

GENETIC DISORDER, HPO, OMIM and ClinVar

Jan 05 2025

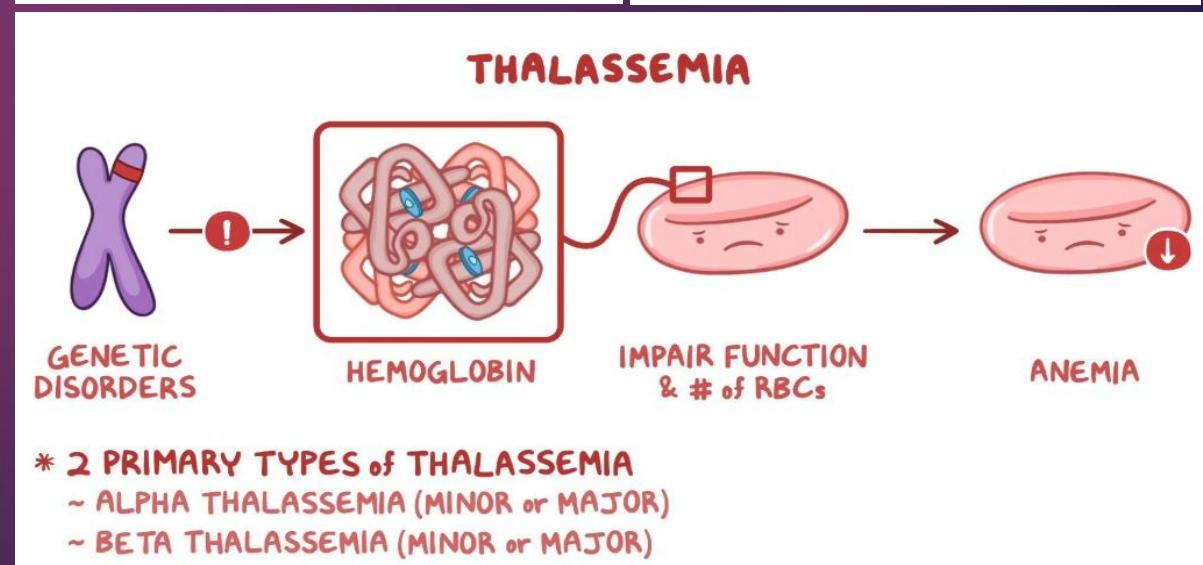
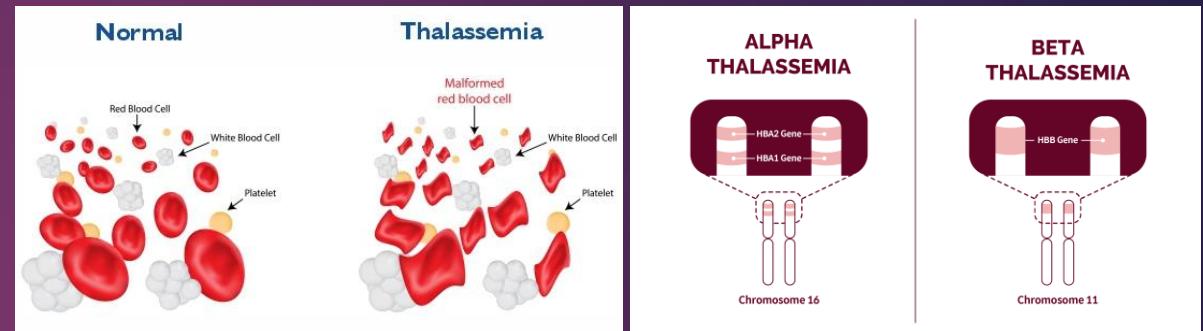
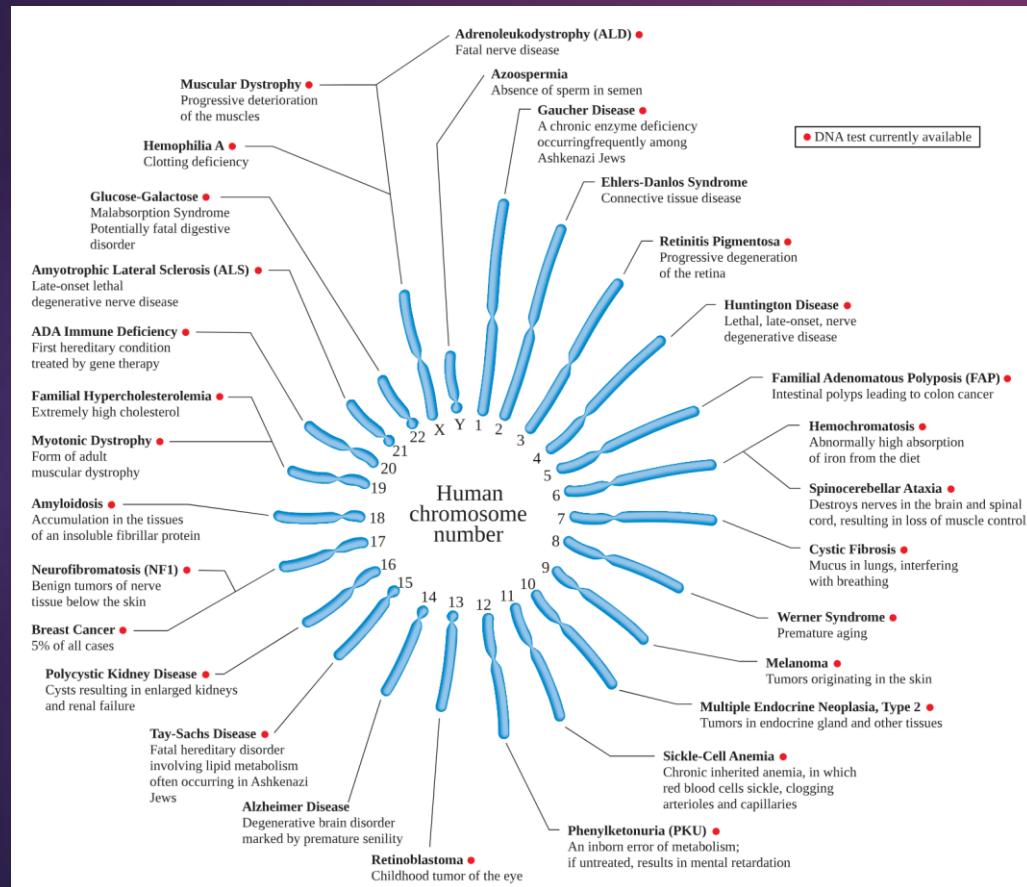
Giảng viên: TS. Lưu Phúc Lợi
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Lecture Content

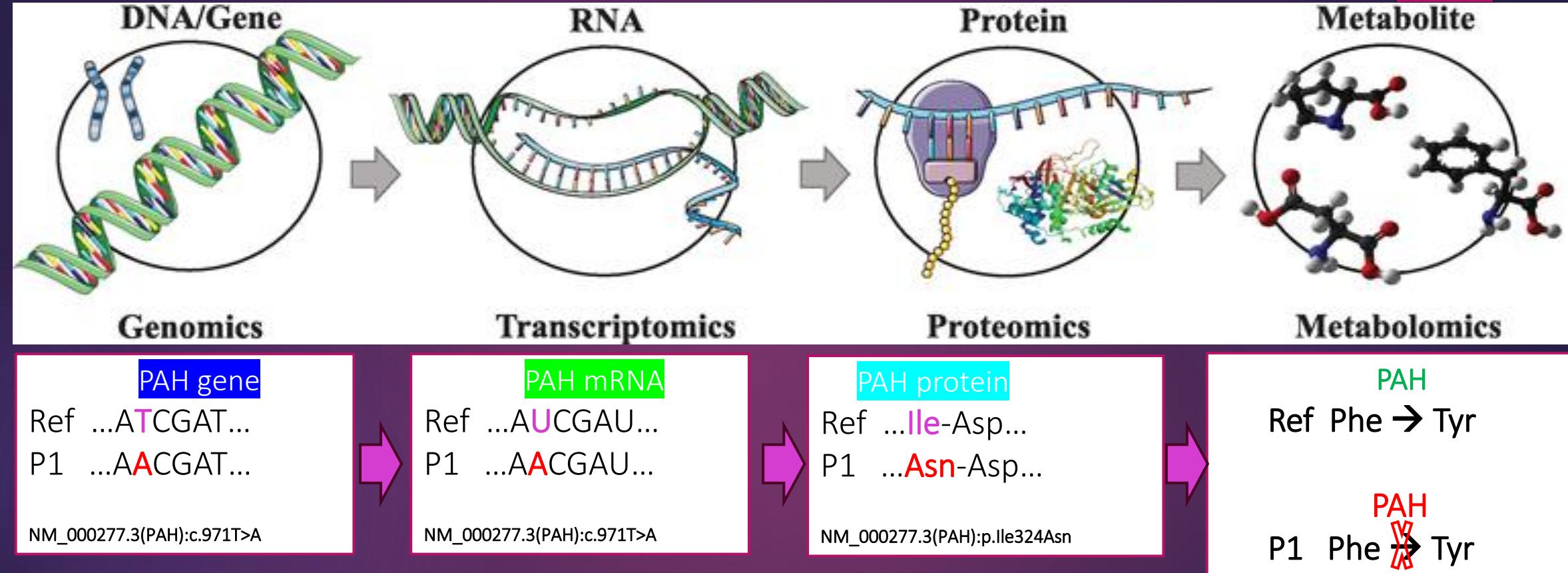
1. Genetic disorder
2. Introduction to HPO (The Human Phenotype Ontology)
3. Introduction to OMIM (Online Mendelian Inheritance in Man)
4. Introduction to ClinVar

Genetic disorder

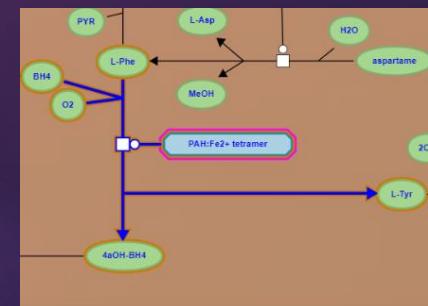
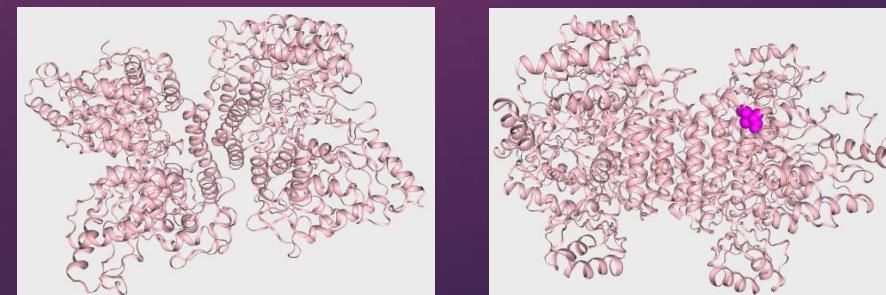
A genetic disorder is a health problem caused by one or more abnormalities in the genome. It can be caused by a mutation in a single gene or multiple genes or by a chromosome abnormality.



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



10.5772/intechopen.71769

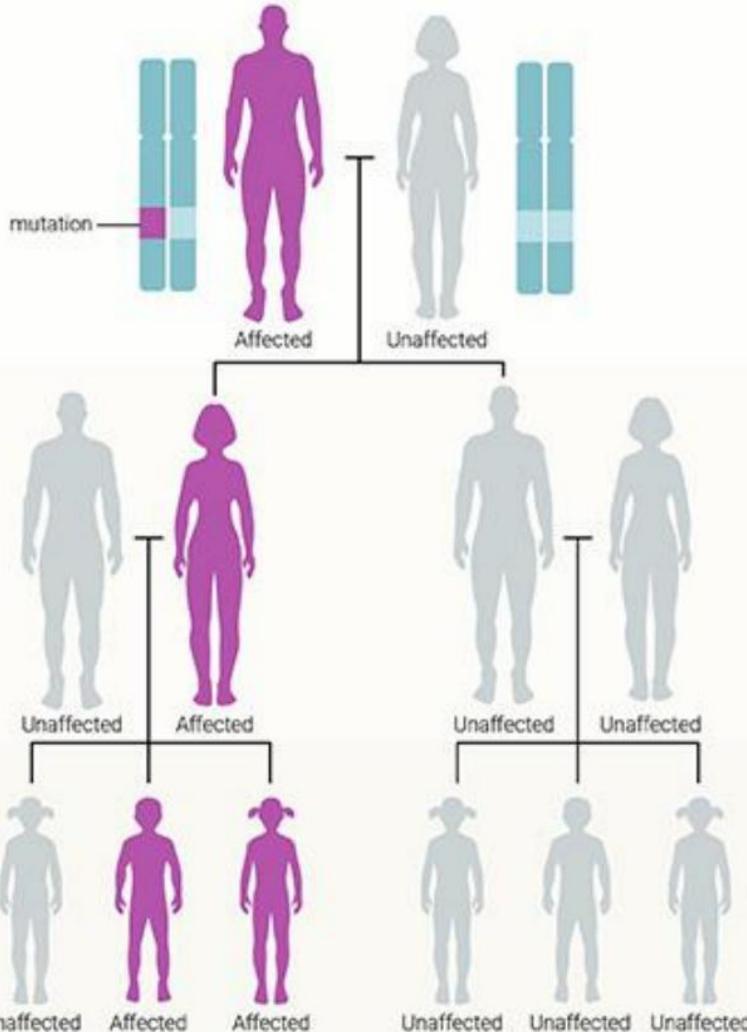


Genetic classification of hereditary diseases

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.

Multigenerational Conditions



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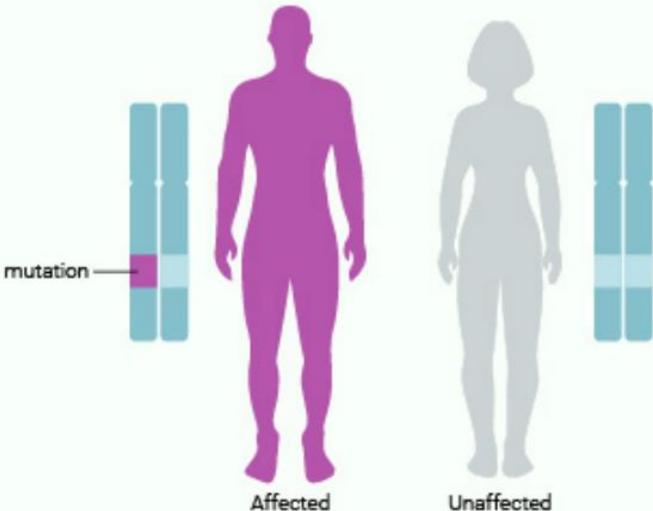
FIGURE 1: Three generations of a family with a genetic disorder.

Single gene inheritance, examples

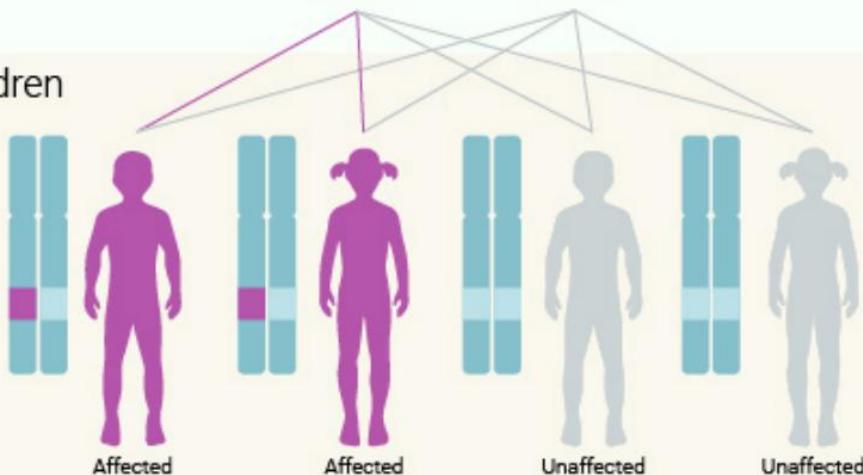
- ▶ Huntington's disease is a progressive neurodegenerative disorder that exhibits autosomal dominant inheritance. Other examples of autosomal dominant diseases include Marfan syndrome, neurofibromatosis, retinoblastoma and polydactyly.
- ▶ Phenylketonuria represents a prominent example of a single gene 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.

Autosomal Dominant

Parents



Children

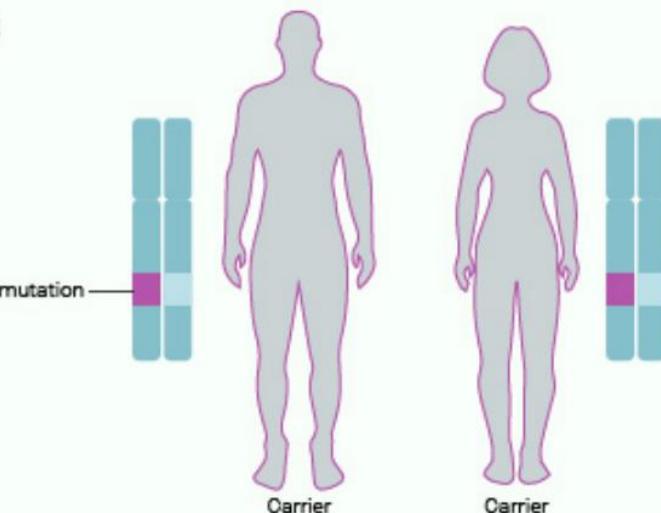


NIH U.S. National Library of Medicine

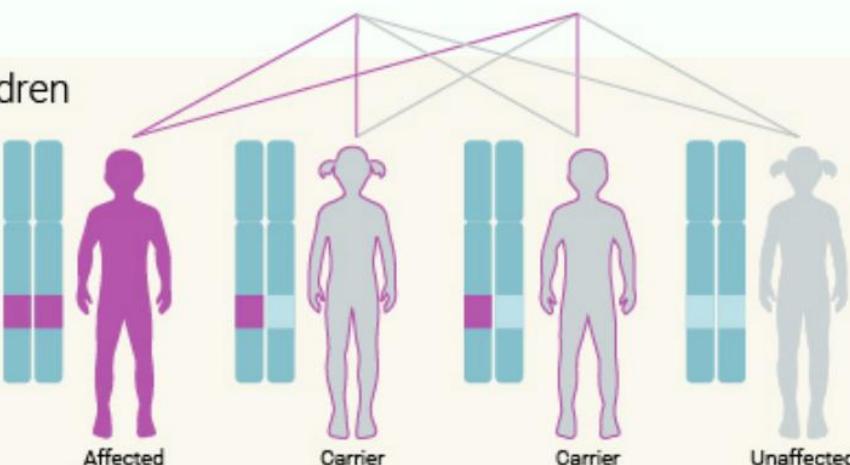
FIGURE 2: A parent with an autosomal dominant condition passes the altered gene to two affected children. Two other children do not receive the altered gene, and are unaffected.

Autosomal Recessive

Parents



Children



U.S. National Library of Medicine

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

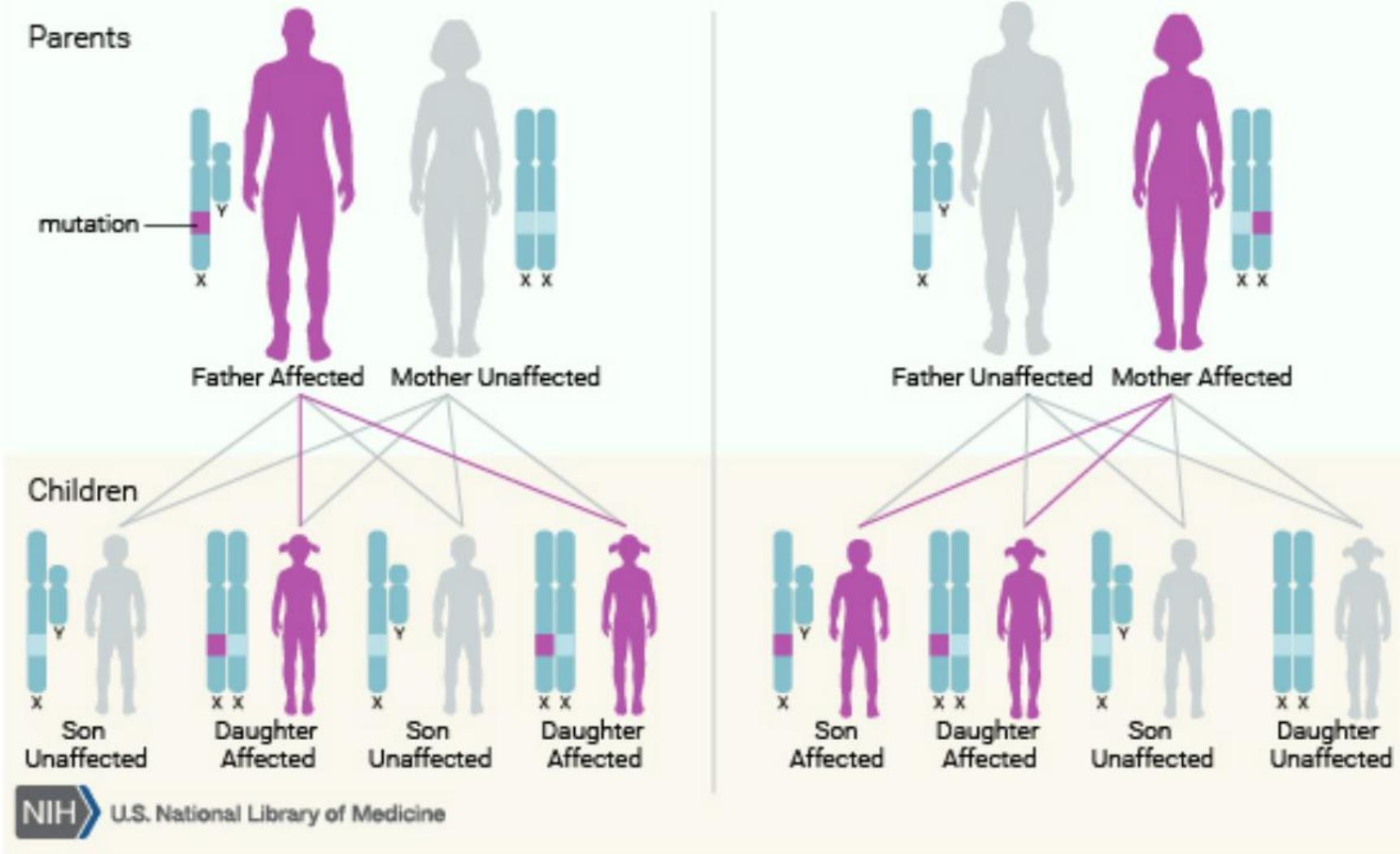


FIGURE 5: Inheritance of an X-linked dominant disorder depends on which parent is affected.

X-Linked Recessive

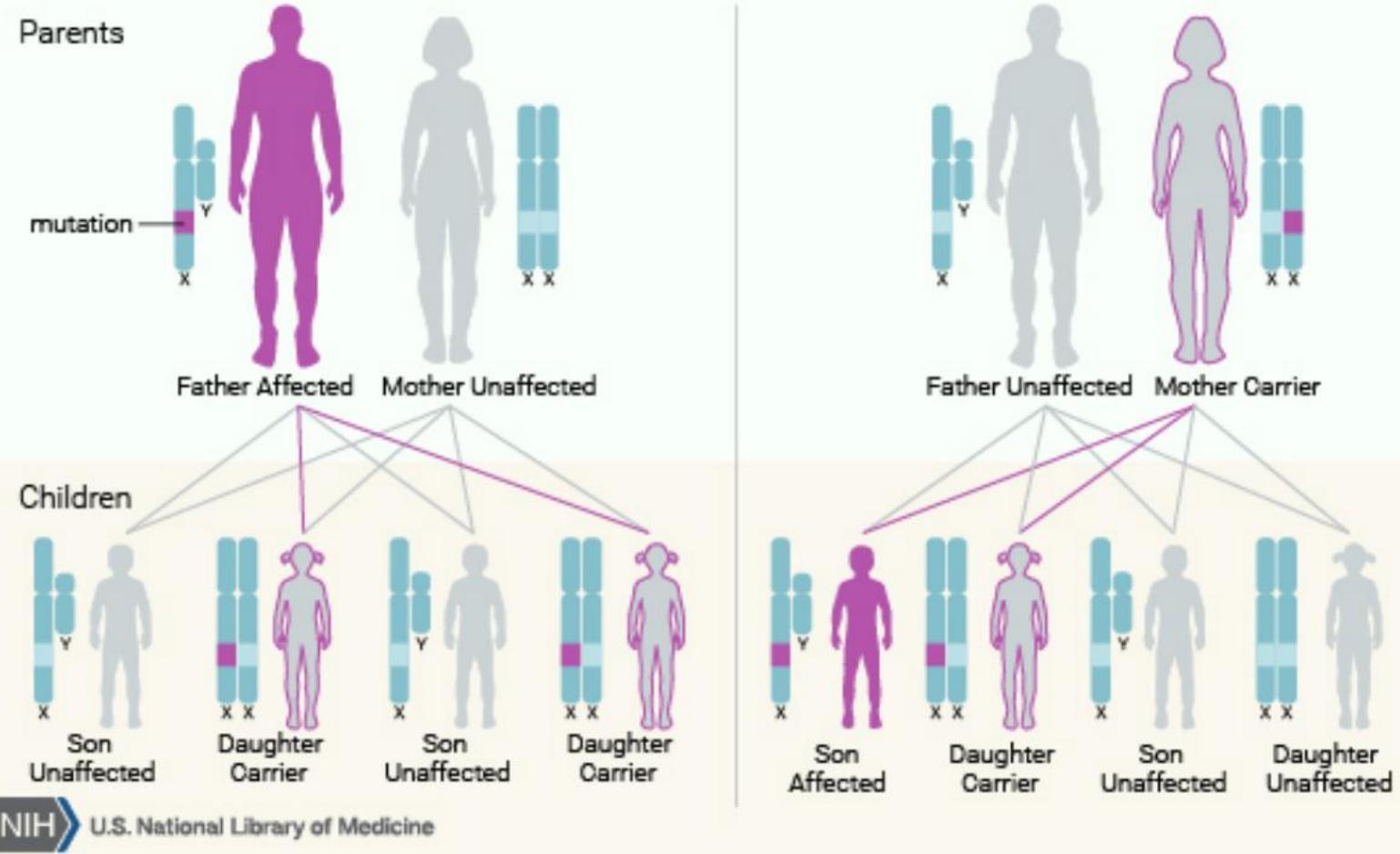
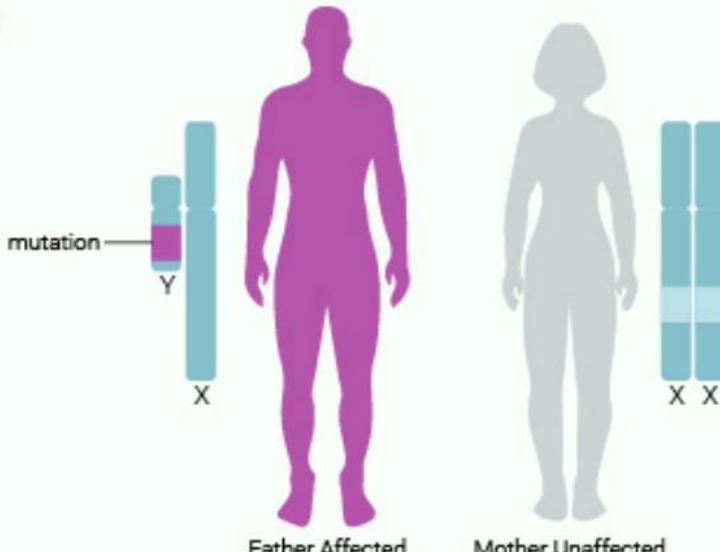


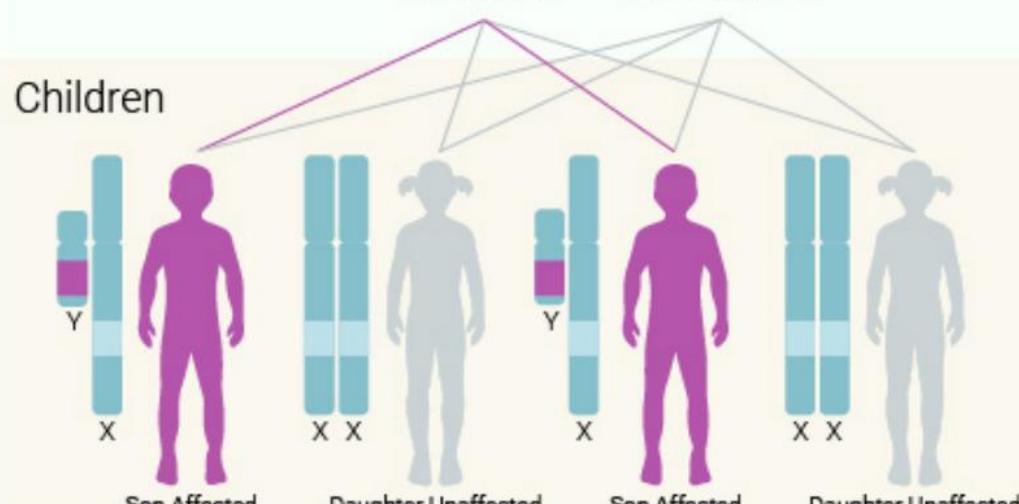
FIGURE 6: Two generations of a family with an X-linked recessive disorder. In this form of inheritance, the chance of being affected or being a carrier depends on whether the mother or the father has the mutated gene on the X chromosome.

Y-Linked

Parents



Children



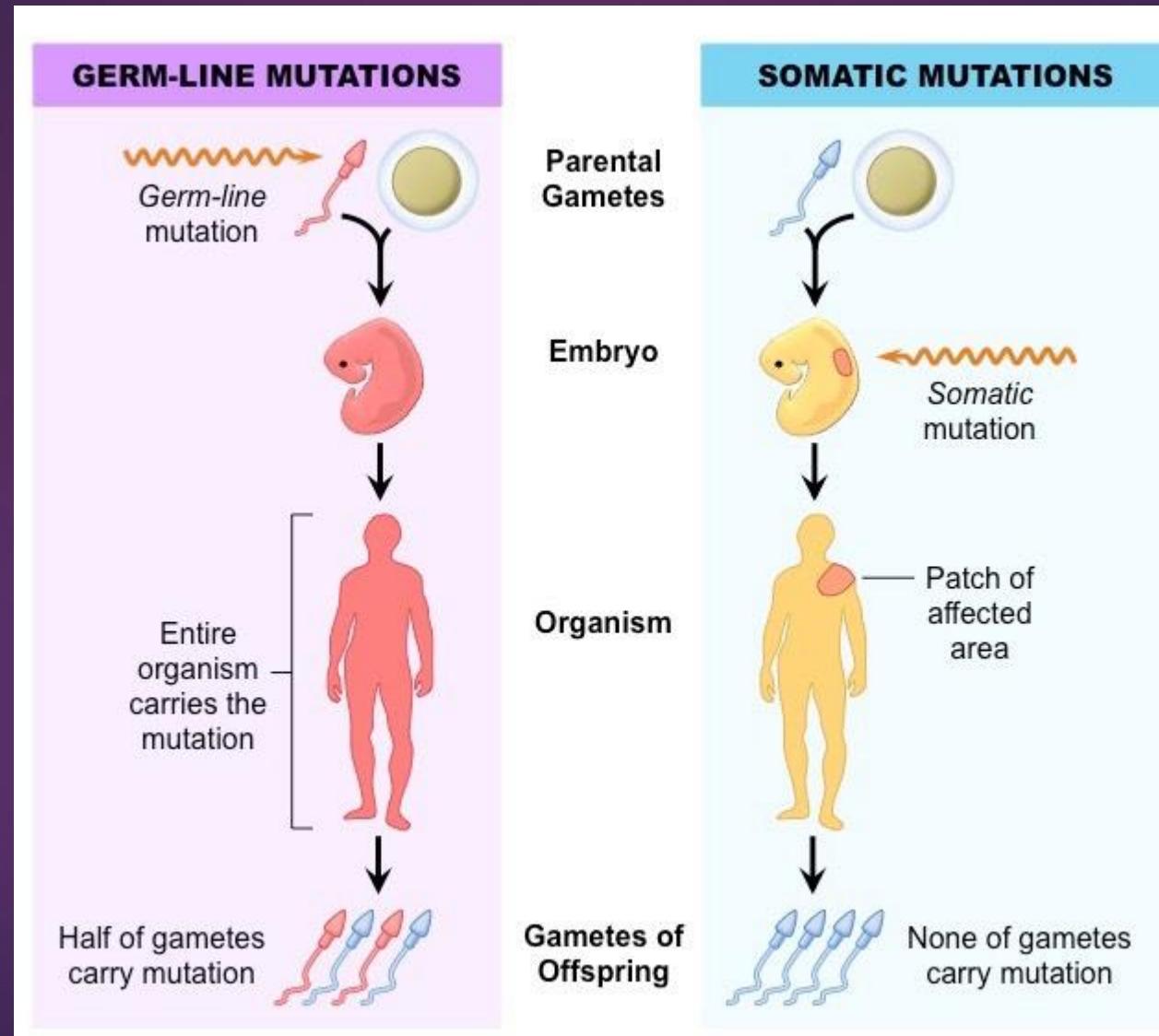
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FIGURE 7: A father and sons are affected with a Y-linked disorder, which is

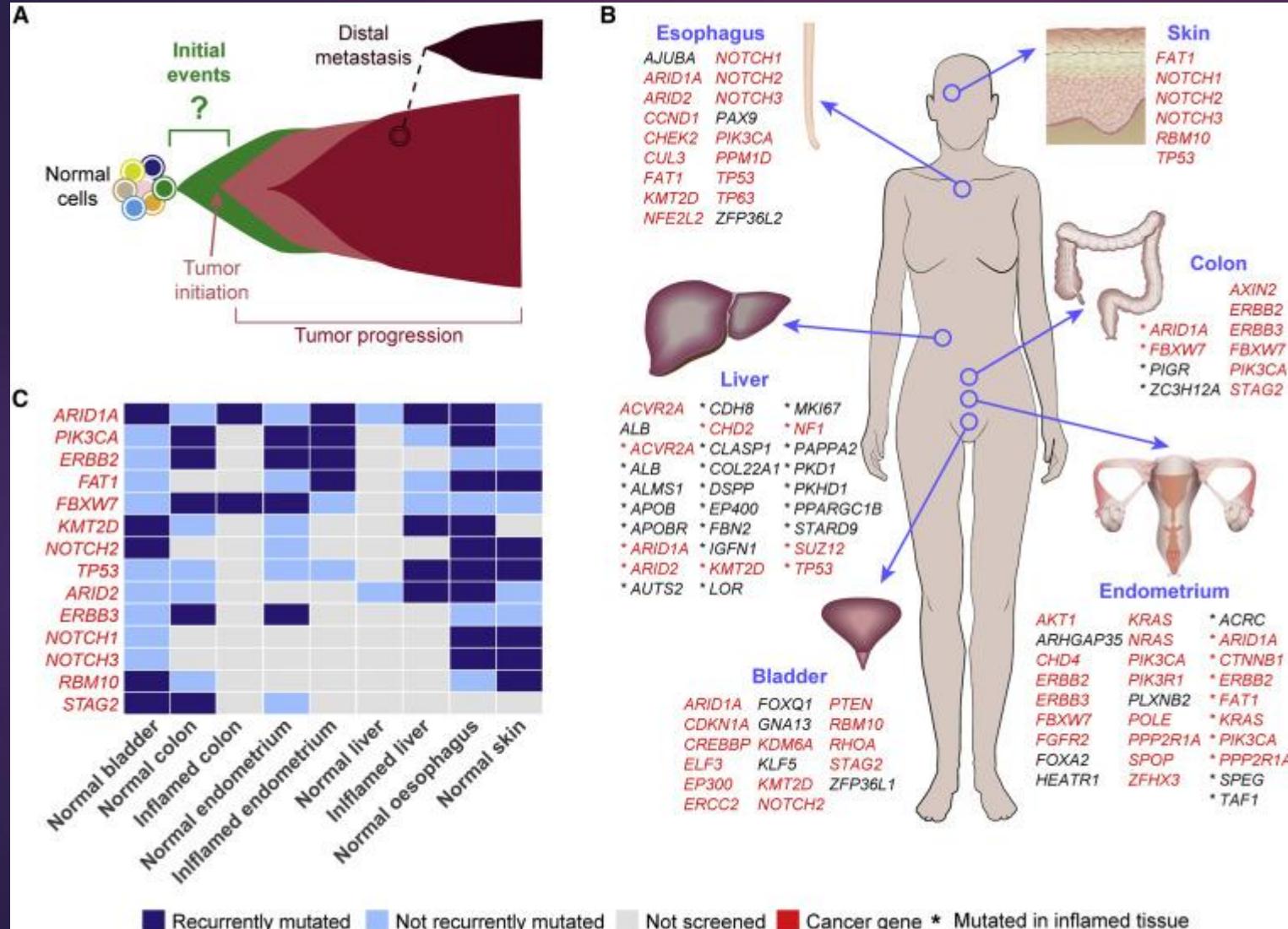
Chromosome diseases, examples

- ▶ 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



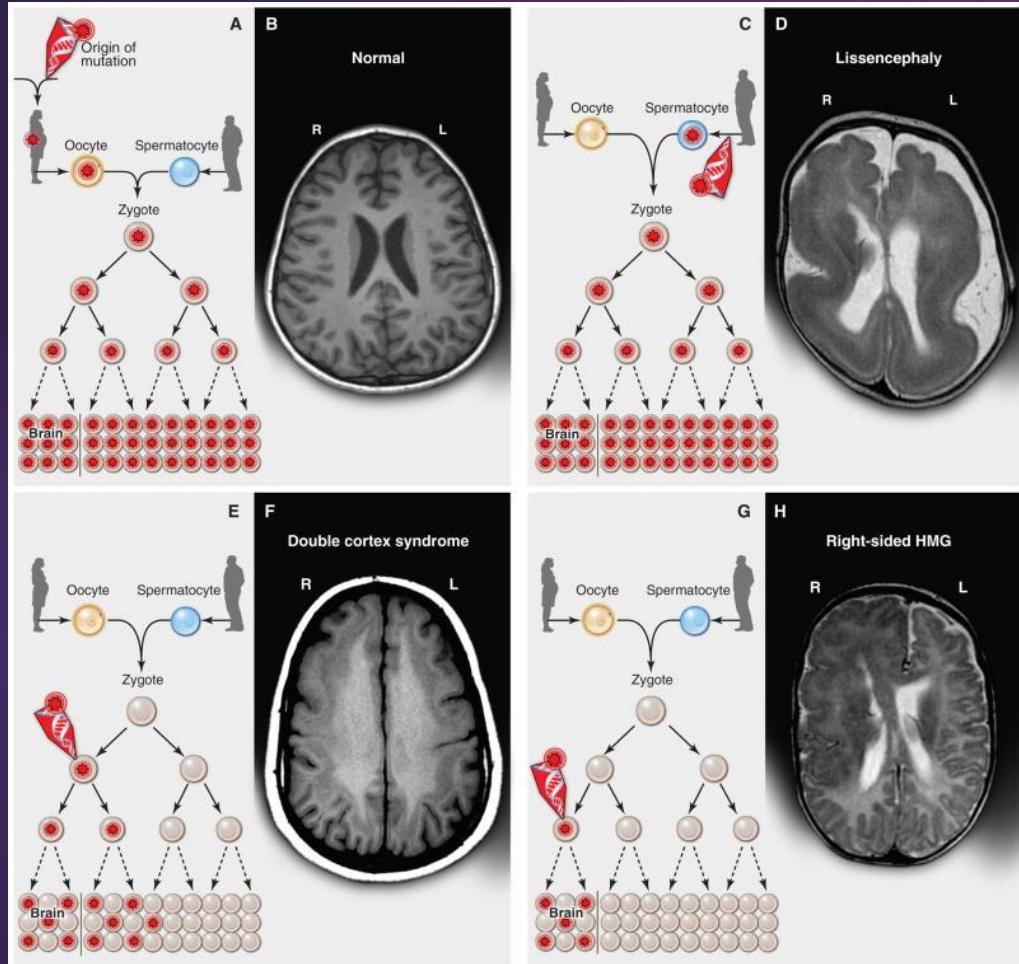
Genetic diseases of somatic cells, example: cancer



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).

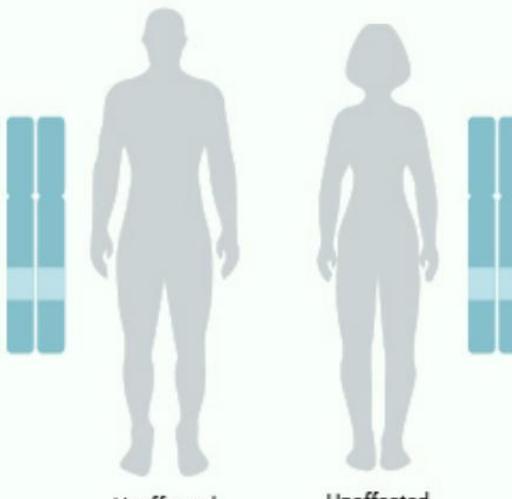
Genetic diseases of somatic cells, example: epilepsy



(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).

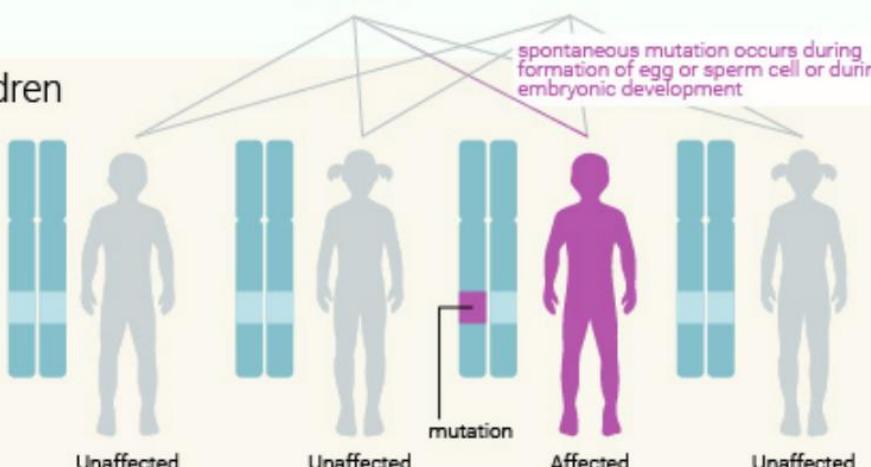
Autosomal Dominant - New Mutation

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.

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

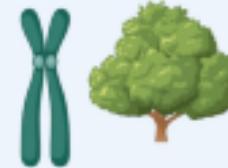
- Yields of genetic testing for diagnosis are between 50-66% in early onset kidney disease



- 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

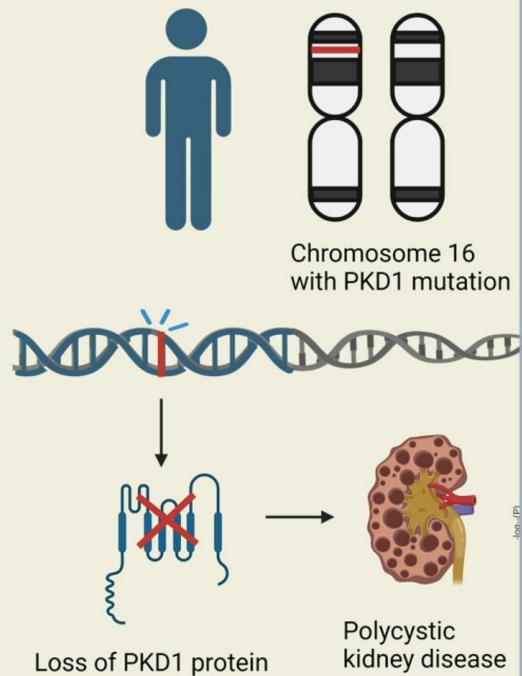


Clinical genomics is well established for monogenic kidney disease, with a developing understanding of polygenic factors in kidney disease. Research is underway to further understand polygenic factors in CKD through development of polygenic risk scores, pharmacogenomics and potential clinical applications.

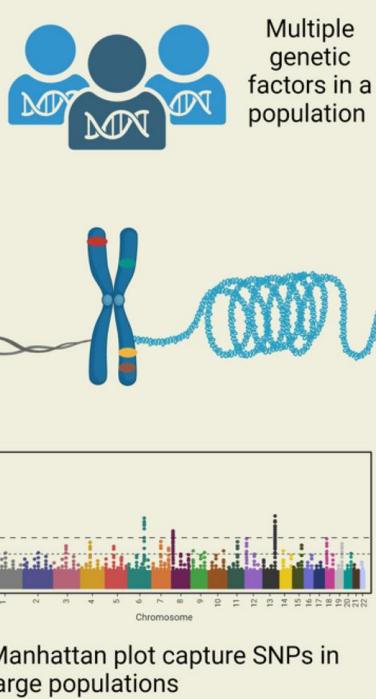
Made with BioRender

Monogenic vs polygenic diseases

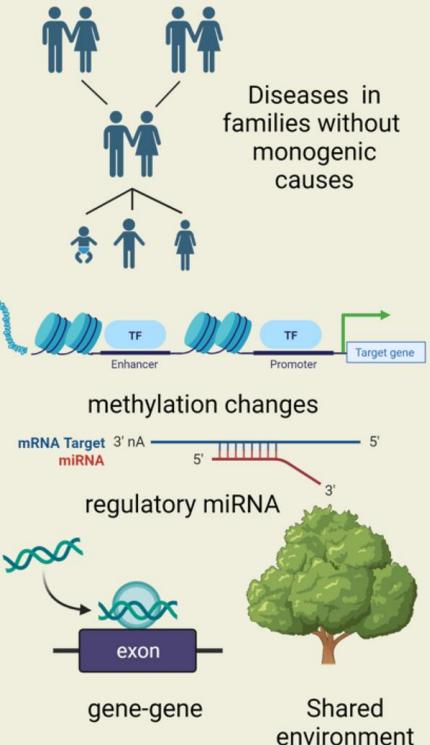
Single gene disorders



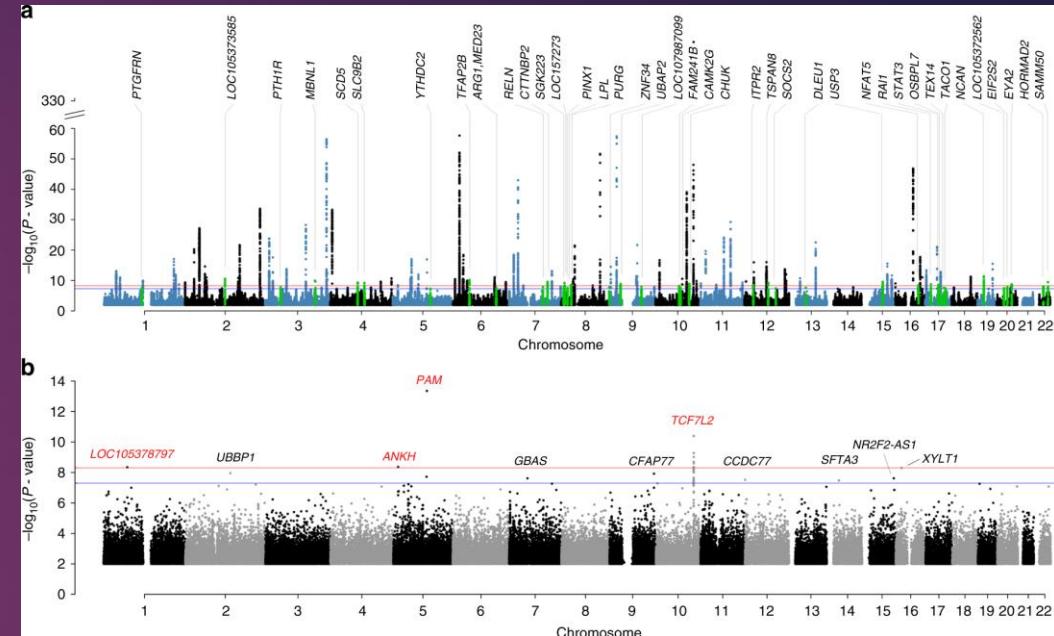
Polygenic risk



Familial risk



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



Manhattan plots of common- and rare-variant associations for T2D. **a** GWAS results for common variants ($\text{MAF} \geq 0.01$) in the meta-analysis. The 39 novel loci are annotated and highlighted in green. **b** GWAS results of rare variants ($0.0001 \leq \text{MAF} < 0.01$) 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 $P < 5 \times 10^{-9}$.

Heritability of kidney function

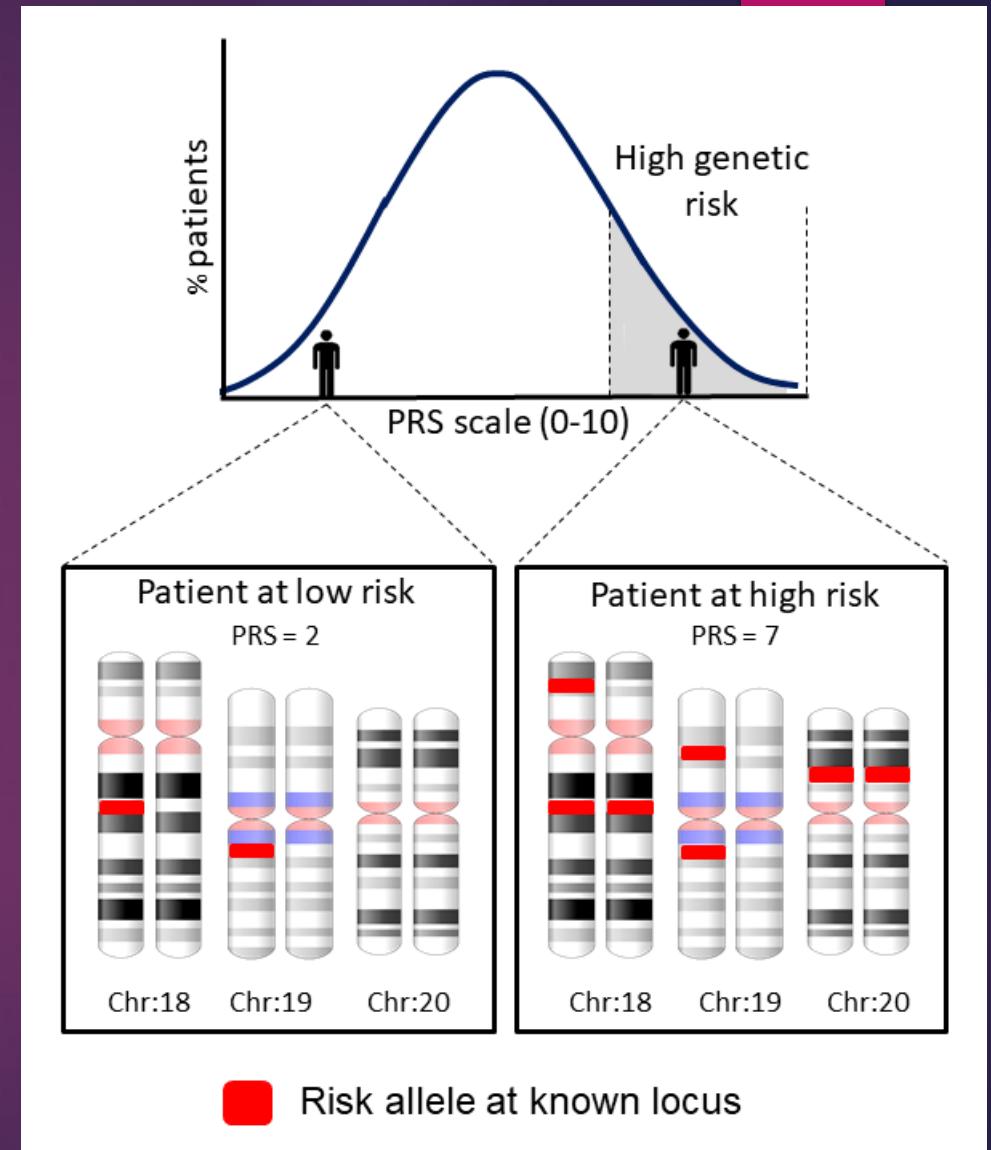
Autosomal dominant: 50%
Autosomal recessive: 25%

GWAS = 7.1-20.3%

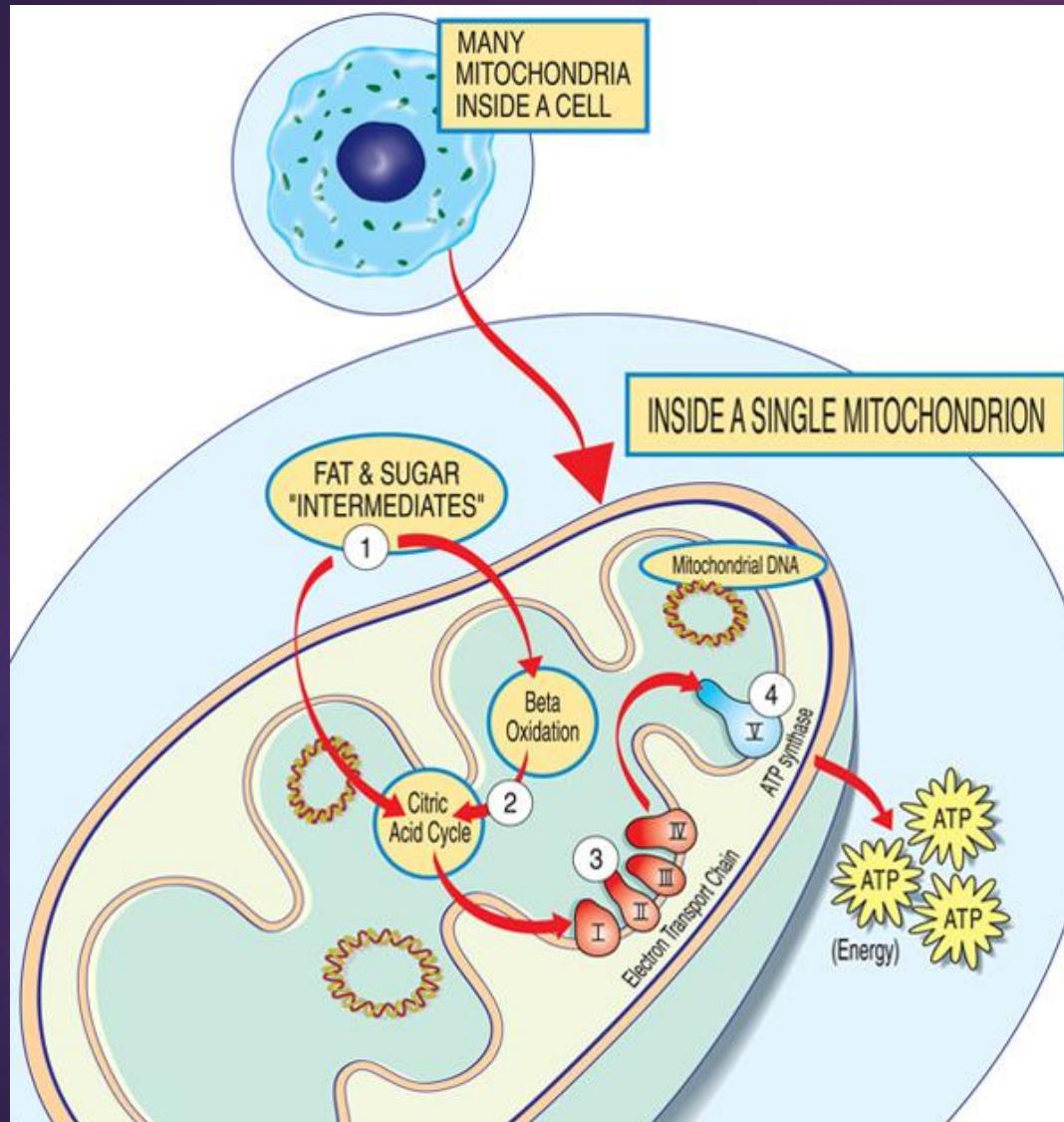
Family studies = 35-69%

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).

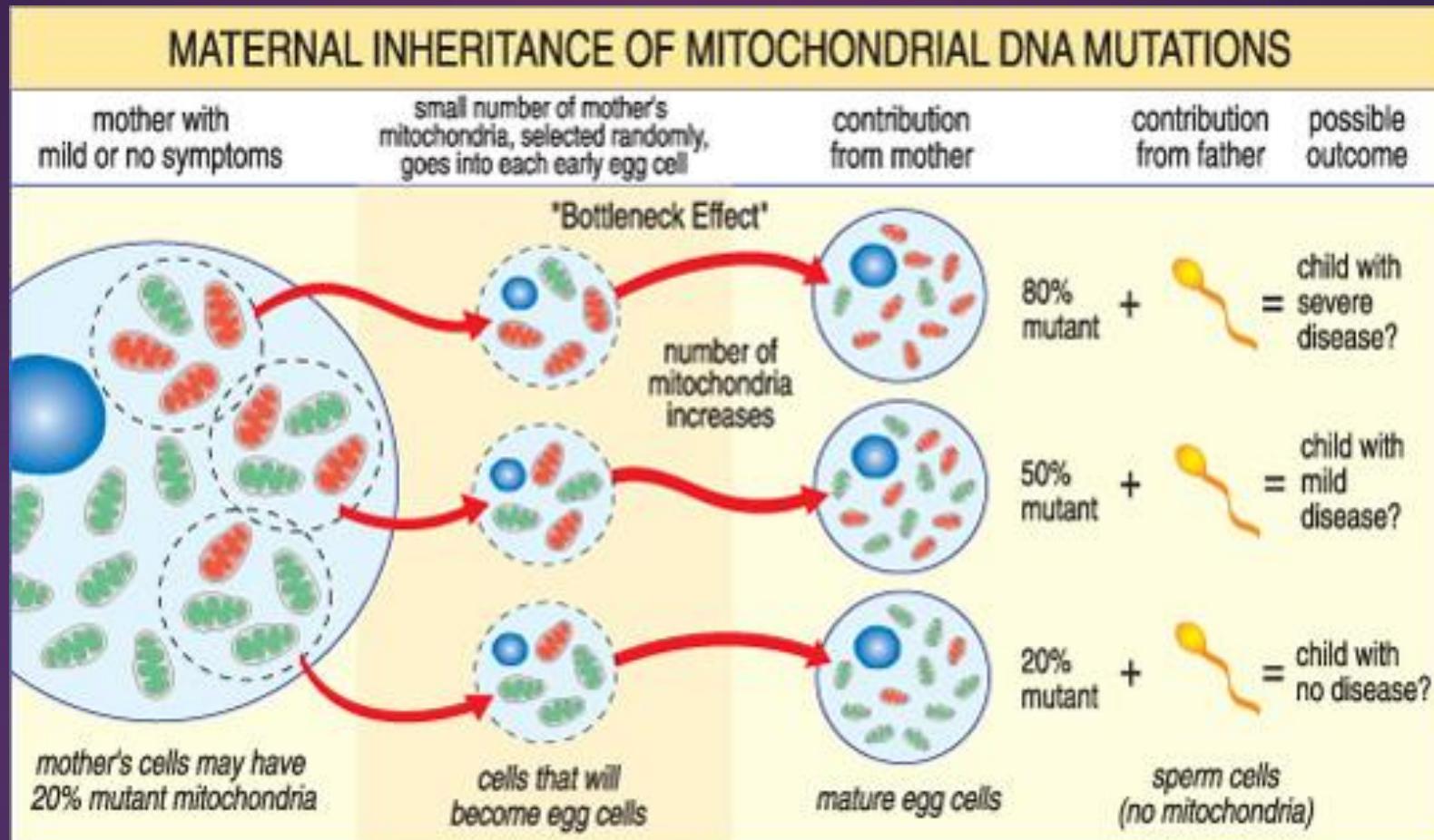


Mitochondrial inheritance



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.

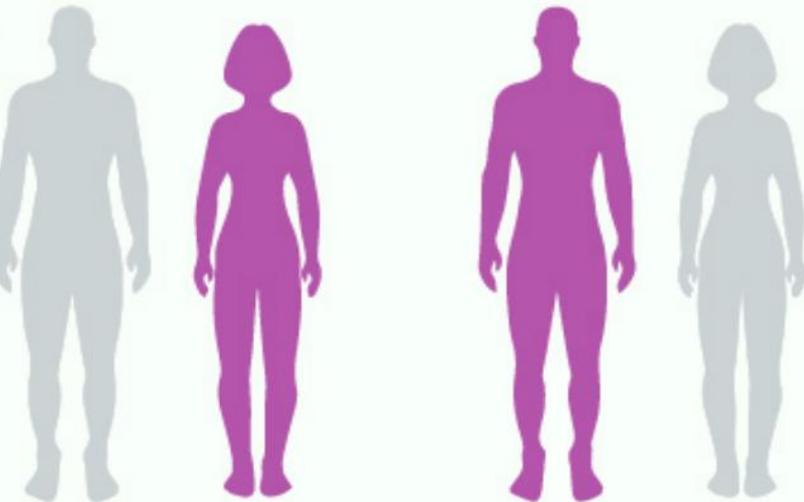
Mitochondrial inheritance



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

Mitochondrial

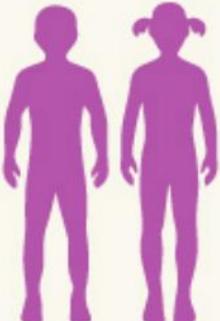
Parents



Father Unaffected Mother Affected

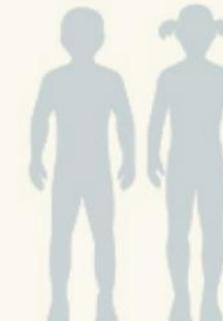
Father Affected Mother Unaffected

Children



Children Affected

Mitochondrial DNA is only
inherited from the mother



Children Unaffected

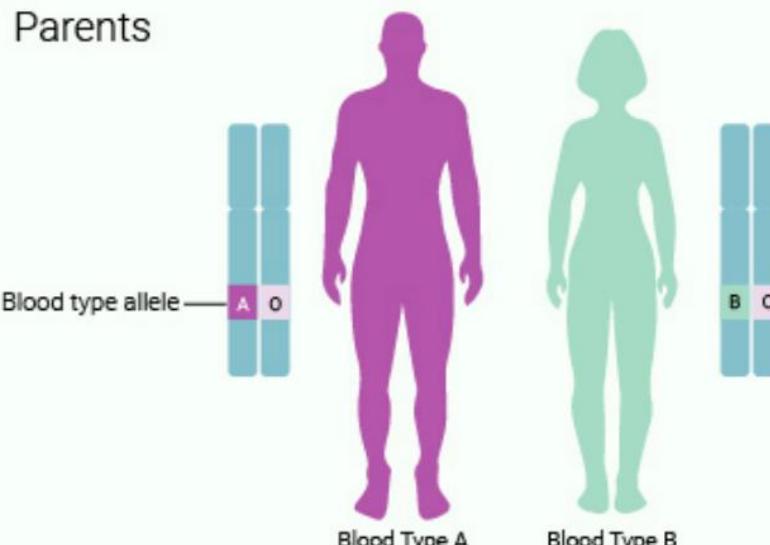


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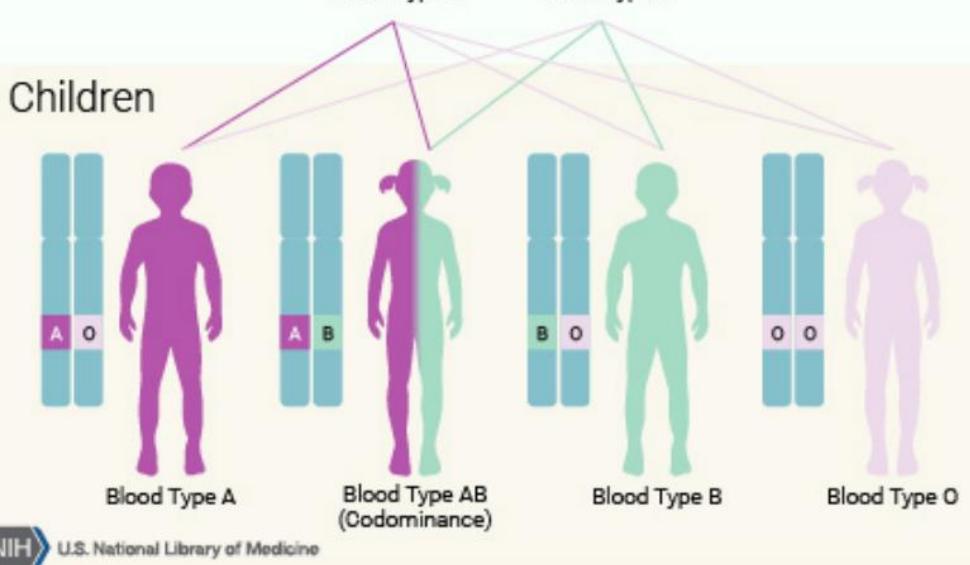
FIGURE 9: The inheritance of a mitochondrial disorder depends whether the mother or the father has the mutation in mitochondrial DNA.

Codominance - example Blood Type

Parents



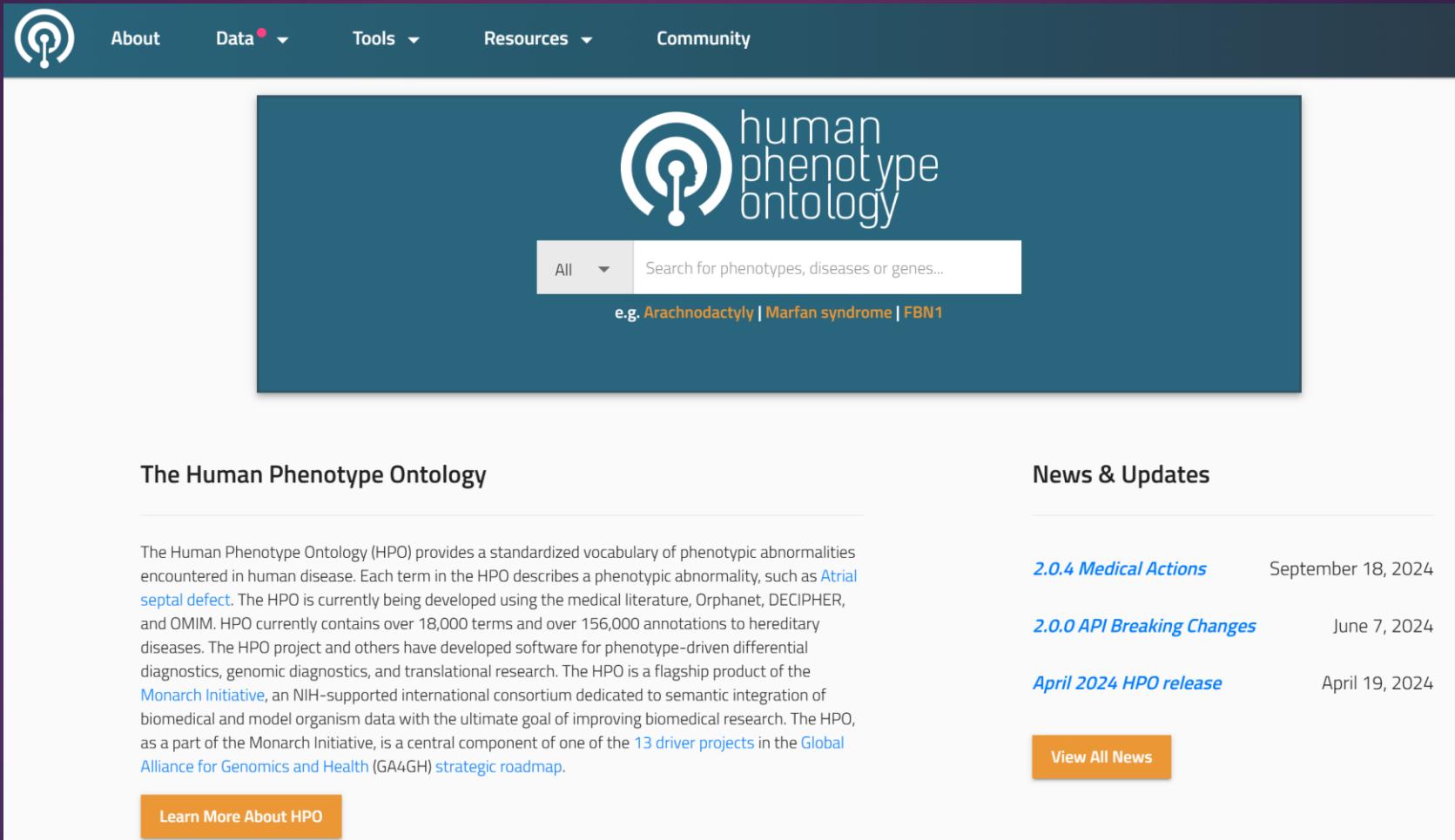
Children



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

The Human Phenotype Ontology (HPO)



The screenshot shows the HPO homepage. At the top, there's a dark green navigation bar with links for "About", "Data" (with a red dot), "Tools", "Resources", and "Community". Below the navigation is a large teal header section featuring the HPO logo (a white icon of a brain with internal structures) and the text "human phenotype ontology". A search bar contains the placeholder "Search for phenotypes, diseases or genes..." and a dropdown menu set to "All". Below the search bar is a suggestion "e.g. Arachnodactyly | Marfan syndrome | FBN1". The main content area has two columns. The left column is titled "The Human Phenotype Ontology" and contains a detailed paragraph about the HPO's purpose, history, and current status. It also includes a blue "Learn More About HPO" button. The right column is titled "News & Updates" and lists three recent news items with their dates: "2.0.4 Medical Actions" (September 18, 2024), "2.0.0 API Breaking Changes" (June 7, 2024), and "April 2024 HPO release" (April 19, 2024). A blue "View All News" button is located at the bottom of this column.

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 HPO is a flagship product of the [Monarch Initiative](#), an NIH-supported international consortium dedicated to semantic integration of biomedical and model organism data with the ultimate goal of improving biomedical research. The HPO, as a part of the Monarch Initiative, is 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

[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)

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- ▶ 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" with 86 results, including links for Disease and Gene results. The bottom section shows a detailed view of the term "Nephrotic syndrome" (HP:0000100), including its hierarchy, synonyms (A nephrosis), comments (adults: protein excretion > 3.5 g/day; children: > 2.5 mg/kg/day), cross-references (SNOMEDCT, UMLS, LOINC), and associations (Disease, Gene, Medical Actions, LDNC).

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:0000100	Nephrotic syndrome		Yes
HP:0000940	Adrenogenital syndrome		Yes
HP:0001071	Angiokeratoma corporis diffusum		Yes
HP:0001097	Keratoconjunctivitis sicca		Yes
HP:0001156	Brachydactyly		Yes
HP:0001357	Plagiocephaly		Yes

Nephrotic syndrome HP:0000100

[English](#) [Chinese](#) [Czech](#) [Dutch](#) [French](#) [German](#) [Italian](#) [Japanese](#) [Spanish](#) [Turkish](#)

Synonyms: A nephrosis

Comments: 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 less than 40 mg/m²24h and hypoalbuminemia < 2.5 mg/dL.

Cross References: SNOMEDCT, UMLS, LOINC

[Export Associations](#) [Translate your language](#)

Disease Associations **Gene Associations (Inferred)** **Medical Actions** **LDNC Associations**

Disease Name: Nephrotic syndrome, type 1

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.

OMIM: An Online Catalog of Human Genes and Genetic Disorders

The screenshot shows the main page of the OMIM website. At the top, there is a navigation bar with links for About, Statistics, Downloads, Contact Us, MIMmatch, Donate, Help, and a question mark icon. Below the navigation bar is the OMIM logo, which includes a circular icon with the letters 'OMIM' inside, followed by the text 'OMIM Human Genetics Knowledge for the World'. The main title 'OMIM®' is prominently displayed in large, bold, black font. Below it, the subtitle 'An Online Catalog of Human Genes and Genetic Disorders' is shown in a smaller, bold, black font. A date 'Updated November 21st, 2024' is also present. A search bar with the placeholder 'Search OMIM for clinical features, phenotypes, genes, and more...' and a magnifying glass icon is located below the main title. Below the search bar are three links: 'Advanced Search : OMIM, Clinical Synopses, Gene Map', 'Need help? : Example Searches, OMIM Search Help, YouTube OMIM Video Tutorials', and 'Mirror site : <https://mirror.omim.org>'. A note at the bottom states 'OMIM is supported by a grant from NHGRI, licensing fees, and generous contributions from people like you.' A blue link 'Make a donation!' is centered below this note. At the bottom left is the logo for 'McKUSICK-NATHANS Department of Genetic Medicine' featuring a stylized blue 'M'. At the bottom right is the logo for 'JOHNS HOPKINS MEDICINE' featuring a blue shield with a white cross.

OMIM Human Genetics Knowledge for the World

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.

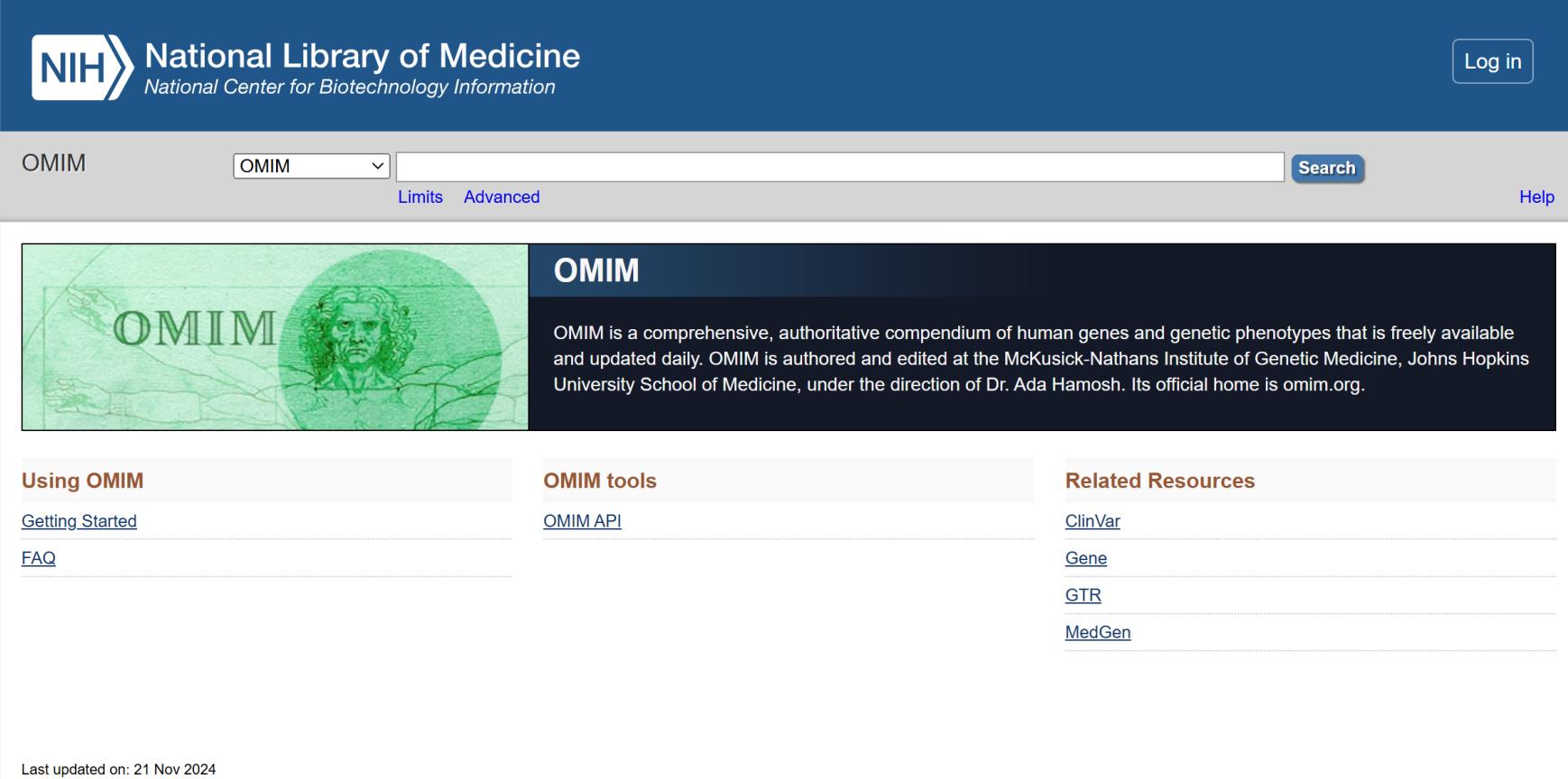
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 McKUSICK-NATHANS
Department of
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 JOHNS HOPKINS
MEDICINE

<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 and the text "National Center for Biotechnology Information". On the right side of the header is a "Log in" button. Below the header, there is a search bar with the word "OMIM" in it, followed by a dropdown menu set to "OMIM", a search input field, a "Search" button, and links for "Limits" and "Advanced". To the right of the search bar is a "Help" link. The main content area has a dark background. On the left, there is a green circular graphic featuring a classical bust and the word "OMIM". To the right of the graphic, the word "OMIM" is written in large white letters. Below this, a 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 main content area, there are three 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 of the page, there is a small text "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 and a "Log in" button. Below the header is a search bar with a dropdown menu, a search input field, and a "Search" button. A "Help" link is also present. The main content area has a dark background. On the left, a vertical DNA sequence is displayed: ACTGATGGTATGGGCCAAGAGATATCTCAGGTACGGCTGTCATCACTTAGACCTCACACAGGGCTGGGCATAAAAGTCAGGGCAGAGCCCATGGTGCATCTGACTCCTGAGGAGAAGTGCAGGTTGGTATCAAGGTTACAAGACAGGTTGGCACTGACTCTCTGCCTATTGGTCTAT. To the right of the sequence, the word "ClinVar" is written in white. Below "ClinVar", a subtitle states: "ClinVar aggregates information about genomic variation and its relationship to human health." At the bottom of the page, there 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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