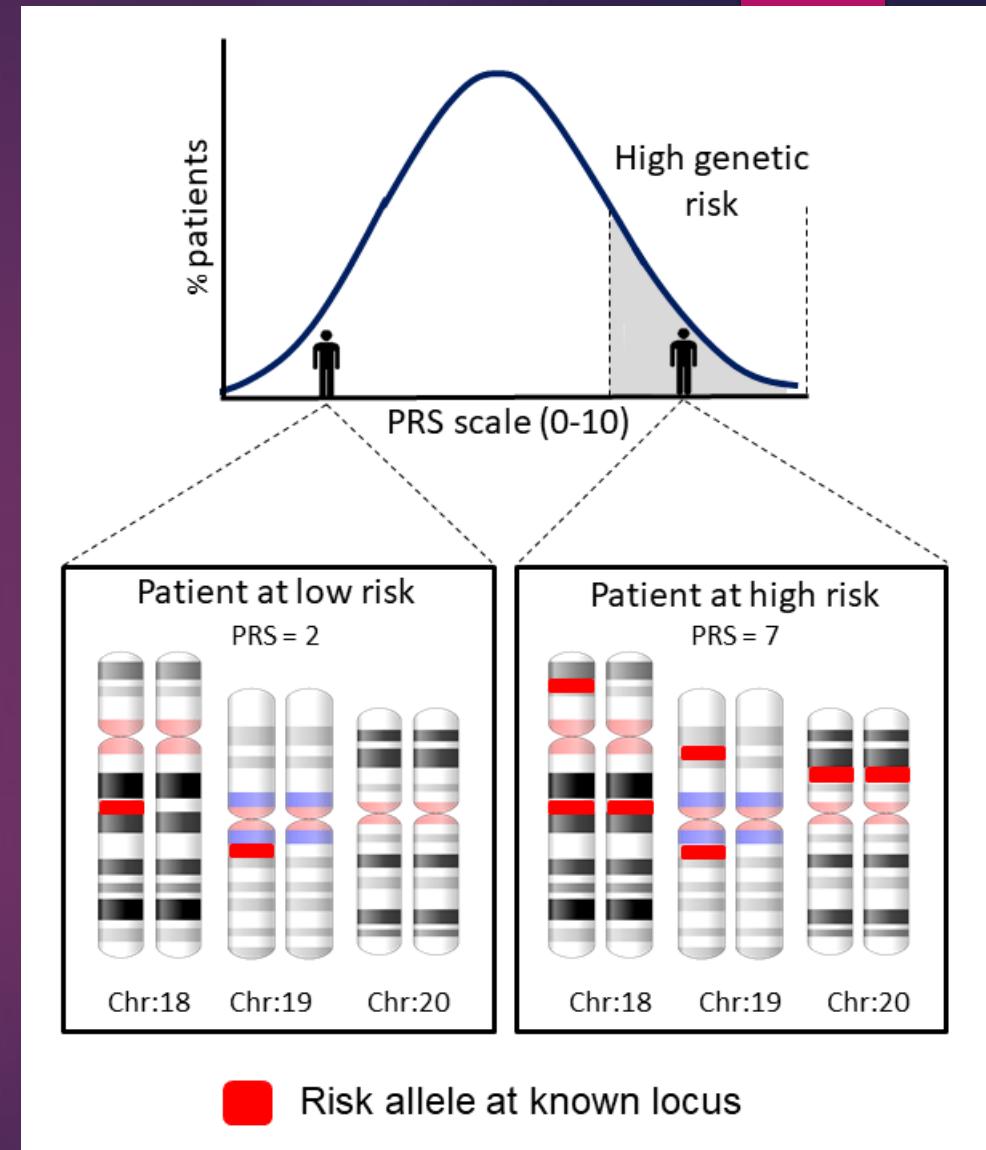
Family studies = 35-69%



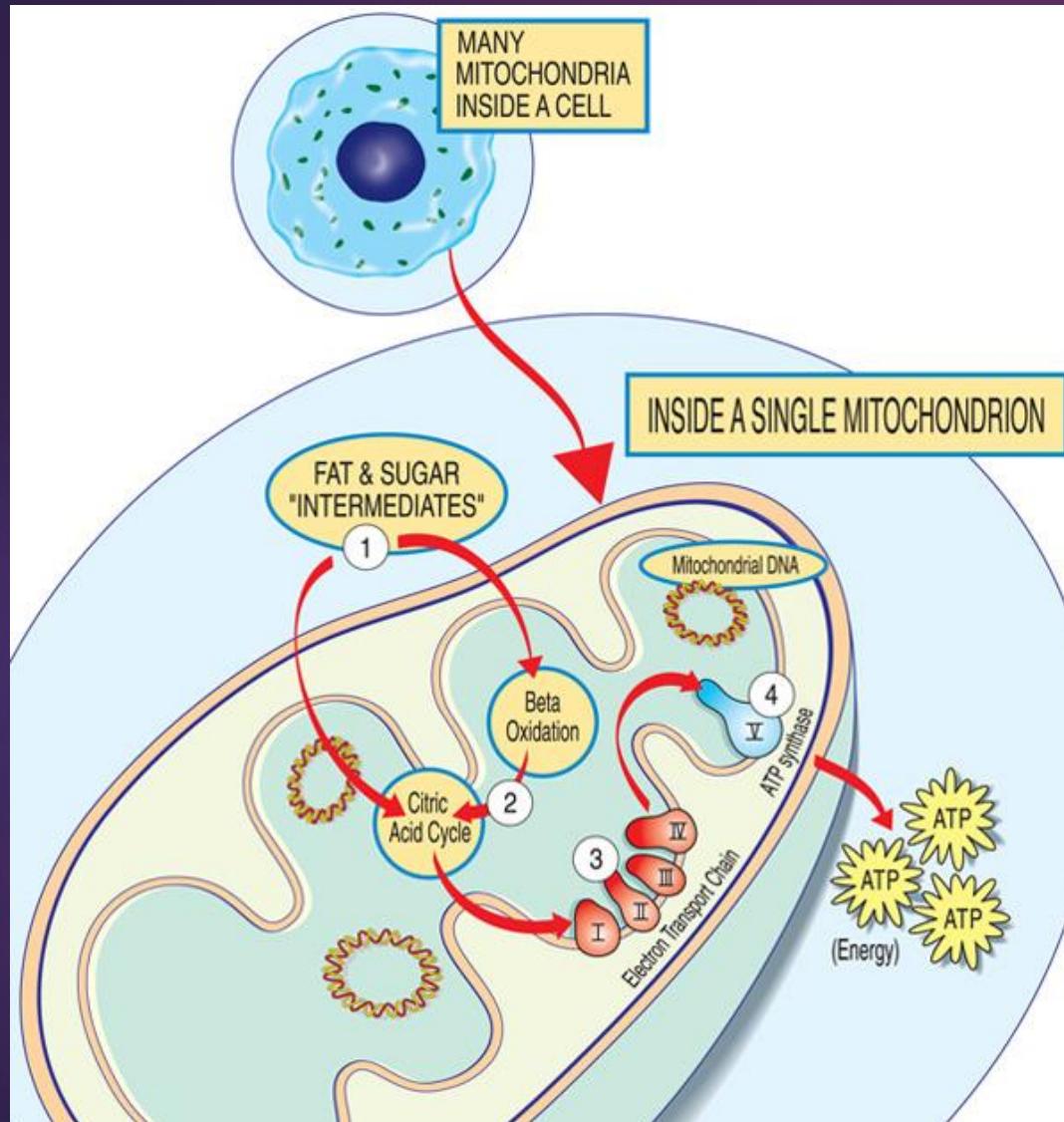
Manhattan plots of common- and rare-variant associations for T2D. **a** GWAS results for common variants ($MAF \geq 0.01$) in the meta-analysis. The 39 novel loci are annotated and highlighted in green. **b** GWAS results of rare variants ($0.0001 \leq MAF < 0.01$) in UKB. Four loci with $P < 5 \times 10^{-9}$ are highlighted in red. The blue lines denote the genome-wide significant threshold of $P < 5 \times 10^{-8}$, and the red lines denote a more stringent threshold of $P < 5 \times 10^{-9}$.

Multifactorial diseases

- ▶ Complex or polygenic diseases caused by a combination of environmental factors and mutations in multiple genes (i.e., both genetic and non-genetic or environmental factors are involved in determining the trait).
- ▶ For example, different genes that influence breast cancer susceptibility have been found on chromosomes 6, 11, 13, 14, 15, 17, and 22. Some common chronic diseases are multifactorial disorders (e.g., atherosclerosis, hypertension, ulcer disease, Alzheimer disease, arthritis, diabetes, cancer, and obesity).

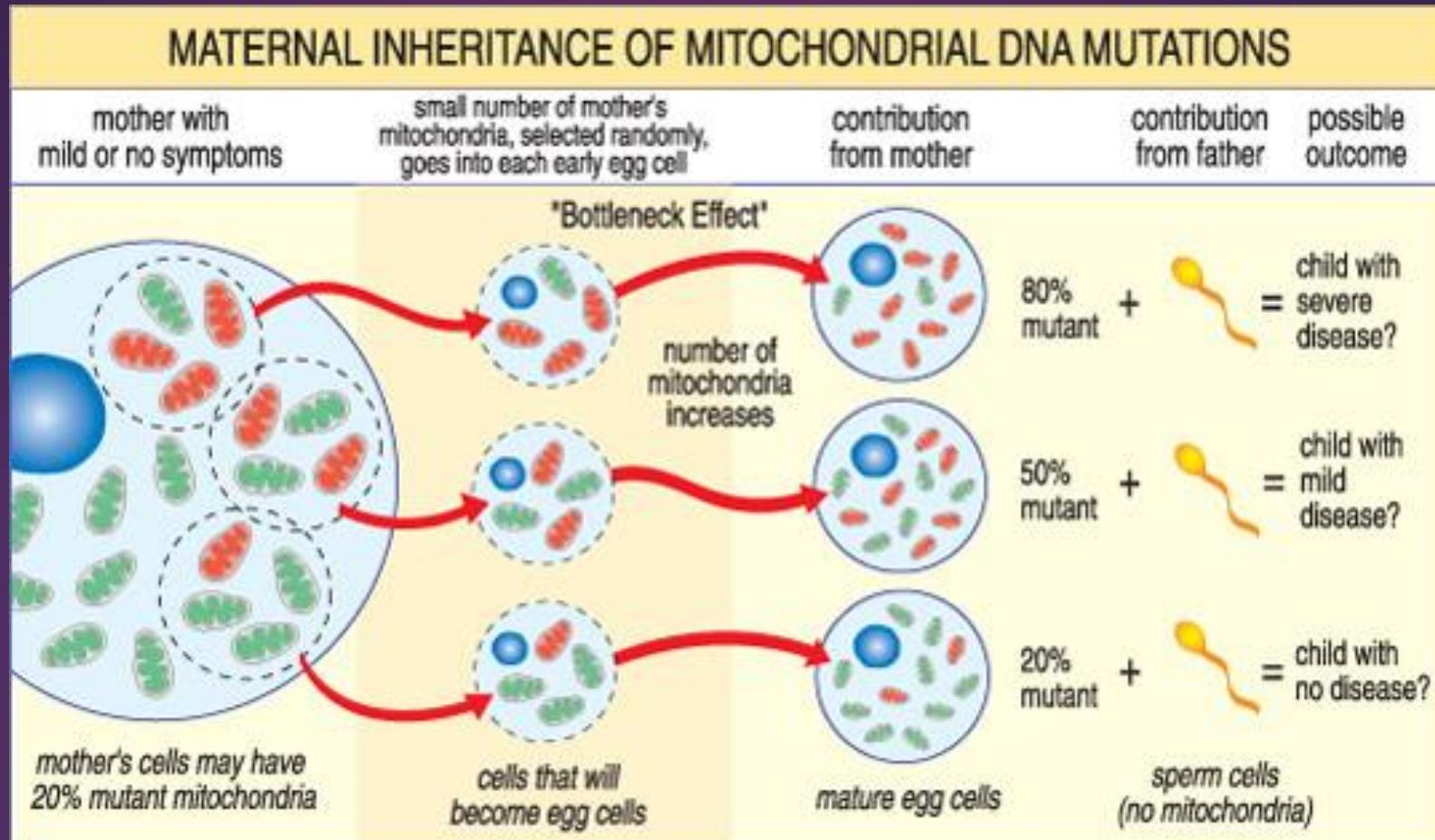


Mitochondrial inheritance



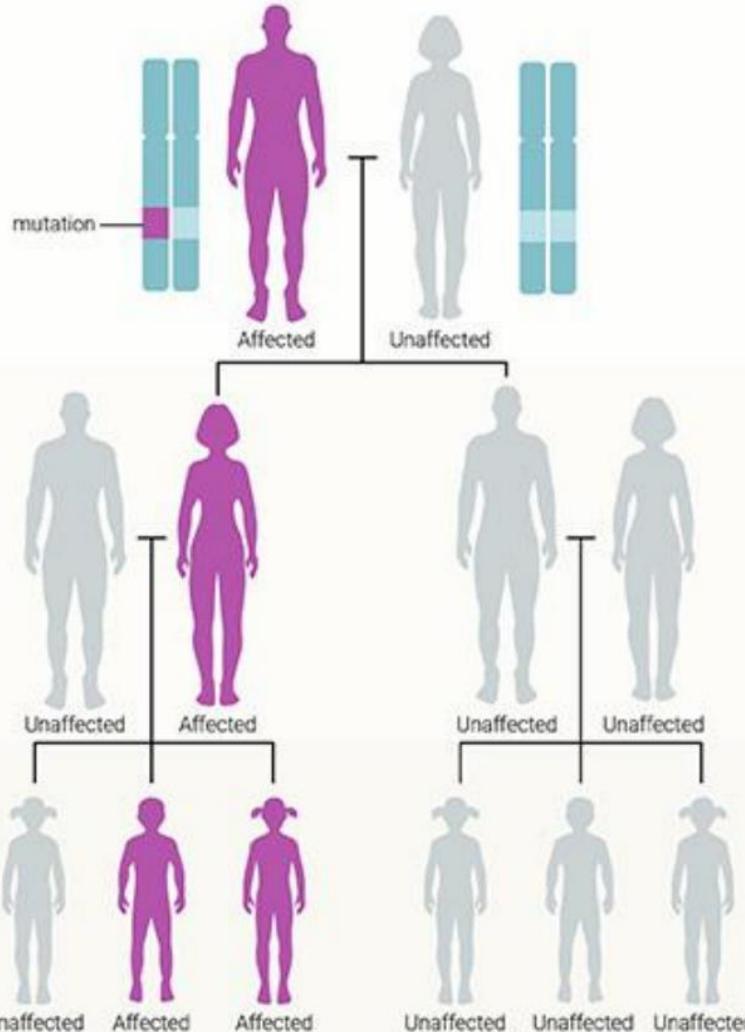
Each mitochondrion is an energy factory that “imports” sugars and fats, breaks them down and “exports” energy (ATP) via these steps: Fat and sugar intermediates enter the mitochondrion. Fatty acids are broken down through beta oxidation and the removal of electrons in the citric acid cycle. Electrons are passed through the major complex of the electron transport chain. ATP is made by ATP synthase.

Mitochondrial inheritance



The severity of a mitochondrial disease in a child depends on the percentage of abnormal (mutant) mitochondria in the egg cell that formed them.

Multigenerational Conditions

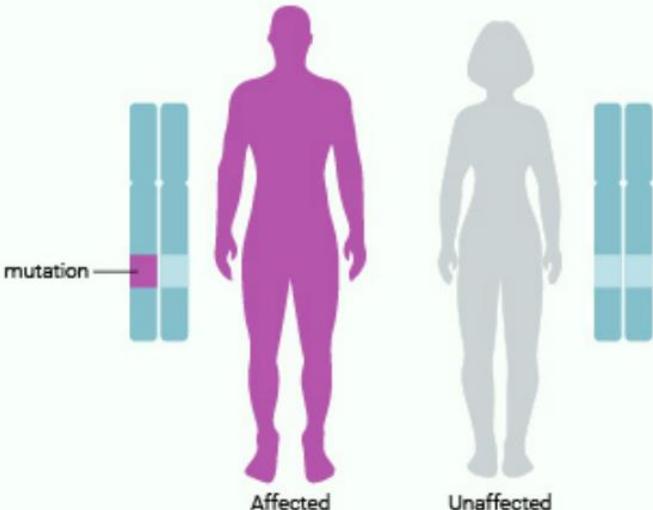


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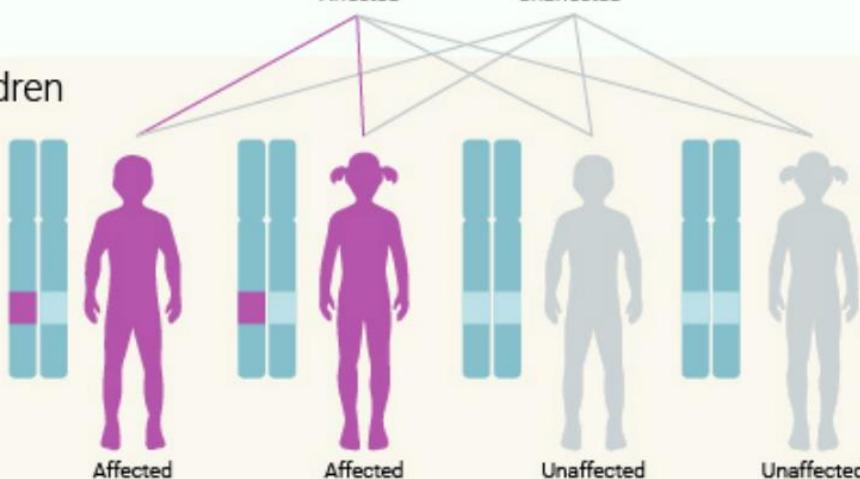
FIGURE 1: Three generations of a family with a genetic disorder.

Autosomal Dominant

Parents



Children

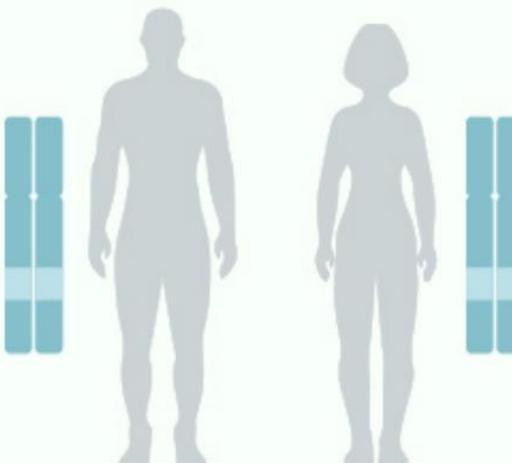


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FIGURE 2: A parent with an autosomal dominant condition passes the altered gene to two affected children. Two other children do not receive the altered gene, and are unaffected.

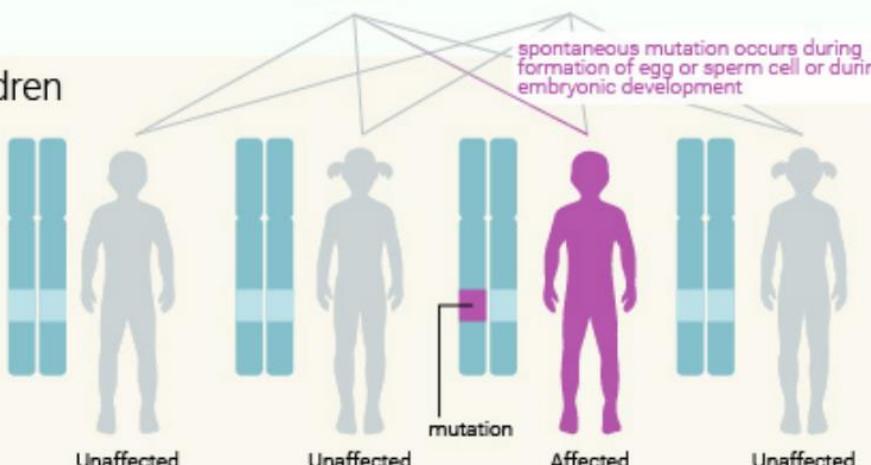
Autosomal Dominant - New Mutation

Parents



Unaffected Unaffected

Children

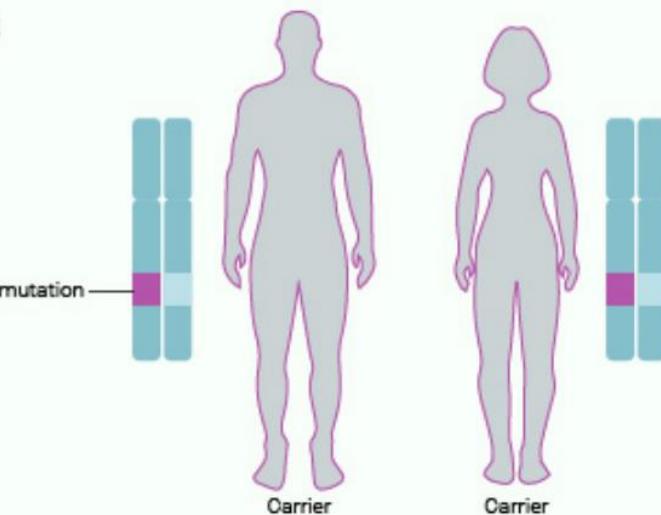


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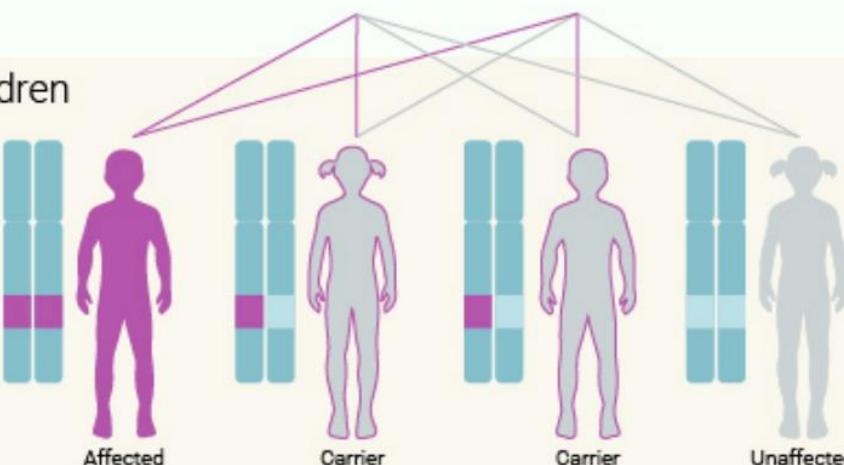
FIGURE 3: Neither parent has the mutated gene. A spontaneous mutation occurs during the formation of an egg or sperm cell during embryonic development, leading to an affected child.

Autosomal Recessive

Parents



Children



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FIGURE 4: Both parents carry one copy of a mutated gene. In the next generation, one child is affected with the condition, two children are carriers, and one is unaffected and not a carrier.

X-Linked Dominant

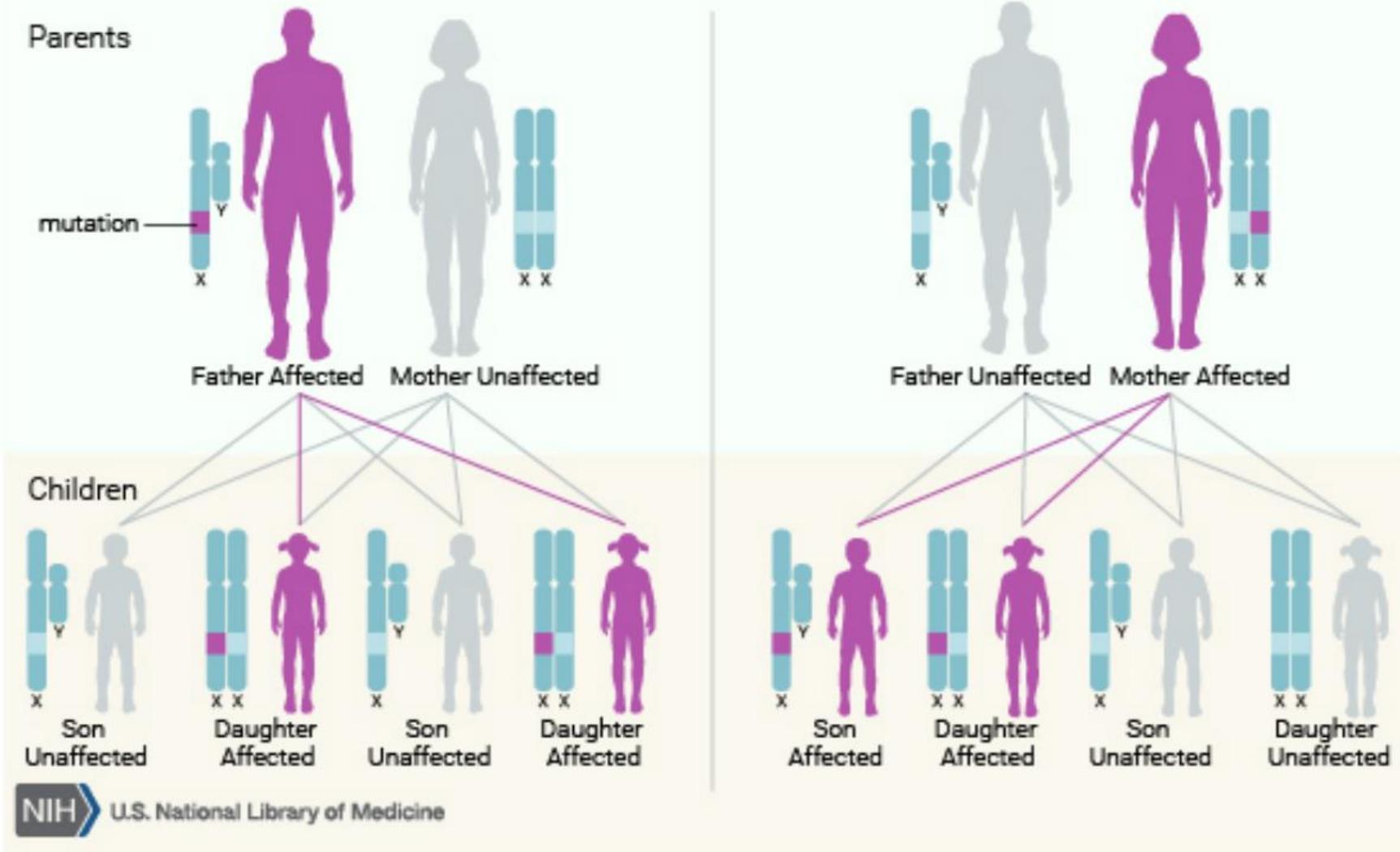


FIGURE 5: Inheritance of an X-linked dominant disorder depends on which parent is affected.

X-Linked Recessive

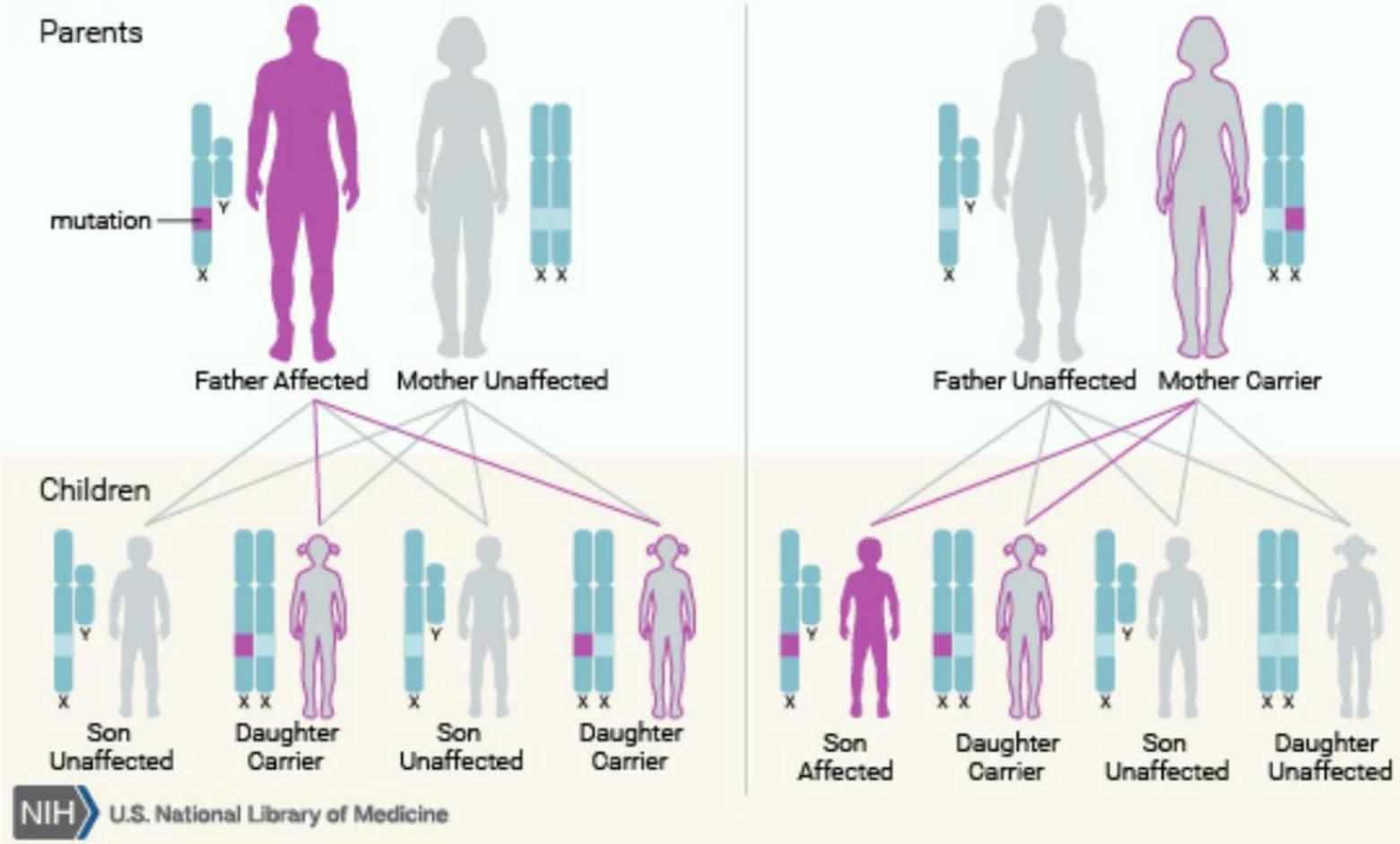
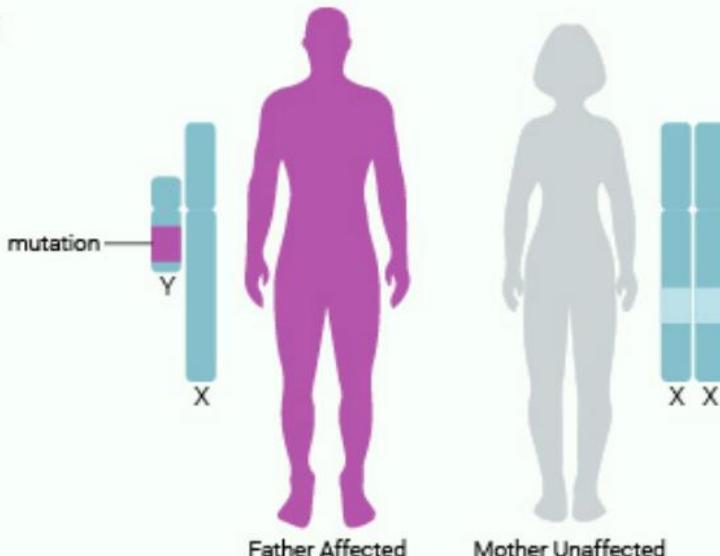


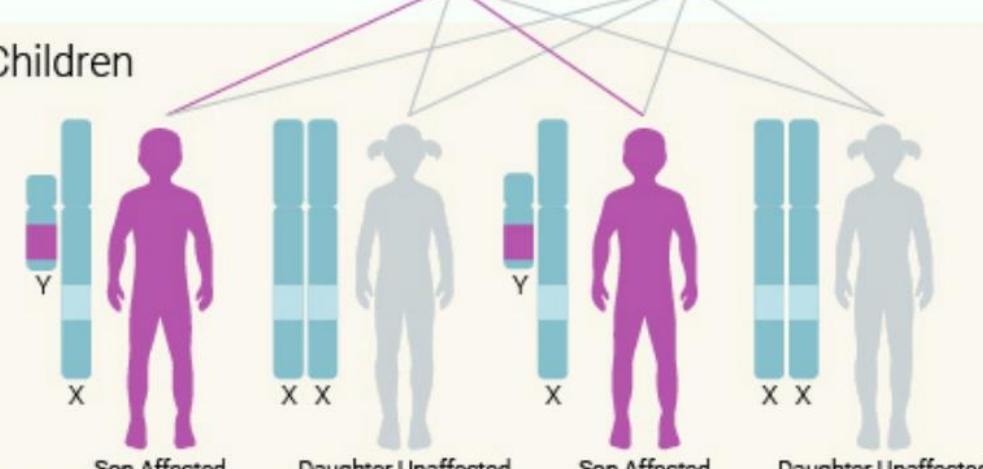
FIGURE 6: Two generations of a family with an X-linked recessive disorder. In this form of inheritance, the chance of being affected or being a carrier depends on whether the mother or the father has the mutated gene on the X chromosome.

Y-Linked

Parents



Children

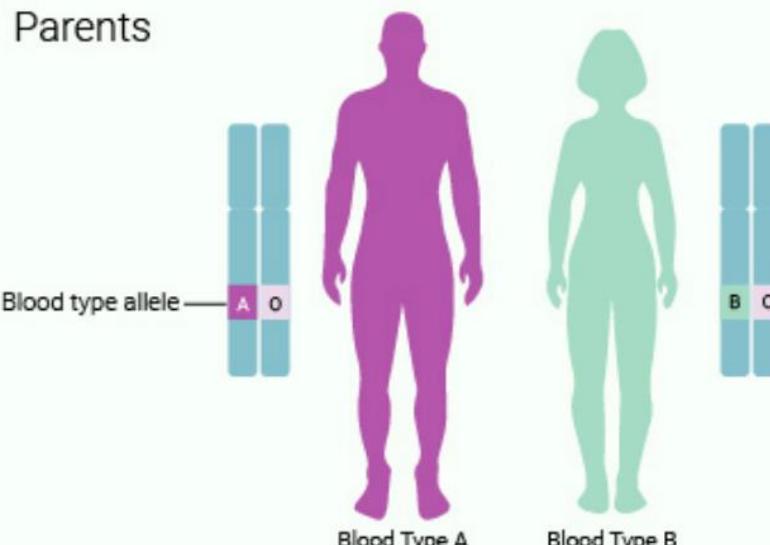


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FIGURE 7: A father and sons are affected with a Y-linked disorder, which is

Codominance - example Blood Type

Parents



Children

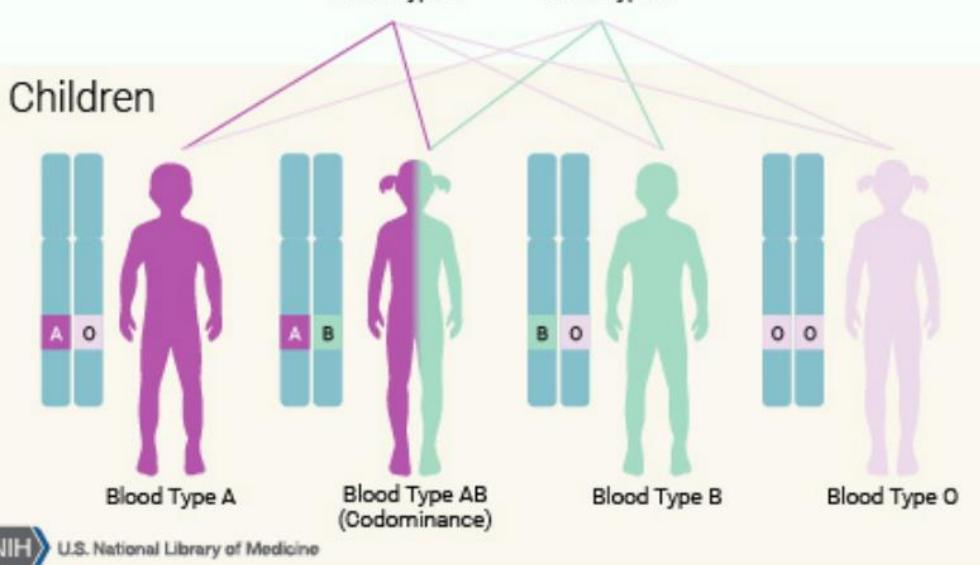
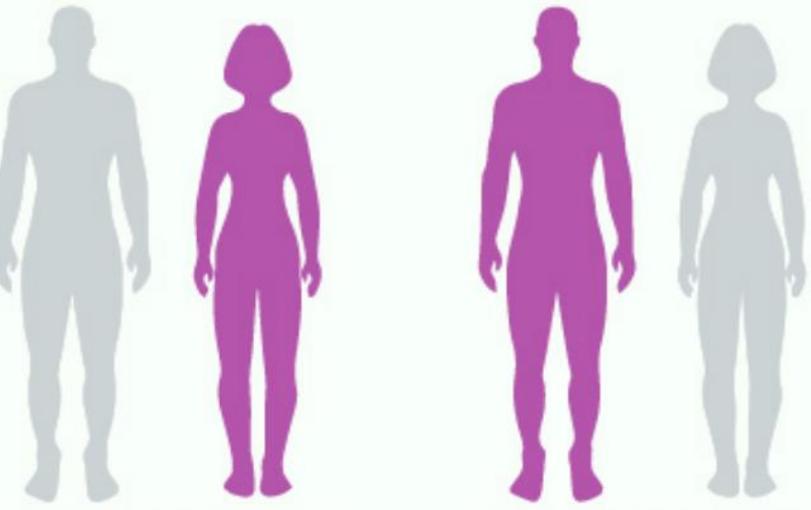


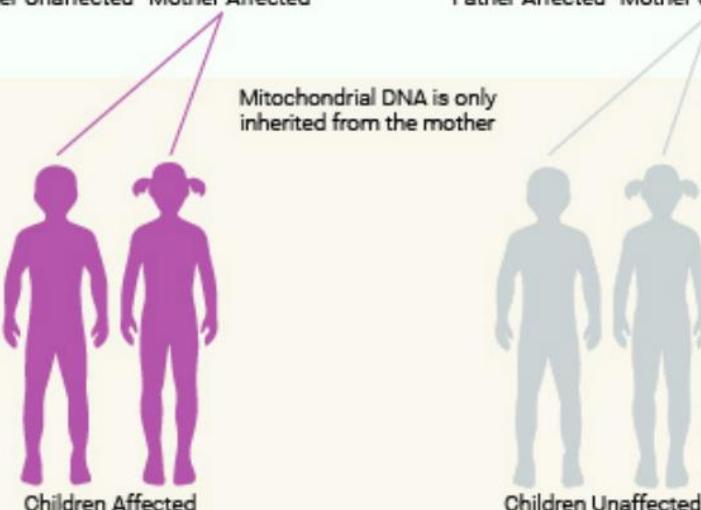
FIGURE 8: ABO blood type is an example of a trait with codominant inheritance.

Mitochondrial

Parents



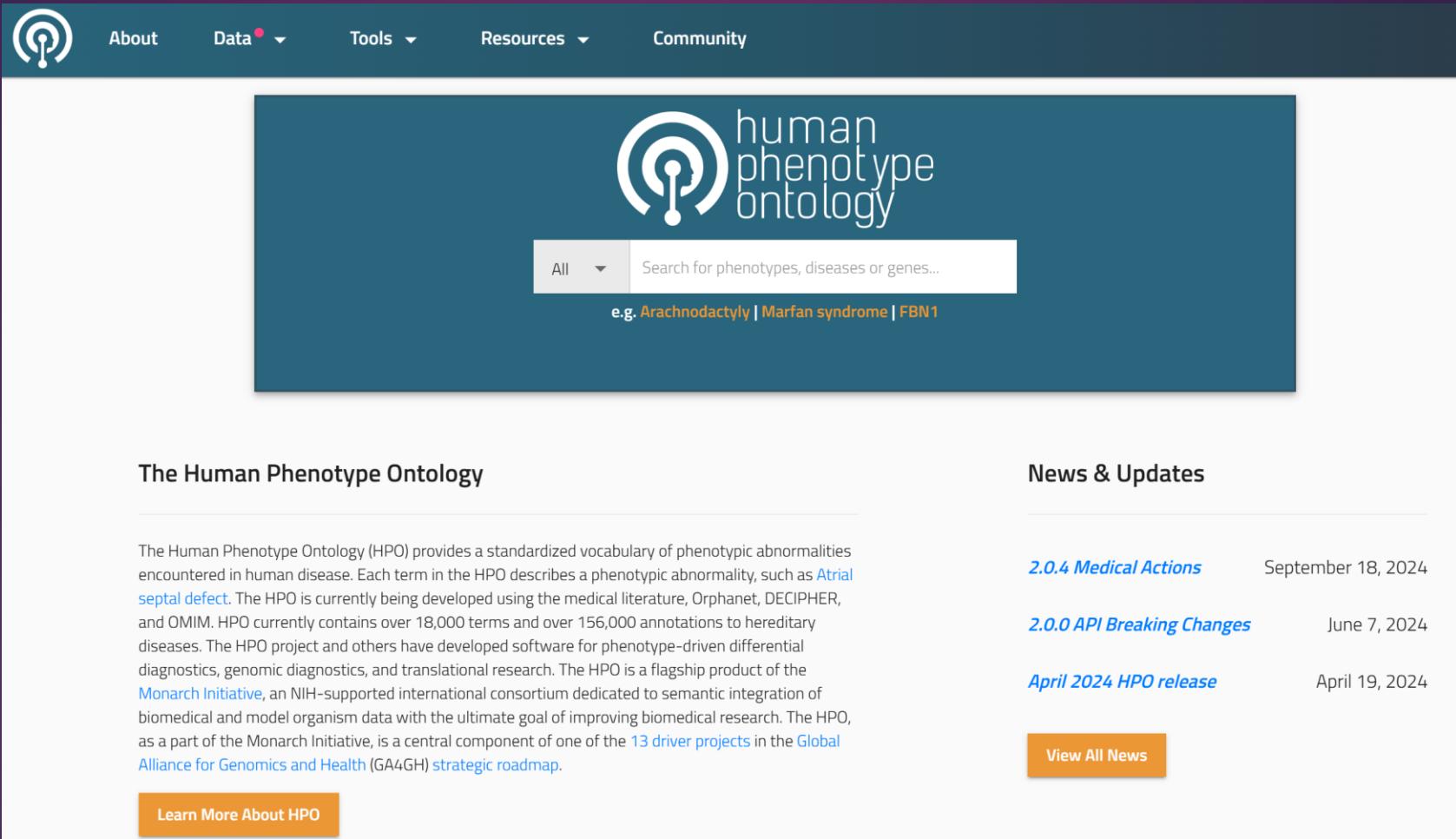
Children



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FIGURE 9: The inheritance of a mitochondrial disorder depends whether the mother or the father has the mutation in mitochondrial DNA.

The Human Phenotype Ontology (HPO)



The screenshot shows the HPO homepage. At the top, there is a dark blue header with the HPO logo (a stylized antenna icon), and navigation links for About, Data (with a red dot indicating updates), Tools, Resources, and Community.

The main content area has a teal header featuring the HPO logo and the text "human phenotype ontology". Below this is a search bar with a dropdown menu set to "All" and a placeholder "Search for phenotypes, diseases or genes...". Underneath the search bar, there is a suggestion "e.g. Arachnodactyly | Marfan syndrome | FBN1".

The page is divided into two main sections: "The Human Phenotype Ontology" on the left and "News & Updates" on the right.

The Human Phenotype Ontology

The text in this section describes the HPO as a standardized vocabulary of phenotypic abnormalities encountered in human disease. It mentions its development using medical literature, Orphanet, DECIPHER, and OMIM, and notes it contains over 18,000 terms and 156,000 annotations. The HPO is described as a flagship product of the Monarch Initiative, a NIH-supported international consortium dedicated to semantic integration of biomedical and model organism data. It is also mentioned as part of the Monarch Initiative, a central component of one of the 13 driver projects in the Global Alliance for Genomics and Health (GA4GH) strategic roadmap.

[Learn More About HPO](#)

News & Updates

The news section lists three recent updates:

- 2.0.4 Medical Actions** September 18, 2024
- 2.0.0 API Breaking Changes** June 7, 2024
- April 2024 HPO release** April 19, 2024

[View All News](#)

<https://hpo.jax.org/>

The Human Phenotype Ontology (HPO)

- ▶ The Human Phenotype Ontology (HPO) provides a standardized vocabulary of phenotypic abnormalities encountered in human disease.
- ▶ Each term in the HPO describes a phenotypic abnormality, such as Atrial septal defect.
- ▶ The HPO is currently being developed using the medical literature, Orphanet, DECIPHER, and OMIM.
- ▶ HPO currently contains over 18,000 terms and over 156,000 annotations to hereditary diseases.
- ▶ The HPO project and others have developed software for phenotype-driven differential diagnostics, genomic diagnostics, and translational research.

The screenshot displays two main sections of the HPO website. The top section shows a search results page for "Marfan syndrome", listing 86 terms. The bottom section shows a detailed view for the term "Nephrotic syndrome".

Search Results For "Marfan syndrome"
Not seeing what you're looking for? [Contribute a term](#)

Term Identifier	Term Name	Matching String	Synonym Match
HP:000012	Urinary urgency		Yes
HP:000100	Nephrotic syndrome		Yes
HP:0000940	Adrenogenital syndrome		Yes
HP:0001071	Angiolipoma corporis diffusum		Yes
HP:0001097	Keratoconjunctivitis sicca		Yes
HP:0001156	Brachydactyly		Yes
HP:0001357	Plagiocephaly		Yes

Hierarchy Nephrotic syndrome (HP:0000100)
↳ English, Chinese, Czech, Dutch, French, German, Italian, Japanese, Spanish, Turkish
↳ Nephrotic syndrome is a collection of findings resulting from glomerular dysfunction with an increase in glomerular capillary wall permeability associated with pronounced proteinuria. Nephrotic syndrome refers to the constellation of clinical findings that result from severe renal loss of proteins, with Proteinuria and hypoalbuminemia, edema, and hypertension.
↳ Synonyms: Nephrosis
↳ Comment: In adults, nephrotic syndrome is characterized by protein excretion of 3.5 g or more per day. In children, nephrotic syndrome is accompanied by protein excretion of more than 40 mg/m²24h and hypoalbuminemia < 2.5 mg/dL
↳ Cross References: SNOMEDCT:U532594009, ICD-10-CM:C002726
↳ Export Associations, Translate your language
Disease Associations Disease Name
Disease Id: OMIM:256100 Nephrotic syndrome, type 1

<https://hpo.jax.org/>

The Human Phenotype Ontology (HPO)

Disease Associations **Gene Associations [Inferred]** Medical Actions LOINC Associations

Filter by gene

Gene Id	Gene Symbol
NCBIGene:4868	NPHS1
NCBIGene:112858	TP53RK
NCBIGene:2013	EMP2
NCBIGene:286204	CRB2
NCBIGene:9688	NUP93
NCBIGene:9863	MAGI2

139 gene associations.

<https://hpo.jax.org/browse/term/HP:0000100>

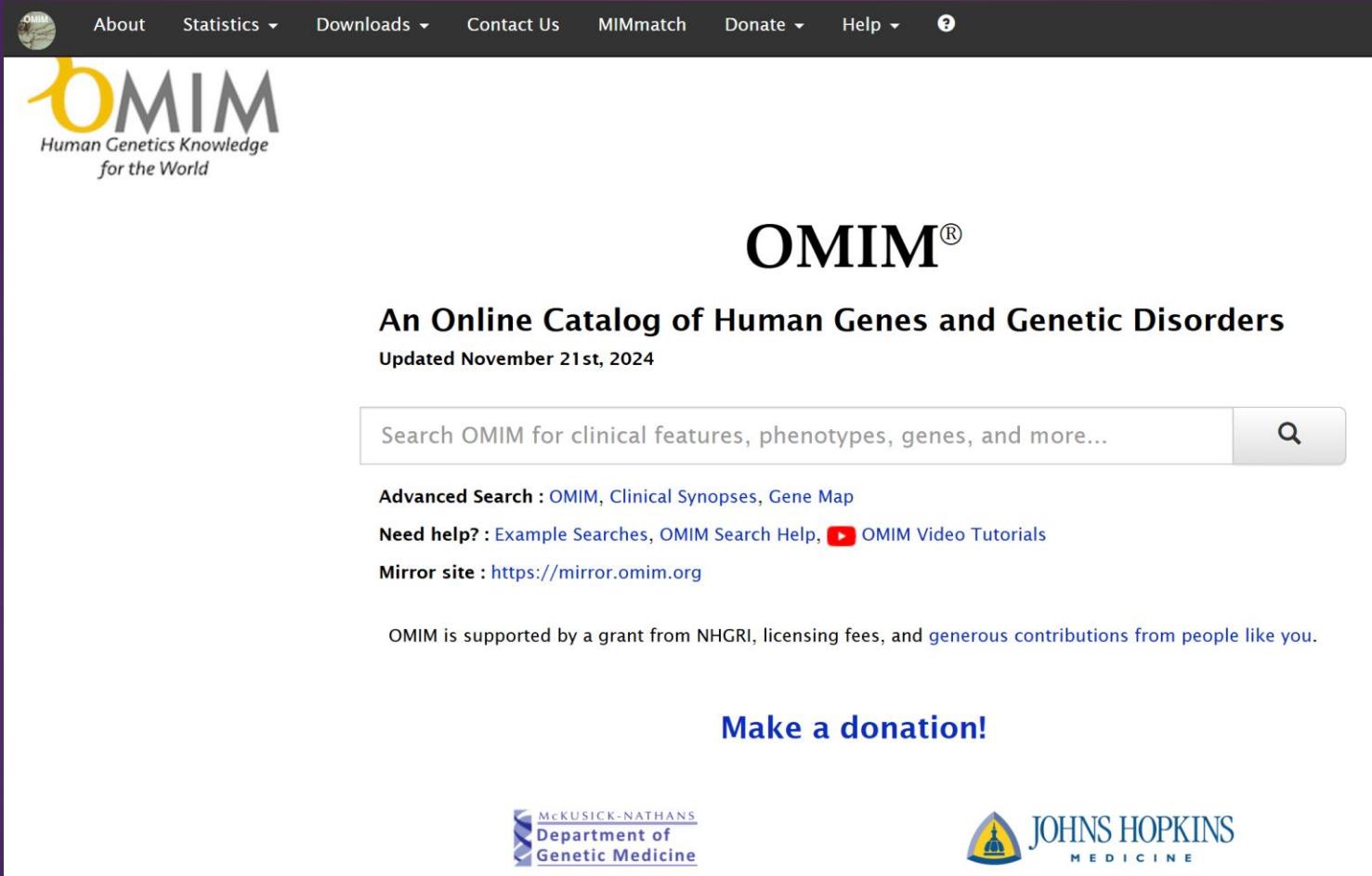
The Human Phenotype Ontology (HPO)

Disease Associations	Gene Associations [Inferred]	Medical Actions	LOINC Associations
MaXo Id	MaXo Name	Relation	Sources
MAXO:0000653	angiotensin receptor blocker therapy	TREATS	PubMed 
MAXO:0000640	corticosteroid agent therapy	TREATS	PubMed 
MAXO:0000297	immune suppressant agent therapy	TREATS	PubMed 
MAXO:0000190	RAAS inhibitor therapy	TREATS	PubMed 
MAXO:0000652	ACE inhibitor therapy	TREATS	PubMed 

5 medical actions.

<https://hpo.jax.org/browse/term/HP:0000100>

OMIM: An Online Catalog of Human Genes and Genetic Disorders



The screenshot shows the official website for OMIM. At the top, there is a dark navigation bar with the following menu items: About, Statistics ▾, Downloads ▾, Contact Us, MIMmatch, Donate ▾, Help ▾, and a question mark icon. Below the navigation bar is the OMIM logo, which consists of a stylized yellow 'M' and 'I' followed by the text "OMIM" and "Human Genetics Knowledge for the World". The main title "OMIM®" is prominently displayed in large black letters. Below it, the subtitle "An Online Catalog of Human Genes and Genetic Disorders" is shown in bold black text. A small note indicates the page was "Updated November 21st, 2024". A search bar at the top right contains the placeholder text "Search OMIM for clinical features, phenotypes, genes, and more..." and a magnifying glass icon. Below the search bar are links for "Advanced Search", "Need help?", and "Mirror site". A note about funding is present: "OMIM is supported by a grant from NHGRI, licensing fees, and generous contributions from people like you." A blue link "Make a donation!" is located near the bottom left. Logos for "McKUSICK-NATHANS Department of Genetic Medicine" and "JOHNS HOPKINS MEDICINE" are at the bottom.

OMIM®

An Online Catalog of Human Genes and Genetic Disorders

Updated November 21st, 2024

Search OMIM for clinical features, phenotypes, genes, and more... 

Advanced Search : [OMIM](#), [Clinical Synopses](#), [Gene Map](#)

Need help? : [Example Searches](#), [OMIM Search Help](#),  [OMIM Video Tutorials](#)

Mirror site : <https://mirror.omim.org>

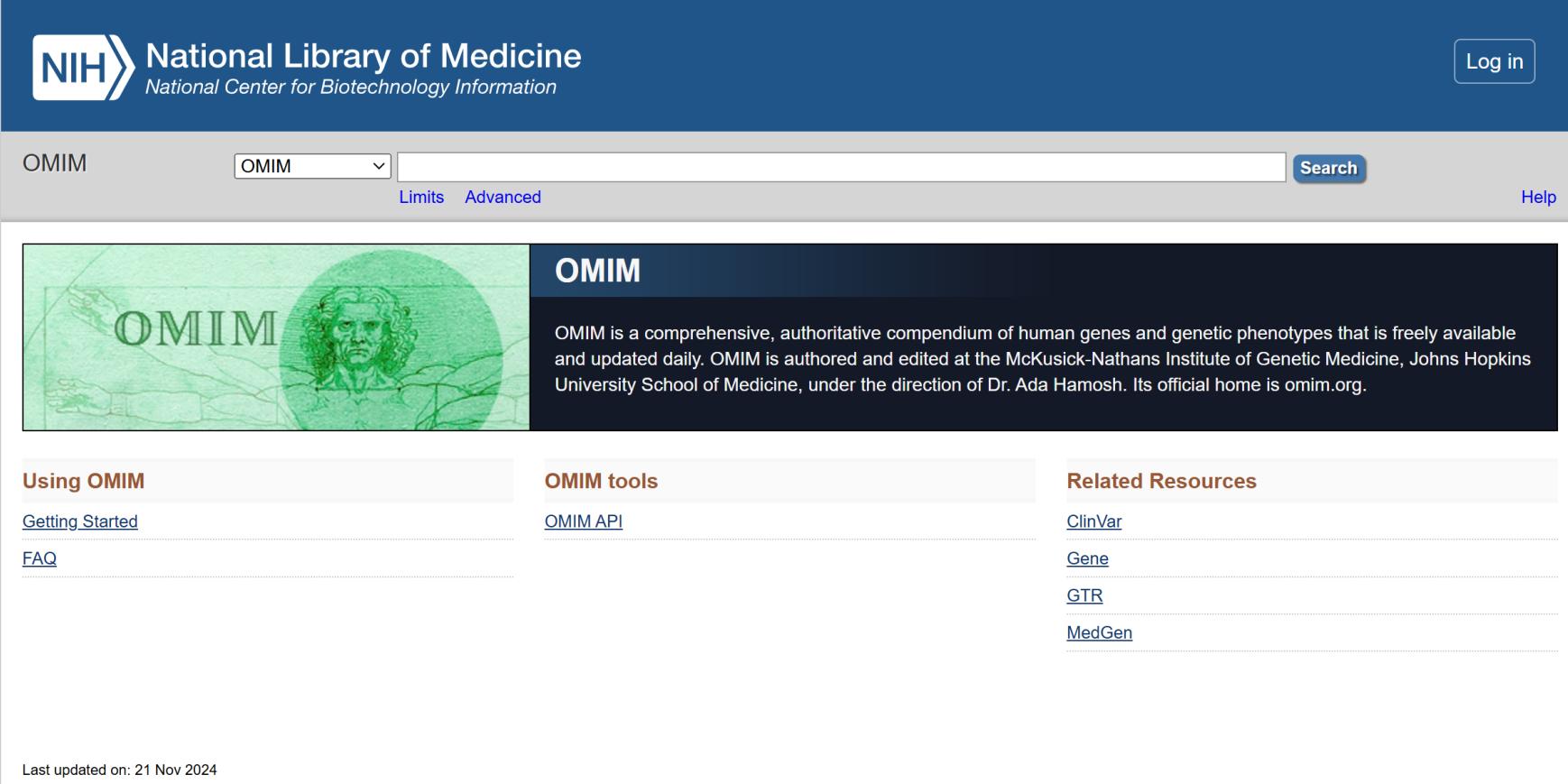
OMIM is supported by a grant from NHGRI, licensing fees, and [generous contributions from people like you](#).

[Make a donation!](#)

<https://omim.org/>

NCBI OMIM: An Online Catalog of Human Genes and Genetic Disorders



The screenshot shows the homepage of the NCBI OMIM website. At the top, there is a blue header bar with the NIH National Library of Medicine logo, the text "National Center for Biotechnology Information", a "Log in" button, and a search bar with dropdown menus for "OMIM" and "Search". Below the header, there is a large banner featuring a green circular graphic with the word "OMIM" and a classical portrait of a man. To the right of the graphic, the word "OMIM" is displayed in white. A descriptive text block states: "OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh. Its official home is omim.org." Below the banner, the page is divided into three main sections: "Using OMIM" (with links to "Getting Started" and "FAQ"), "OMIM tools" (with a link to "OMIM API"), and "Related Resources" (with links to "ClinVar", "Gene", "GTR", and "MedGen"). At the bottom left, a small note says "Last updated on: 21 Nov 2024".

<https://www.ncbi.nlm.nih.gov/omim>

ClinVar: Reports of human variations classified for diseases and drug responses

The screenshot shows the ClinVar website homepage. At the top, there is a blue header bar with the NIH National Library of Medicine logo, the text "National Library of Medicine", and "National Center for Biotechnology Information". On the right side of the header is a "Log in" button. Below the header is a search bar with the word "ClinVar" and a dropdown menu, followed by a "Search" button and a "Help" link. A navigation menu below the search bar includes links for Home, About, Access, Help, Submit, Statistics, and FTP. To the left of the main content area is a vertical sidebar containing a sequence of DNA base pairs: ACTGATGGTATGGGCCAAGAGATATATCTCAGGTACGGCTGTCACTTAGACCTCAC. The main content area features a dark blue header with the "ClinVar" logo and a descriptive text: "ClinVar aggregates information about genomic variation and its relationship to human health." Below this is a large black rectangular area. At the bottom of the page are three columns: "Using ClinVar" (links to About ClinVar, Data Dictionary, Downloads/FTP site, FAQ, Contact Us, and Subscribe to the ClinVar mailing list), "Tools" (links to ACMG Recommendations for Reporting of Secondary Findings, ClinVar Submission Portal, Submissions, Variation Viewer, and RefSeqGene/LRG), and "Related Sites" (links to ClinGen, GeneReviews®, GTR®, MedGen, OMIM®, and Variation).

<https://www.ncbi.nlm.nih.gov/clinvar/>



Xin chân thành cảm ơn!

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