Common Genetic Problems in Internal Medicine

Review in Internal Medicine for Resident 2

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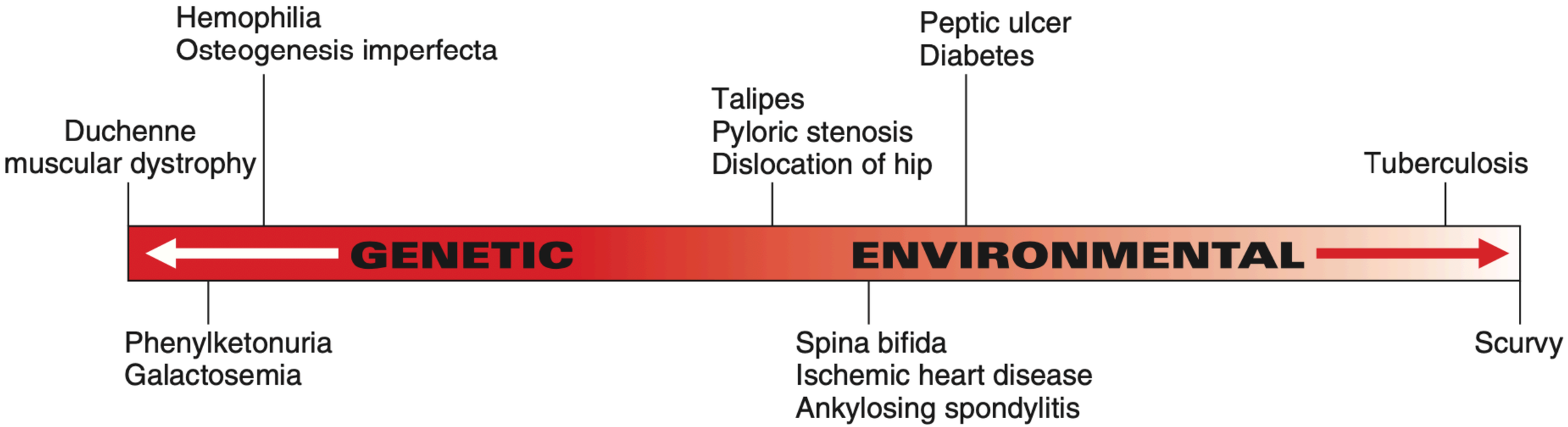
MEDICAL GENETICS AND GENOMICS ASSOCIATION

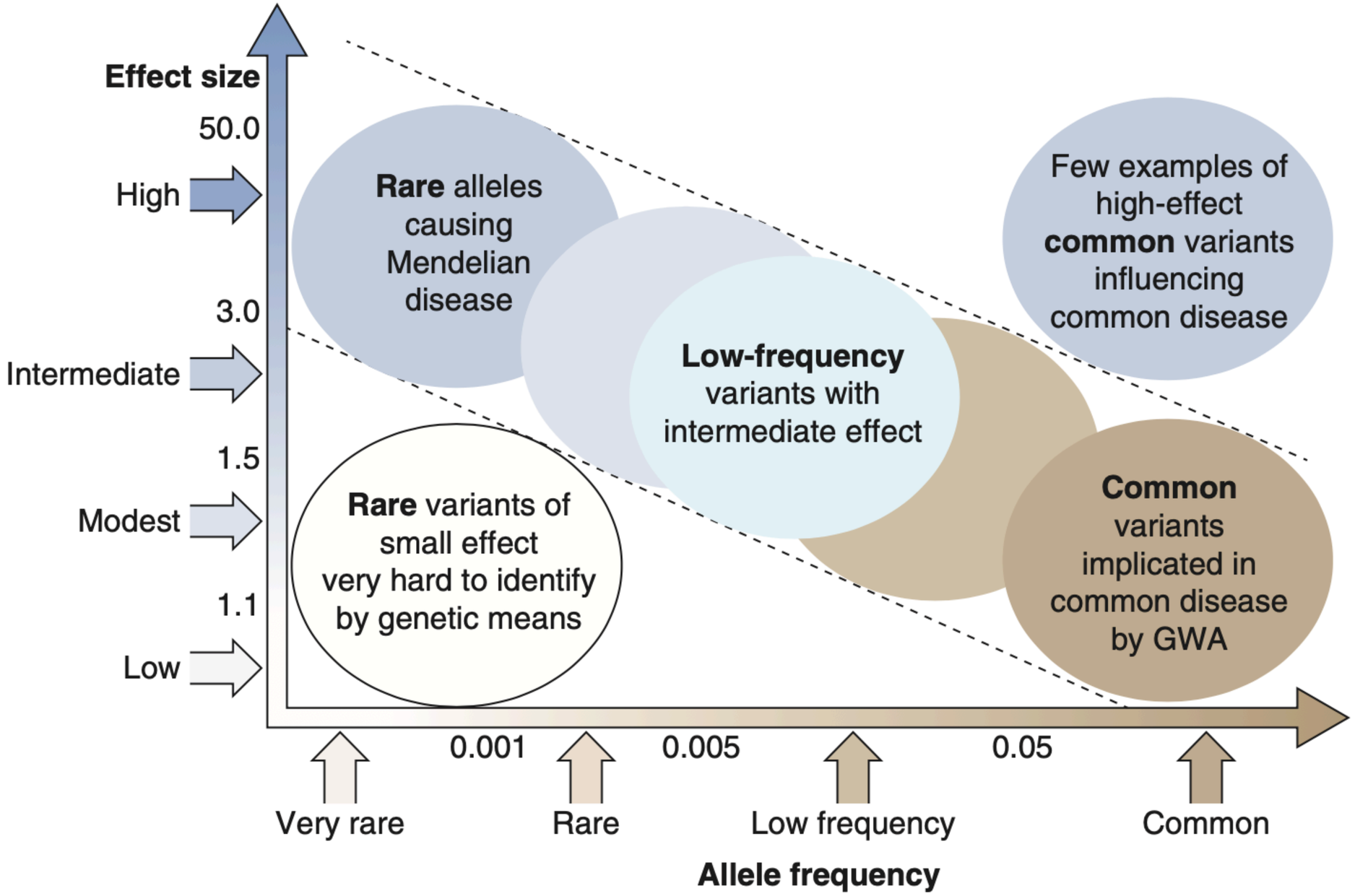
Mahidol University
Faculty of Medicine Ramathibodi Hospital

Genetic Disease = Action of genes + Environment



*"Every individual has his or her own unique constitution of gene products, produced in response to the **combined** inputs of the **genome sequence** and one's particular set of **environmental exposures** and experiences"*

Thompson & Thompson Genetics in Medicine 8th Edition, Emery's Elements of Medical Genetics 15th Edition



Emery's Elements of Medical Genetics 15th Edition.

Genetics and Genomics in Medicine

Classical Categories of Genetic Disease

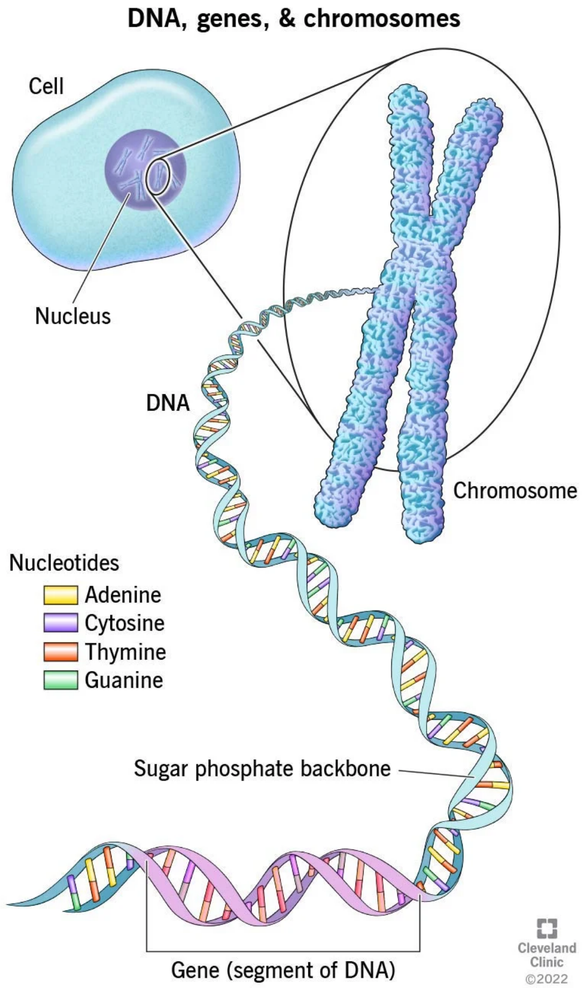
Chromosome Disorders

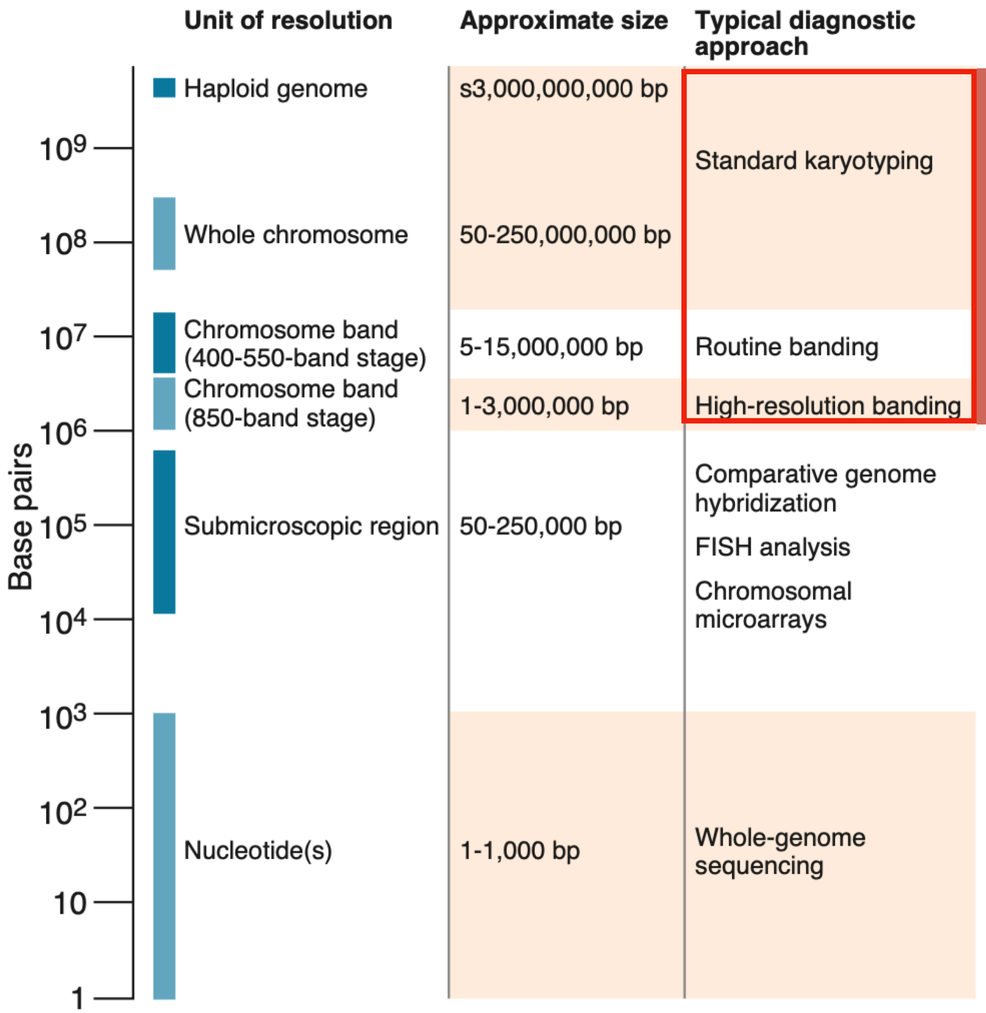
Single-Gene Defect

Multifactorial Disease with Complex Inheritance

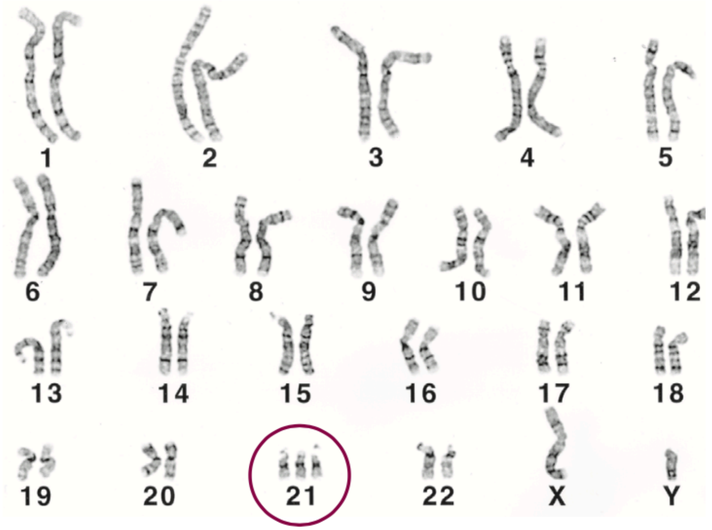
Thompson & Thompson Genetics in Medicine 8th Edition

Chromosome Disorders



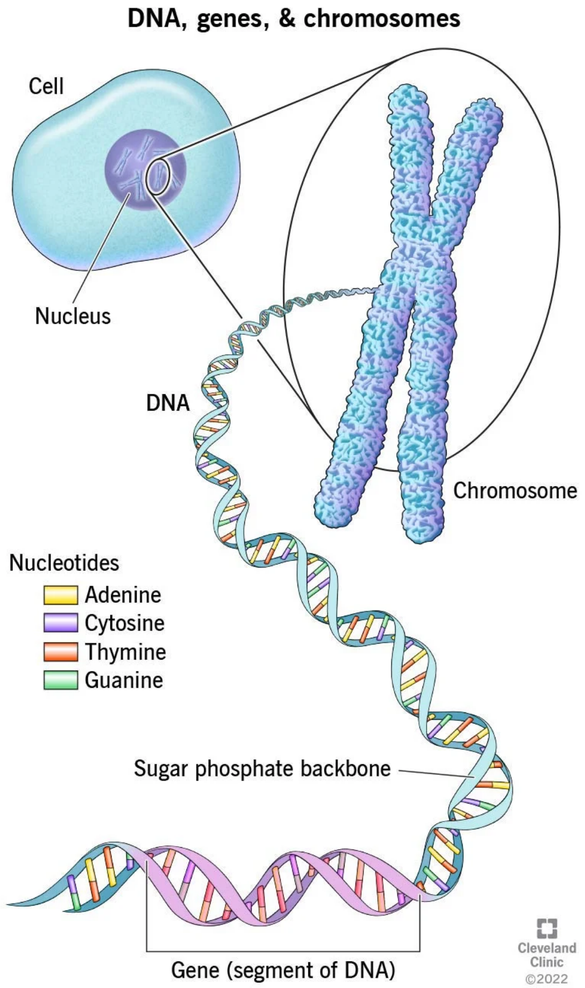


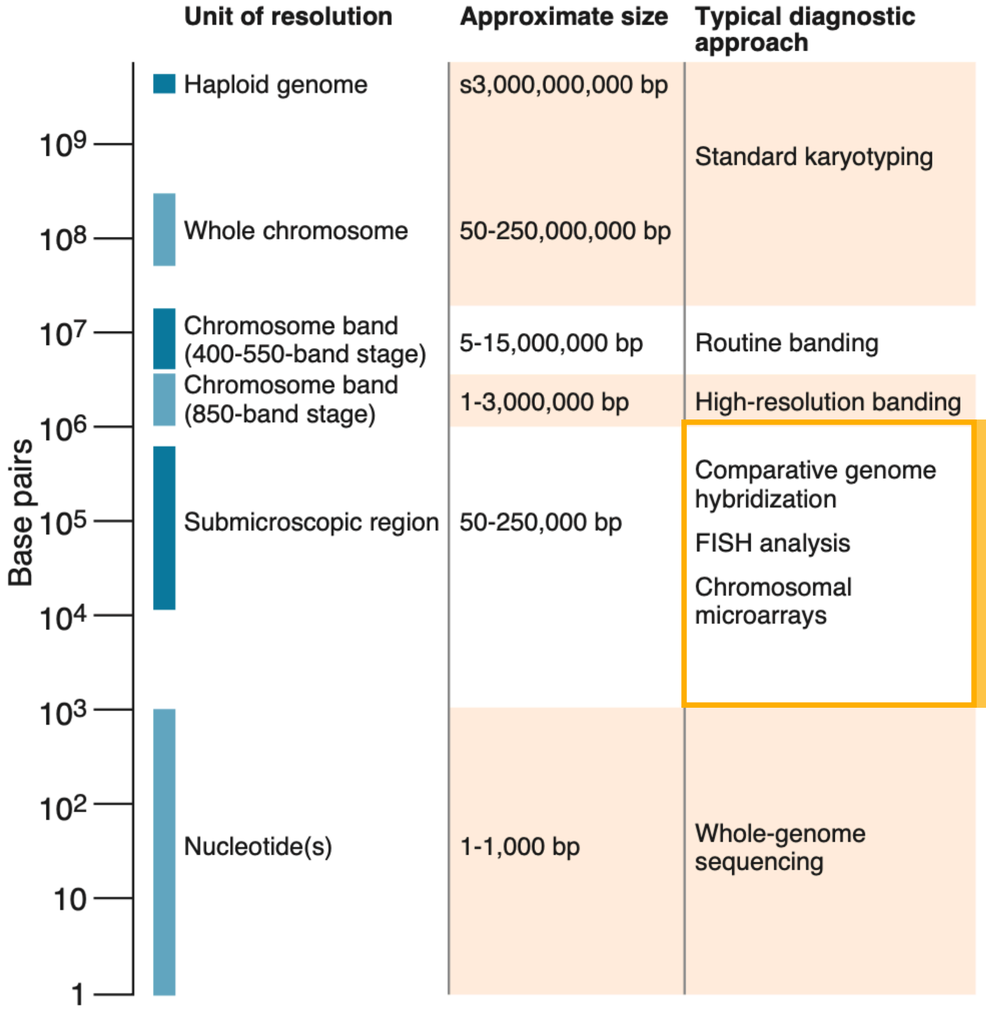
Chromosome Disorders



Thompson & Thompson Genetics in Medicine 8th Edition

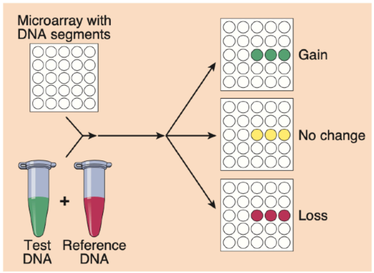
Microdeletion





Disorder	Location
1q21.1 deletion/duplication syndrome	1q21.1
Williams syndrome	7q11.23
Prader-Willi/Angelman syndrome	15q11-q13
16p11.2 deletion/duplication syndrome	16p11.2
Smith-Magenis syndrome	17p11.2
dup(17)(p11.2p11.2)	
DiGeorge syndrome/velocardiofacial syndrome	22q11.2
Cat eye syndrome/22q11.2 duplication syndrome	
Azoospermia (AZFc)	Yq11.2

Microdeletion



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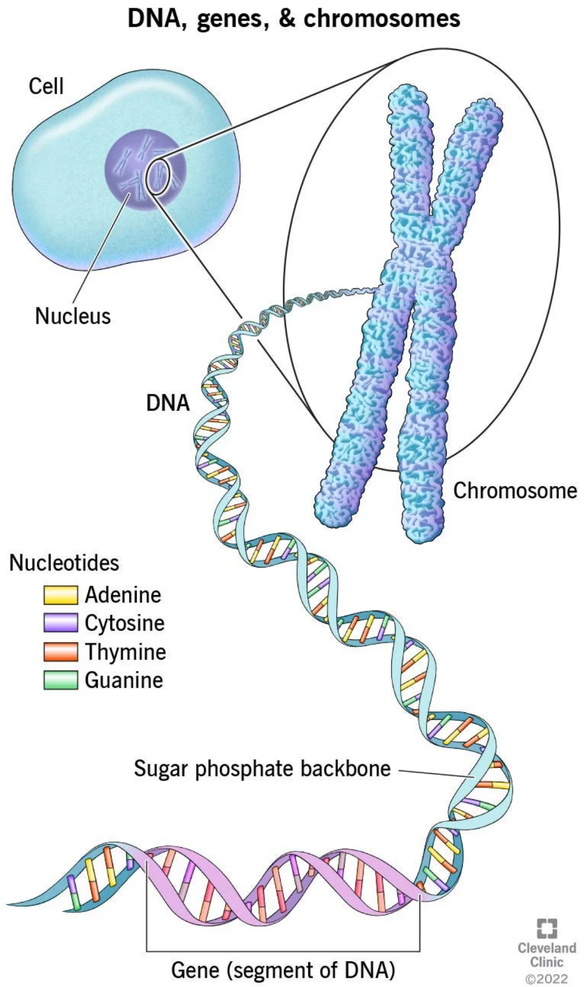
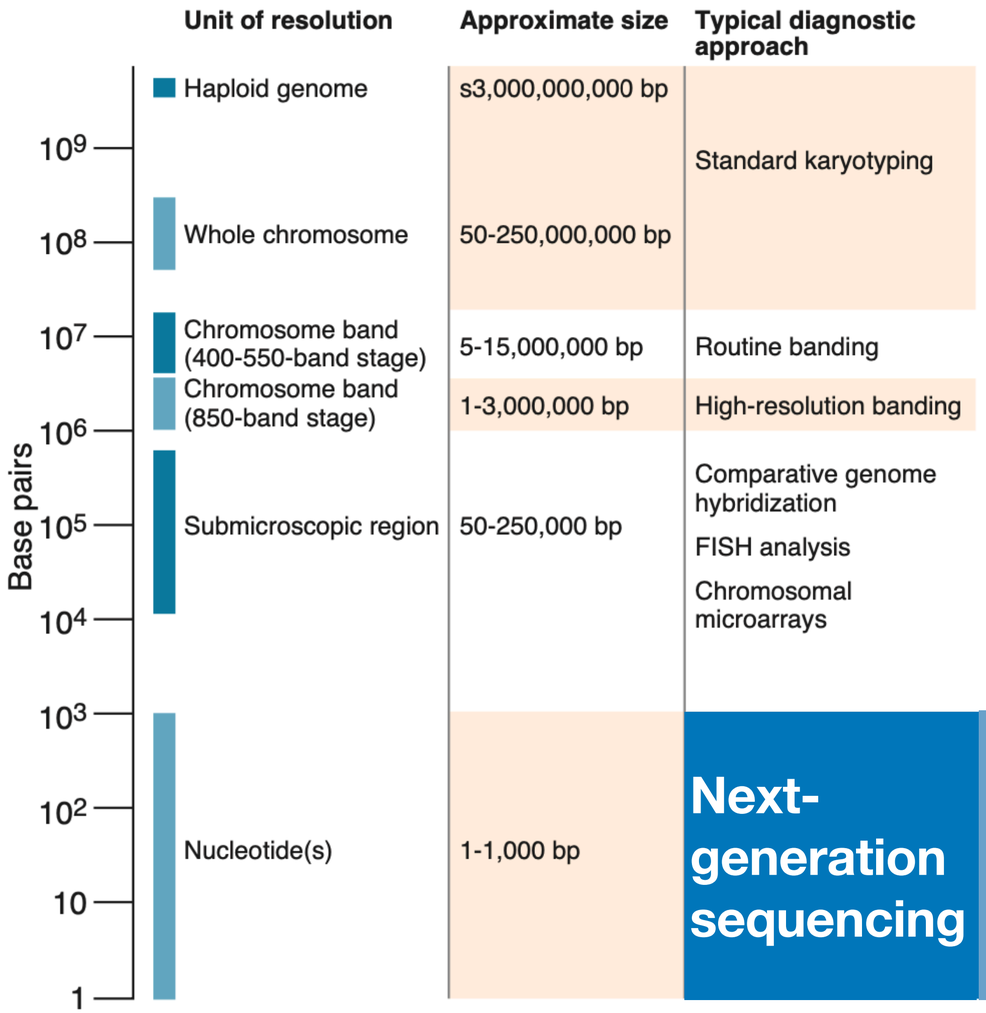
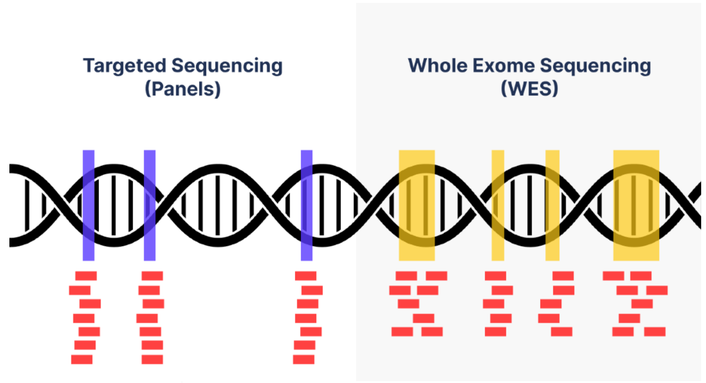
Single-Gene Defect







Single-Gene Defect

Thompson & Thompson Genetics in Medicine 8th Edition

General Considerations

Terminology

Mutation ≠ **Polymorphism**

A **permanent change** in the nucleotide sequence

A variant with a frequency **above 1%**

Replace both terms by

Variant

Genet Med 17, 405–423 (2015).

General Considerations

Variant Modifiers; 5-tier System of Classification

1. Pathogenic	> 95% certainty of pathogenicity
2. Likely Pathogenic	> 90% certainty of pathogenicity
3. Uncertain Significance	
4. Likely Benign	> 90% certainty of benign
5. Benign	> 95% certainty of benign

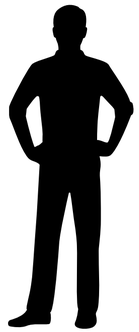
Clinicians and patients were willing to tolerate a slightly higher chance of error, leading to the 90-95% decision

Genet Med 17, 405–423 (2015).

Pedigree

Individual

Male	Female	Gender not specified	Comments
b. 1925	30y	4 mo	Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol.

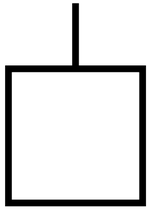
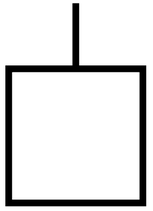
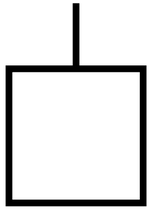
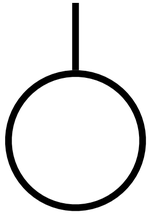
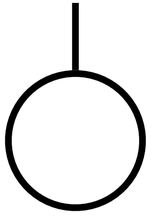
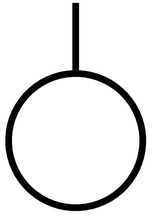
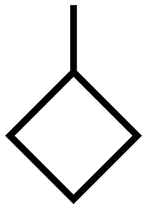
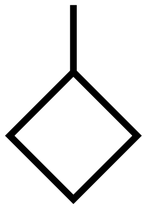
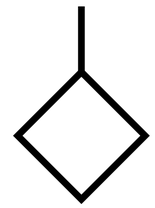


?

J Genet Counsel (2008) 17:424-433

Pedigree

Individual

Gender	Sex		
	Male	Female	Unassigned at Birth
Man/Boy	 56 years old	 AFAB 34 years old	 UAAB 28 years old
Woman/Girl	 AMAB 56 years old	 34 years old	 UAAB 28 years old
Non-binary/ Gender Diverse	 AMAB 56 years old	 AFAB 34 years old	 UAAB 28 years old

AMAB = Assigned Male at Birth, AFAB = Assigned Female at Birth, UAAB = Unassigned at Birth

J Genet Couns. 2022; 00:1–11.

Penetrance

The **probability** of the **carrier** of a germline mutation **showing signs of the disease**, from the most trivial to the most severe.

- **Fully Penetrance** = 100% penetrance

All individuals who have a disease genotype show the disease phenotype

- **Incomplete Penetrance** (eg. HNPCC, cancer)

Not all mutation carriers will manifest the disorder during a natural lifespan

- **Age-dependent Penetrance** (eg. Huntington, HSP, HMSN)

Features of the condition are not present at birth but become evident over time.

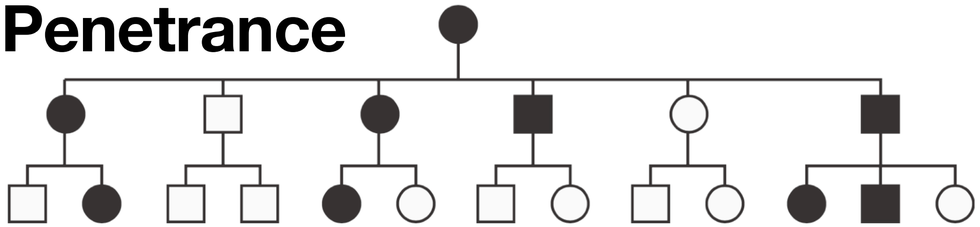
Oxford Desk Reference: Clinical Genetics and Genomics 2nd Edition

Penetrance

Pedigree

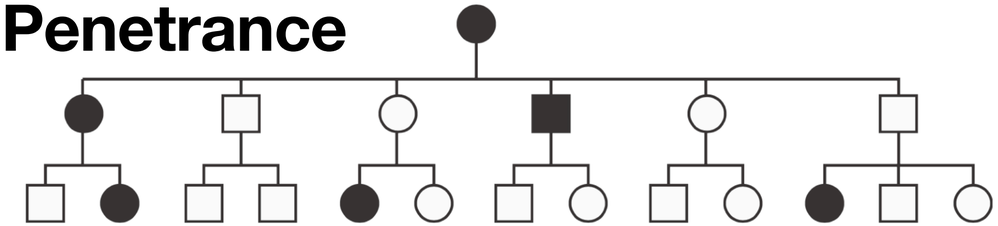
Complete Penetrance

100% Penetrance

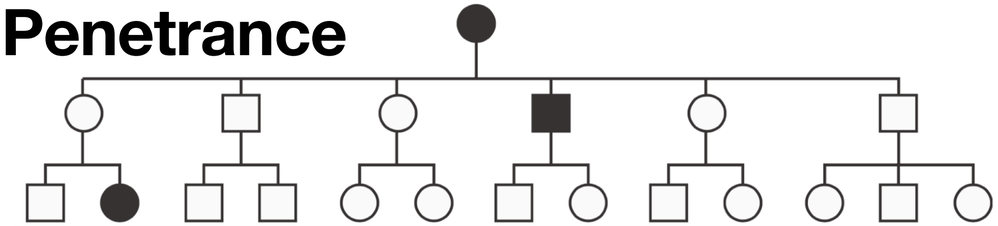


Incomplete Penetrance

67% Penetrance



33% Penetrance



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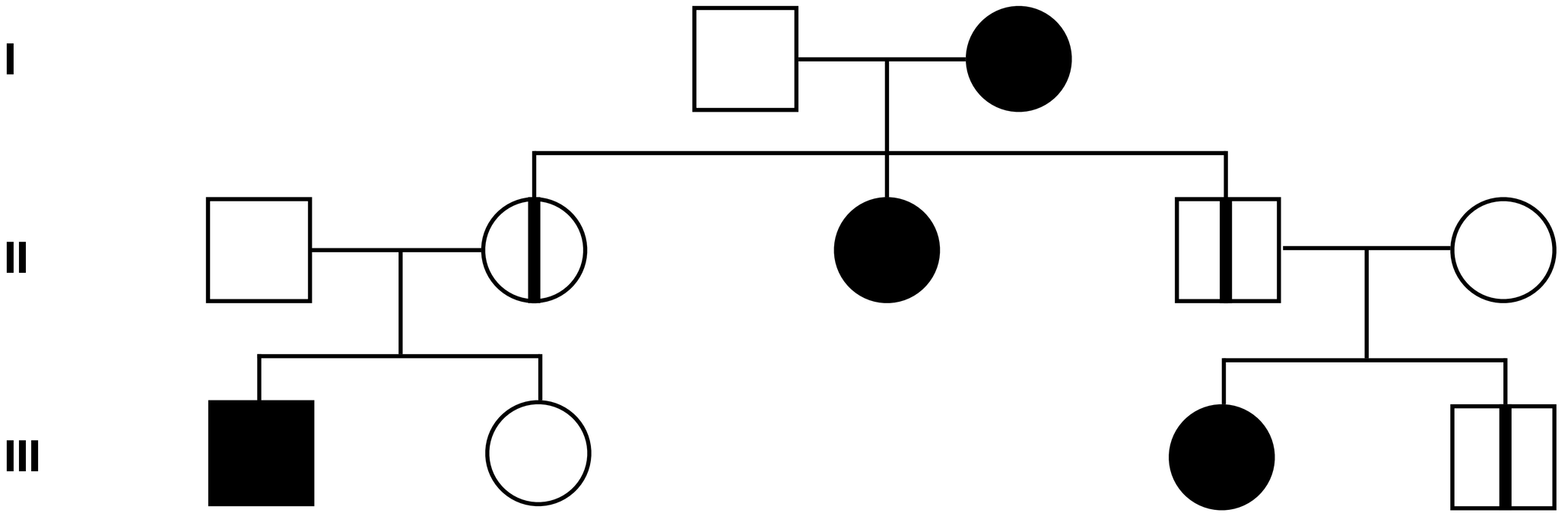
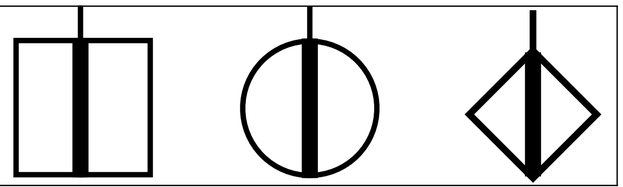
Penetrance

Asymptomatic/Presymptomatic Carrier



Asymptomatic/presymptomatic carrier :no clinical symptoms now, but could later exhibit symptoms	

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Expressivity

Variation in the **severity** of a disorder in individuals who have inherited the **same disease** alleles.

Note: the difference from penetrance, which is the percentage of individuals expressing the disorder to any degree, from the most trivial to the most severe

Variable Expression eg. TSC

Interfamilial Variation striking variation in severity between family

Intrafamilial Variation within families carrying the same mutation

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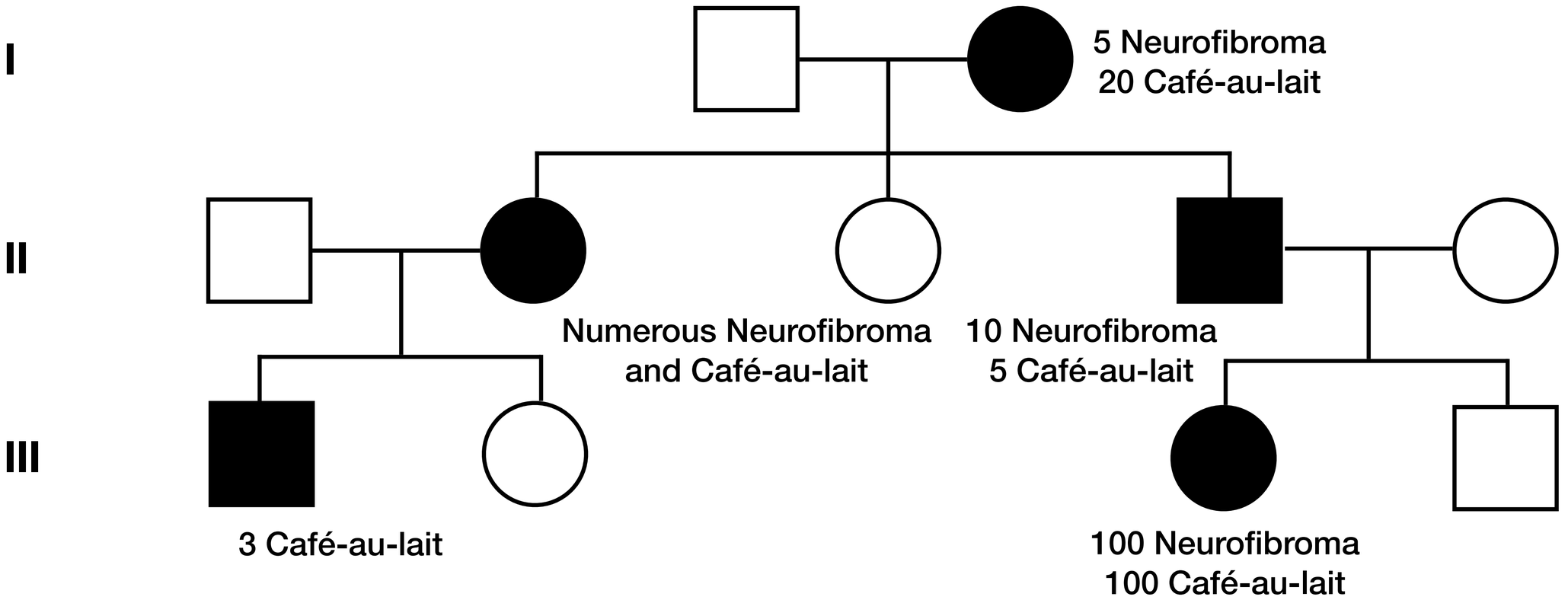
Expressivity

Intrafamilial Variation



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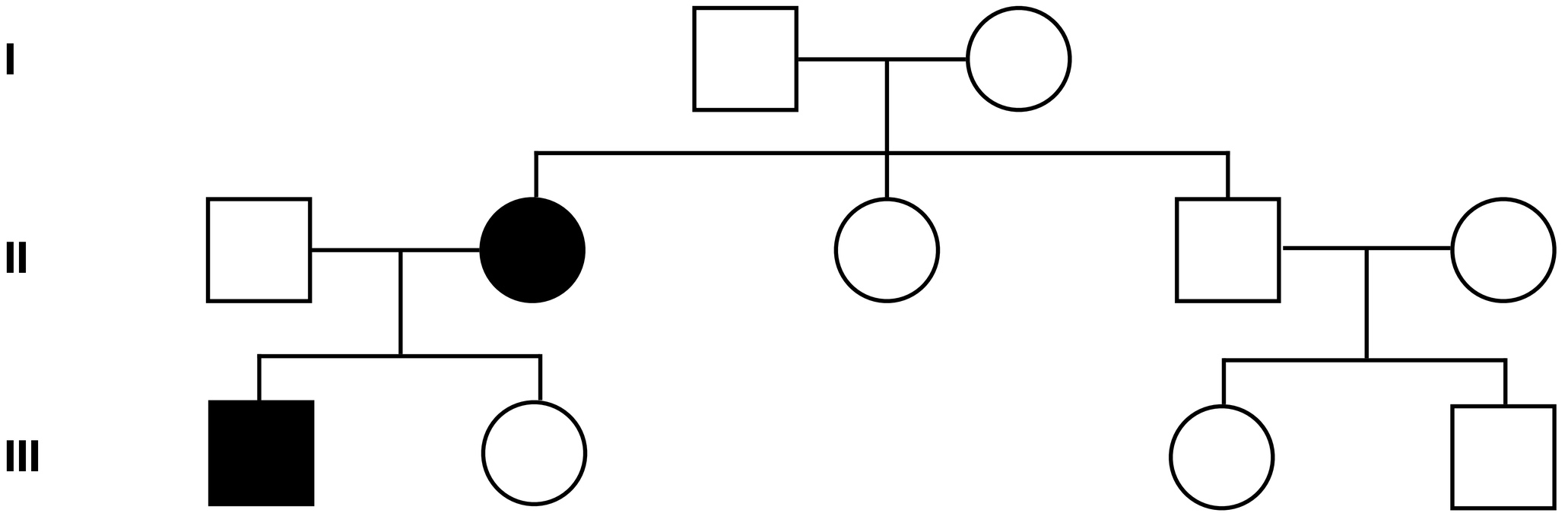
New Mutation Rate



The de novo mutation rate varies between different AD conditions.

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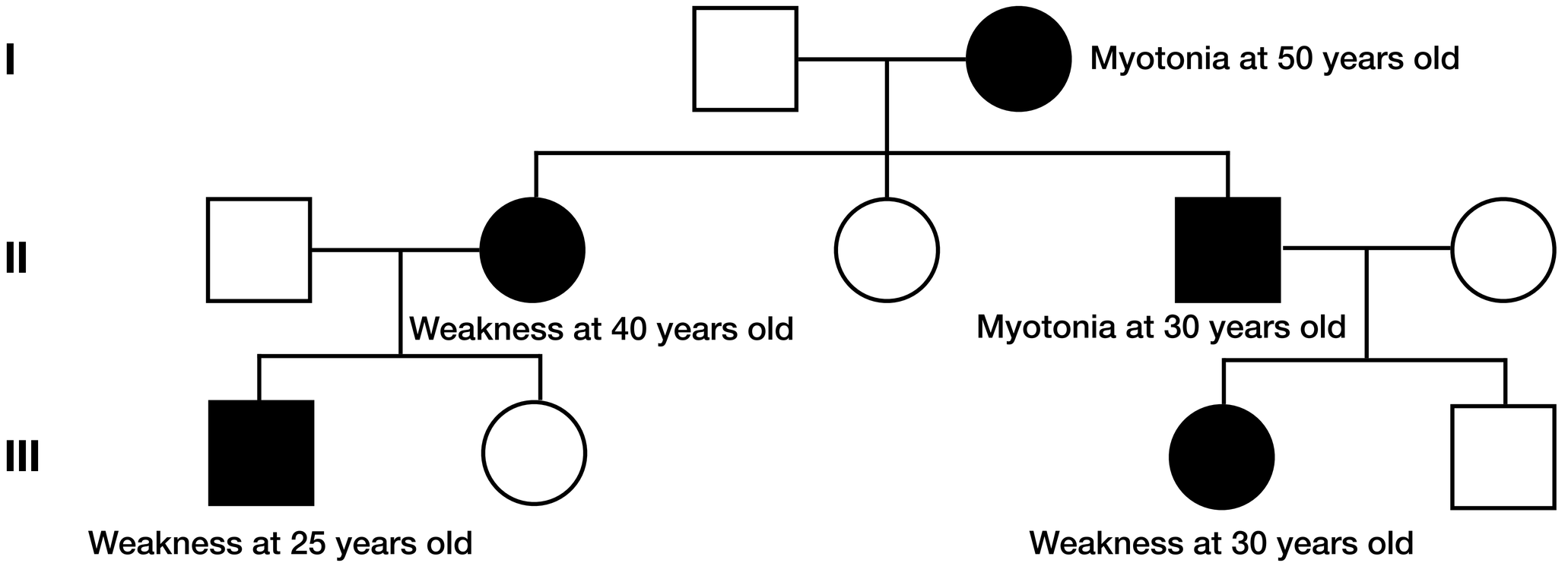
Anticipation



The worsening of disease severity in successive generations.

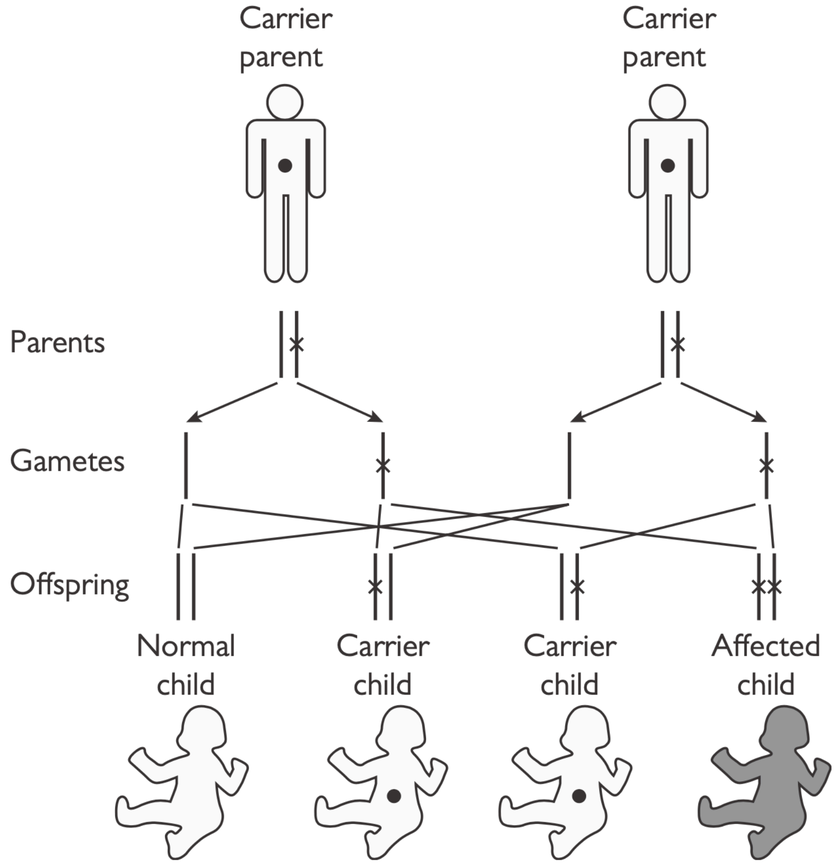
Oxford Desk Reference: Clinical Genetics and Genomics 2nd Edition

Inheritance

Autosomal Recessive

Aspect

- Homozygotes & Compound Heterozygotes
- Heterozygote - no or very mild phenotype
- Broadly similar clinical course
- Consanguinity
- Heterozygote advantage
- Founder effect
- Carrier determination



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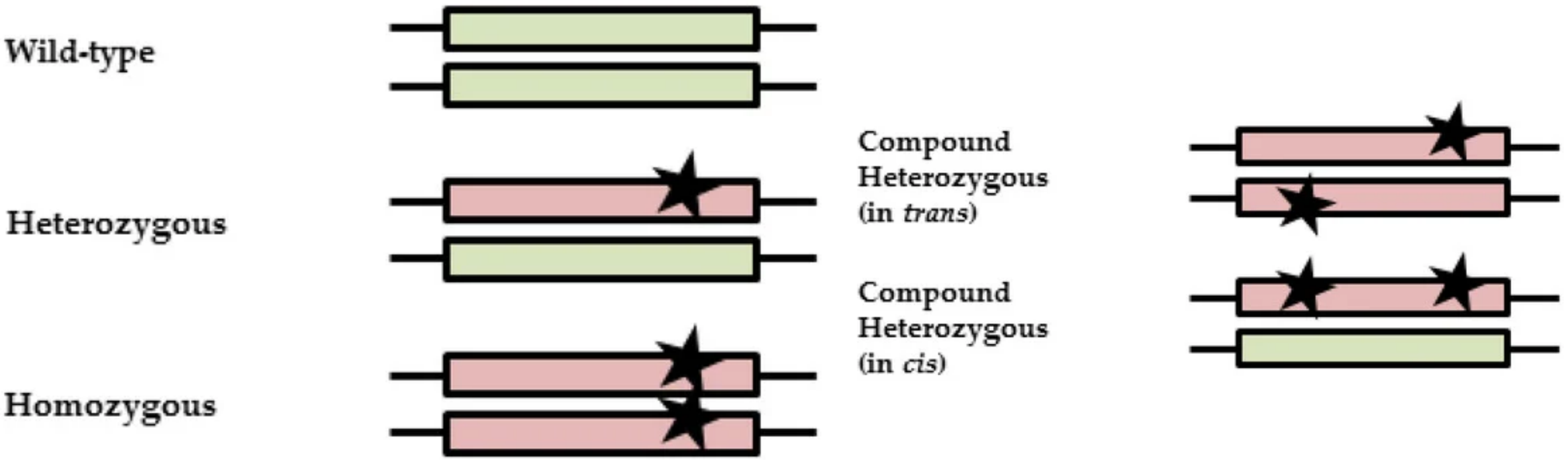
Inheritance

Autosomal Recessive



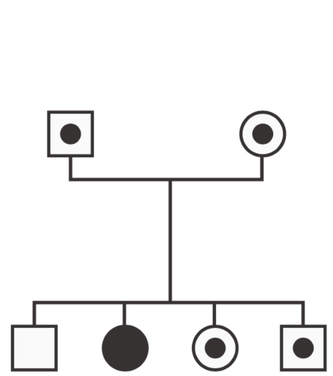
Genet Med 17, 405–423 (2015).

Inheritance

Autosomal Recessive

Typical Family Tree

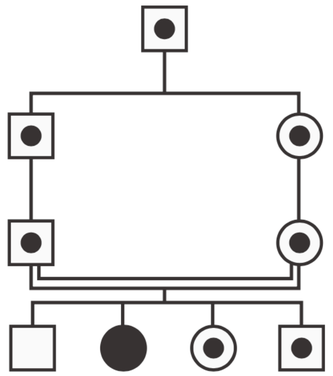
- Disease expressed only in **homozygotes** and **compound heterozygotes**.
- Parents are obligate carrier.
- **25% Risk** of affected child to carrier parents
- Risk of carrier diminish by one-half with every degree of relationship distanced from parents



25% unaffected

50% risk of carrier

25% risk of affected



Consanguinity

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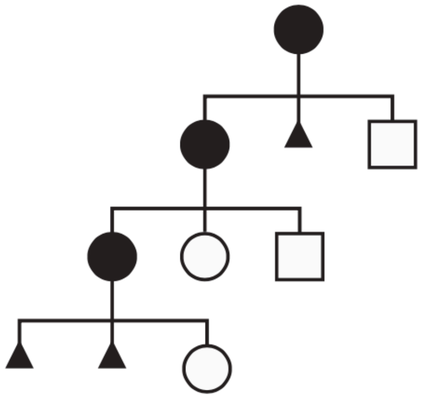
Inheritance

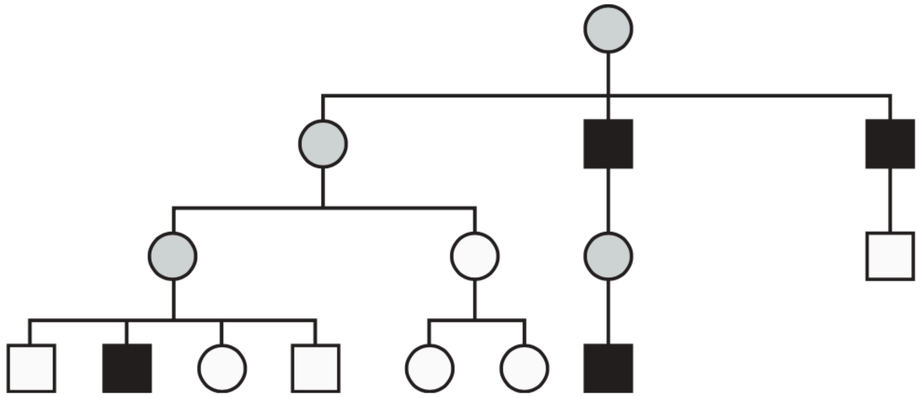
X-linked Dominant

Aspect

- Male sparing X-linked disorder
- X-linked semi-dominant
- Manifests **very severe in males** leading to
  - **Spontaneous loss**
  - **Neonatal death**



Spontaneous loss of affected male pregnancy



X-linked semi-dominant inheritance

- severely in males and mildly in females
- For a mildly affected female, 50% of her sons will be severely affected and 50% of her daughters will be mildly affected
- Daughters of an affected male are mildly affected and none of his sons inherit the condition.

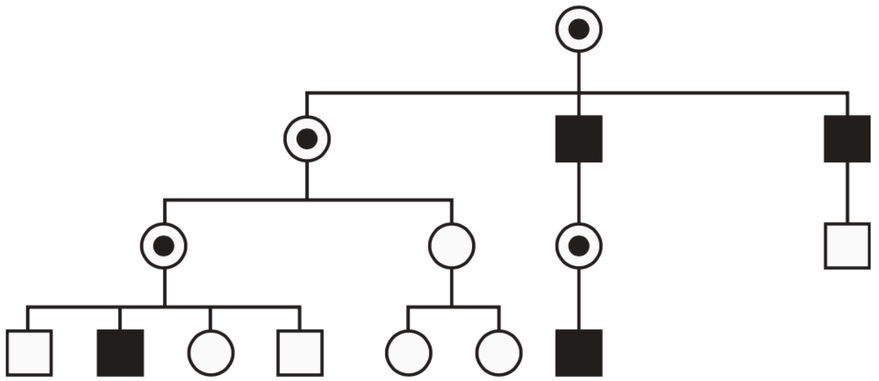
Oxford Desk Reference: Clinical Genetics and Genomics 2nd Edition

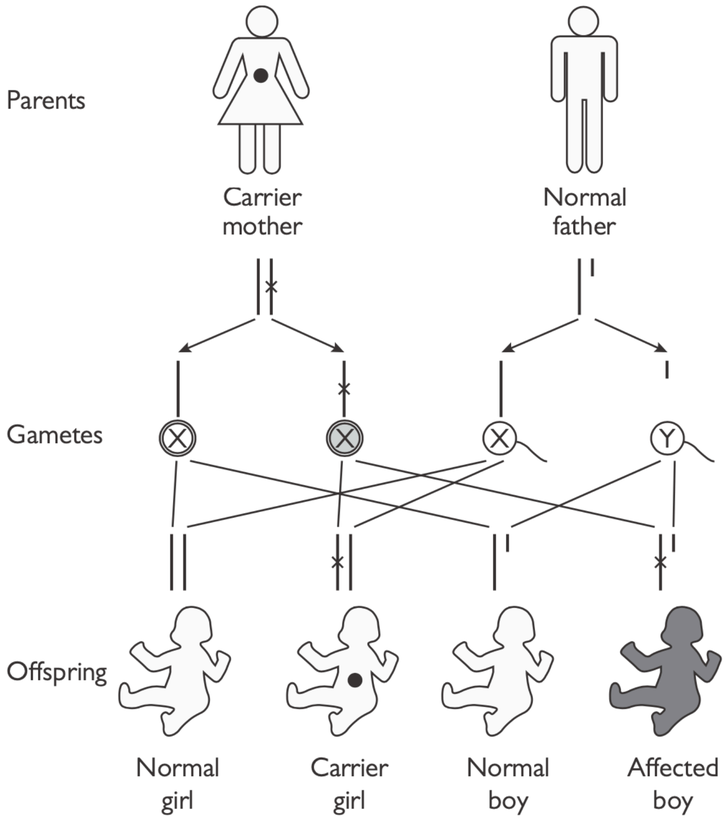
Inheritance

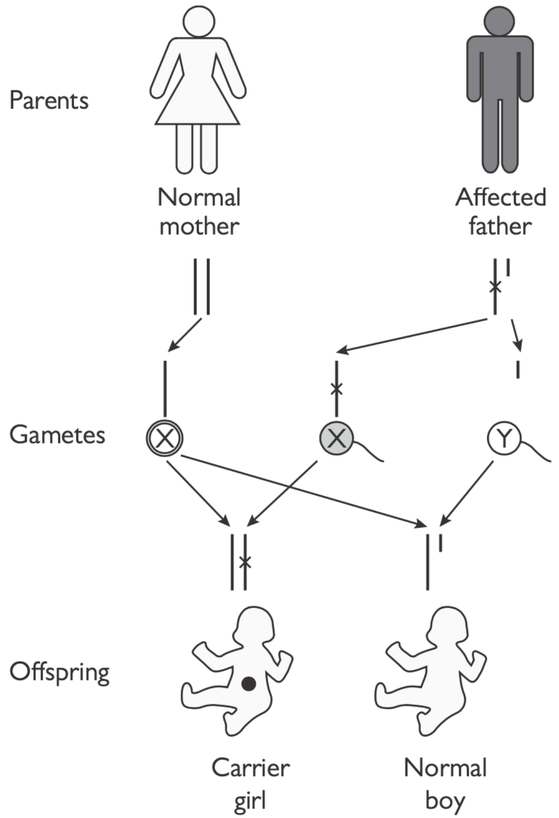
X-linked Recessive

Aspect

- X-inactivation
- Manifesting Carriers
- No male-to-male transmission





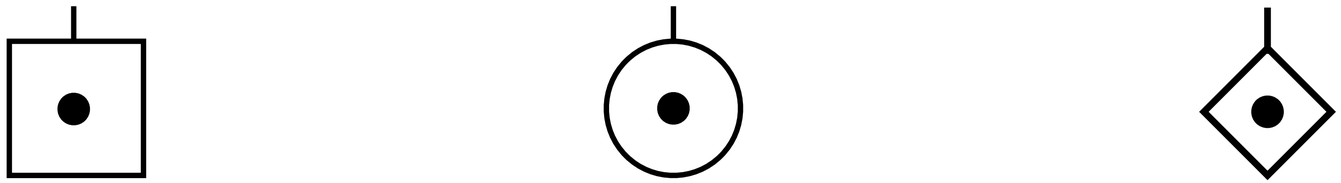


Oxford Desk Reference: Clinical Genetics and Genomics 2nd Edition

Inheritance

Carrier

Carrier - not likely to manifest disease regardless of inheritance



2008 Guideline Recommendation:

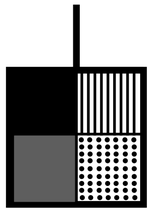
Previous guidelines recommended that the symbol for a heterozygous carrier of an **autosomal or X-linked condition** be identified by a dot in the center of the appropriate symbol shape.

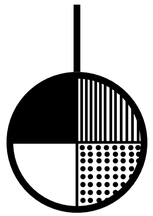
J Genet Counsel (2008) 17:424-433

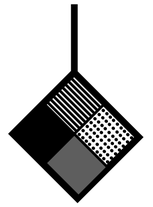
Inheritance

Carrier

Carrier - not likely to manifest disease regardless of inheritance







2022 Guideline Recommendation:

- The **dot no longer** be used to indicate carrier status.
- A unique fill pattern in each **subsection** to indicate the different carrier results and/or clinical manifestations.

J Genet Couns. 2022; 00:1–11.

ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–124
https://doi.org/10.1093/eurheartj/ehad194

ESC GUIDELINES

2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

European Heart Journal (2023) 44, 3503–3626.

Suspected cardiomyopathy

Morphological/ functional characterization

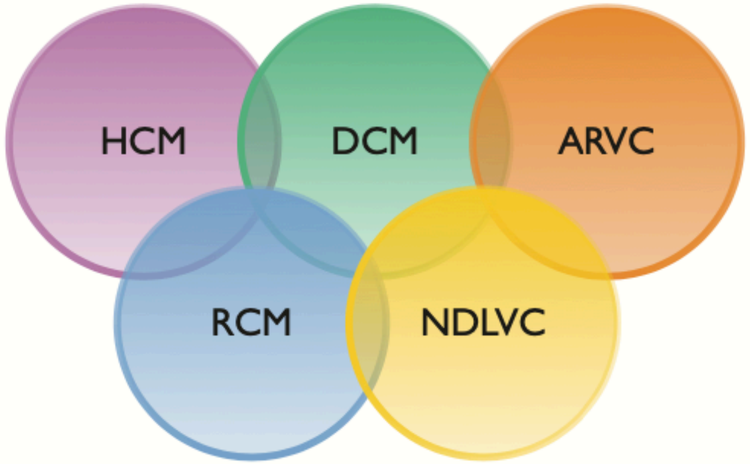
Ventricular morphology/function

- Hypertrophy
- Dilatation
- Systolic/diastolic function

Ventricular scar/fatty replacement

- Non-ischaemic ventricular scar on CMR/pathological examination
- Other tissue characterization parameters on CMR

Phenotype



Additional traits

- **Arrhythmias/conduction disease** (atrial, ventricular, atrioventricular block)
- Pedigree analysis
- Genetic testing
- Extracardiac involvement
- Laboratory markers
- Pathology

ESC

Phenotype-based integrated aetiological diagnosis

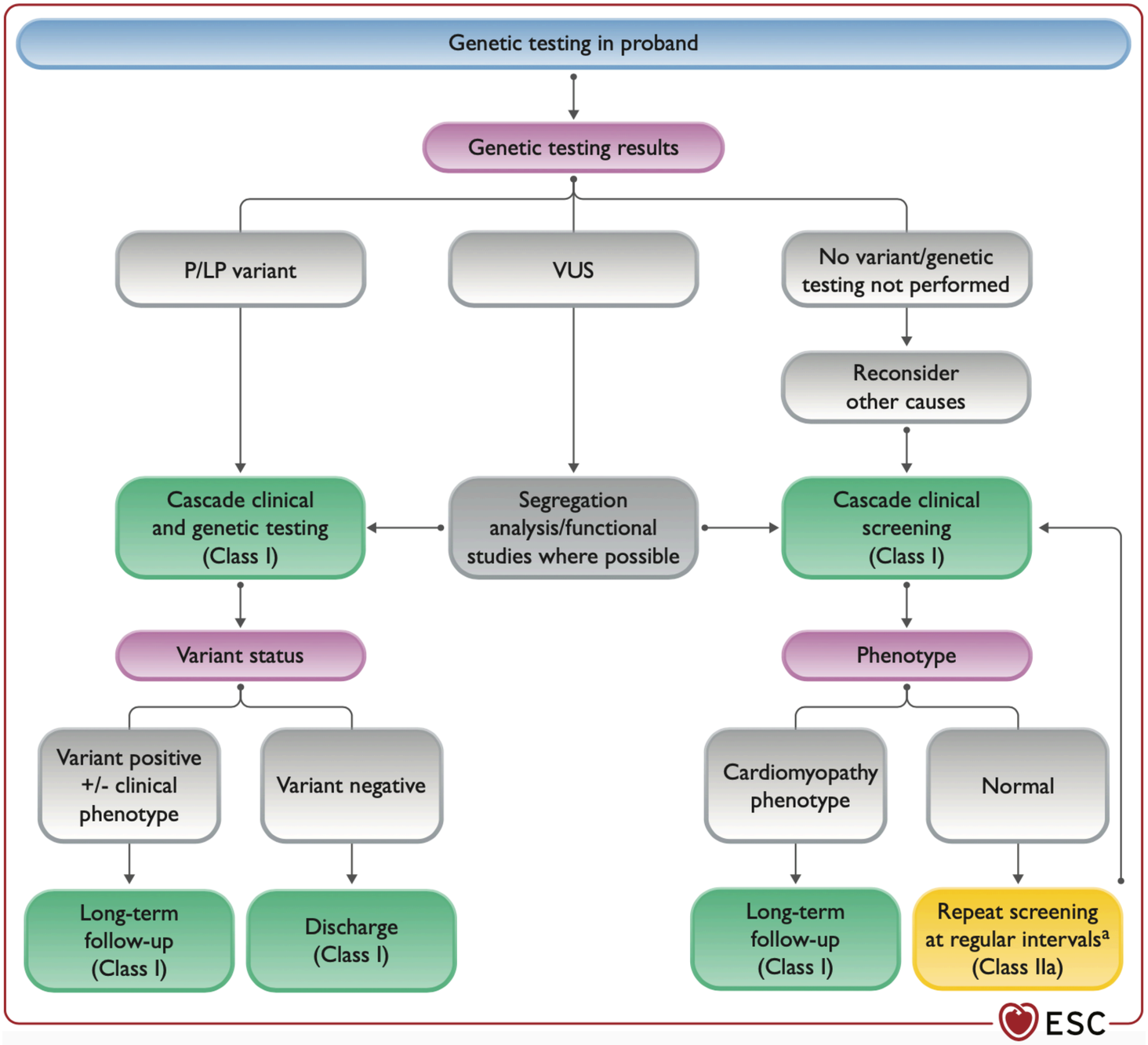
European Heart Journal (2023) 44, 3503–3626.

Genetic Testing in Cardiomyopathy

For Index Patient

Recommendation	Class	Level
Genetic testing is recommended in **patients fulfilling diagnostic criteria for cardiomyopathy** in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance.	I	B

European Heart Journal (2023) 44, 3503–3626.



European Heart Journal (2023) 44, 3503–3626.

HFSA & ACMG Guideline 2018

Clinical (phenotypic) screening for cardiomyopathy in **at-risk first-degree relatives** is recommended.

- Baseline Phenotypic Screening

Study	DCM	HCM	ARVC	LVNC	RCM
CK-MM*	X			X	
ECG	X	X	X	X	X
ETT		X			X†
Holter monitoring		X	X		X
CMR‡	X	X	X	X	X
Metabolic disease screening§	X	X		X	X

J Cardiac Fail 2018;24:281-302

HFSA & ACMG Guideline 2018

Surveillance

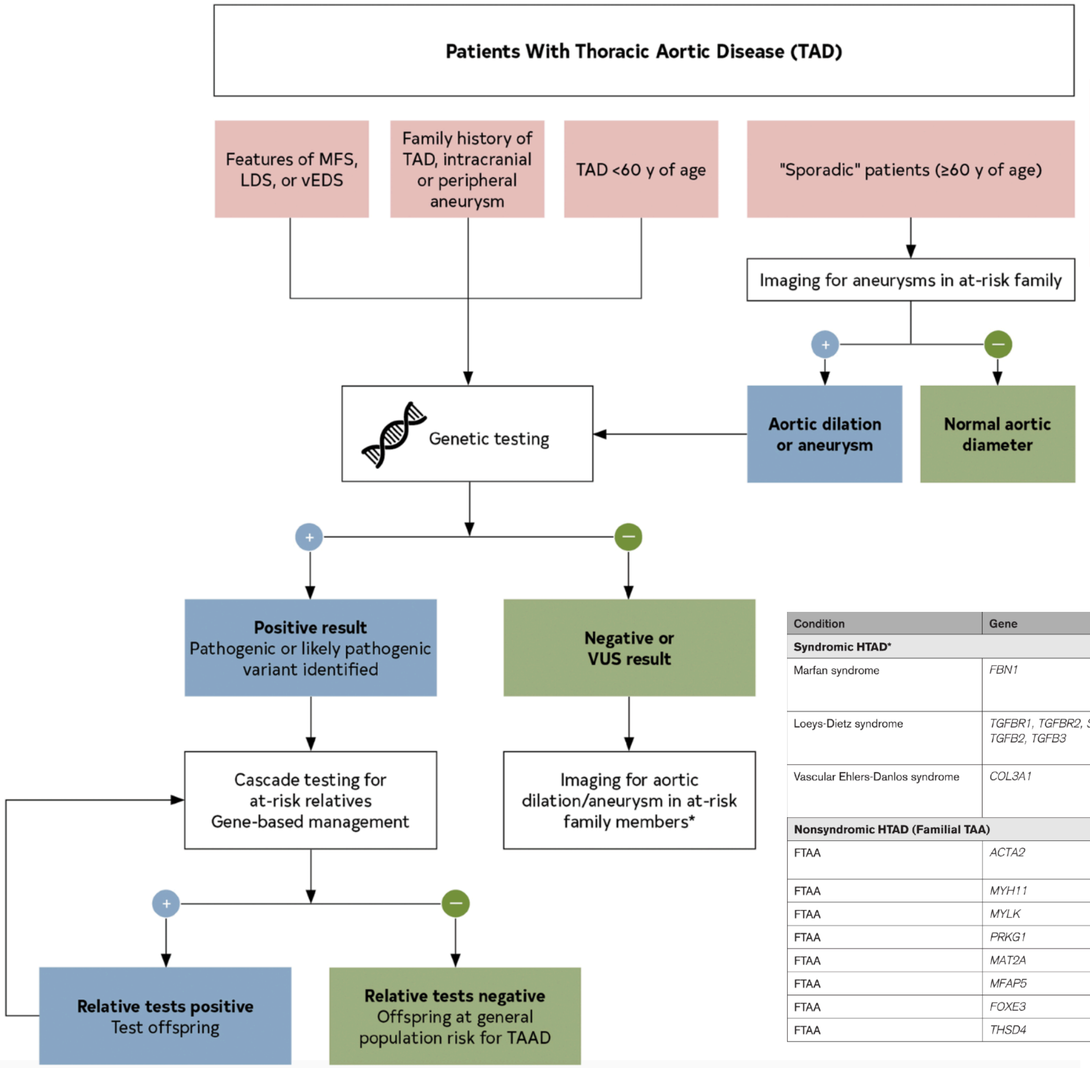
Clinical (phenotypic) screening for cardiomyopathy in **at-risk first-degree relatives** is recommended.

- Clinical **screening intervals** for at-risk family members

Cardiomyopathy	0–5 Years†	6–12 Years	13–19 Years	20–50 Years	>50 Years
DCM	Annually with positive FDR*	Every 1–2 years with positive FDR*	Every 1–3 years	Every 2–3 years	Every 5 years
HCM	Annually with positive FDR*	Every 1–2 years with positive FDR*	Every 2–3 years	Every 5 years	Every 5 years
ARVC	Consider once with positive FDR*	Every 5 years	Every 1–3 years	Every 2–3 years	Every 3 years
RCM	Annually with positive FDR*	Every 1–2 years with positive FDR*	Every 2–3 years	Every 3 years	Every 5 years

J Cardiac Fail 2018;24:281-302

Aortopathy



TAD and syndromic features of Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome
TAD presenting at age <60 y
A family history of either TAD or peripheral/intracranial aneurysms in a first- or second-degree relative
A history of unexplained sudden death at a relatively young age in a first- or second-degree relative

Condition	Gene	Clinical Features
Syndromic HTAD*		
Marfan syndrome	*FBN1*	Aortic root aneurysm, aortic dissection, TAA, MVP, long bone overgrowth, arachnodactyly, dolichostenomelia, scoliosis, pectus deformities, ectopia lentis, myopia, tall stature, pneumothorax, dural ectasia
Loeys-Dietz syndrome	*TGFBR1, TGFBR2, SMAD3,† TGFB2, TGFB3*	TAA, branch vessel aneurysms, aortic dissection, arterial tortuosity, MVP, craniosynostosis, hypertelorism, bluish sclera, bifid/broad uvula, translucent skin, visible veins, club feet, dural ectasia, and premature osteoarthritis and peripheral neuropathy†
Vascular Ehlers-Danlos syndrome	*COL3A1*	TAA, AAA, arterial rupture, aortic dissection, MVP, bowel and uterine rupture, pneumothorax, translucent skin, atrophic scars, small joint hypermobility, easy bruising, carotid-cavernous fistula
Nonsyndromic HTAD (Familial TAA)		
FTAA	*ACTA2*	TAA, aortic dissection, premature CAD and moyamoya-like cerebrovascular disease, livedo reticularis, iris flocculi
FTAA	*MYH11*	TAA, aortic dissection, PDA
FTAA	*MYLK*	Aortic dissection at relatively small aortic size
FTAA	*PRKG1*	Aortic dissection at young ages at small aortic sizes
FTAA	*MAT2A*	TAA, aortic dissection, BAV
FTAA	*MFAP5*	TAA, aortic dissection, skeletal features may be present
FTAA	*FOXE3*	TAA, aortic dissection
FTAA	*THSD4*	TAA, aortic dissection

HTAD (see Table 7): syndromic
- Marfan syndrome
- Loeys-Dietz syndrome
- Vascular Ehlers-Danlos syndrome
- Smooth muscle dysfunction syndrome
- Others: attributable to pathogenic variants in FLNA, BGN, LOX

HTAD (see Table 7): nonsyndromic
- ACTA2, MYH11, PRKG1, MYLK, and others
- Familial thoracic aortic aneurysm without identified pathogenic variants in a known gene for HTAD

20%

Congenital conditions
- Bicuspid aortic valve
- Turner syndrome
- Coarctation of the aorta
- Complex congenital heart defects (tetralogy of Fallot, transposition of the great vessels, truncus arteriosus)

Hypertension

Atherosclerosis

Degenerative

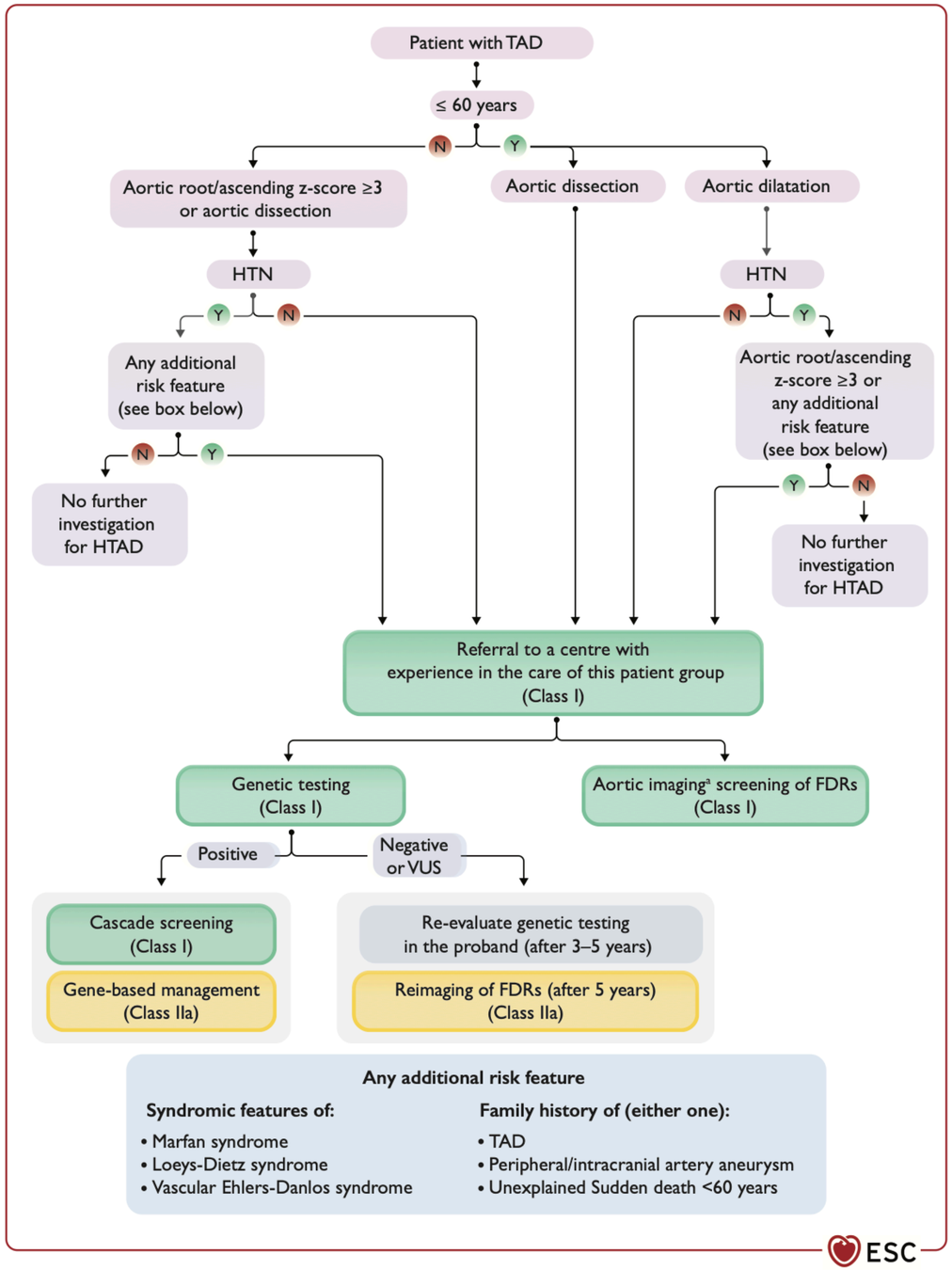
Previous aortic dissection

Inflammatory aortitis
- Giant cell arteritis
- Takayasu arteritis
- Behçet disease
- Immunoglobulin G4-related disease, antineutrophil cytoplasmic antibody-related, sarcoidosis

Infectious aortitis
- Bacterial, fungal, syphilitic

Previous traumatic aortic injury

Circulation. 2022;146:e334–e482.



European Heart Journal, Volume 45, Issue 36, 21 September 2024, Pages 3538–3700

Marfan Syndrome

Revised Ghent 2010

The revised Ghent nosology for the Marfan syndrome

Bart L Loeys,[1] Harry C Dietz,[2] Alan C Braverman,[3] Bert L Callewaert,[1]
Julie De Backer,[1] Richard B Devereux,[4] Yvonne Hilhorst-Hofstee,[5]
Guillaume Jondeau,[6] Laurence Faivre,[7] Dianna M Milewicz,[8] Reed E Pyeritz,[9]
Paul D Sponseller,[10] Paul Wordsworth,[11] Anne M De Paepe[1]

J Med Genet 2010;47:476e485.

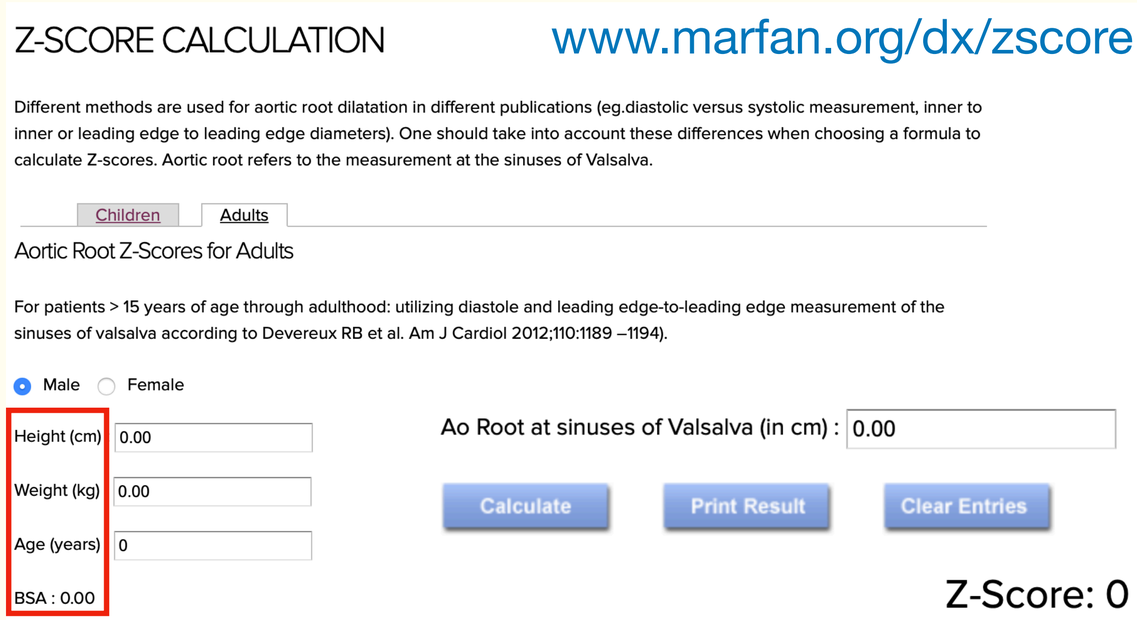
Marfan Syndrome

Revised Ghent 2010

Revised Ghent Criteria 2010 for diagnosis of Marfan

In the absence of family history

- Ao (Z ≥2) **AND** EL
- Ao (Z ≥2) **AND** FBN1 with known Ao
- Ao (Z ≥2) **AND** Syst (≥7)
- EL **AND** FBN1 with known Ao



J Med Genet 2010;47:476e485.

Marfan Syndrome

Revised Ghent 2010

Revised Ghent Criteria 2010 for diagnosis of Marfan

In the presence of family history

- EL **AND** Family History of Marfan syndrome (as defined)
- Syst (≥7) **AND** Family History of Marfan
- Ao (Z ≥2; above 20 years old, Z ≥3; below 20 years) **AND** Family History

J Med Genet 2010;47:476e485.

Marfan Syndrome

Revised Ghent 2010

Related Conditions

- **Ectopia Lentis Syndrome:**

  EL **with** or **without** Systemic Score

  AND FBN1 not known with Ao **OR** no FBN1

- **MASS Phenotype:**

  Ao (Z <2) **AND** Syst (≥5 with at least one skeletal feature) **without** EL

- **Mitral Valve Prolapse Syndrome:**

  MVP **AND** Ao (Z <2) **AND** Syst (<5) **without** EL

Myopia/**M**VP

Aortic root

Striae

Skeletal finding

J Med Genet 2010;47:476e485.

Marfan Syndrome

Revised Ghent 2010

Systemic Score (Total 20 points); score ≥ 7 indicate systemic involvement

Wrist Sign/Thumb Sign	Wrist **AND** Thumb = 3, Wrist **OR** Thumb = 1
Pectus Deformity	Carinatum = 2, excavatum/chest wall asymmetry = 1
Hindfoot deformity	Hindfoot deformity =2, flat foot =1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabuli	2
Upper : Lower Ratio **AND** Arm span : Height Ratio	1
Scoliosis/kyphosis	1
Reduced elbow extension	1
3 of 5 Facial Features	1
Skin Striae	1
Myopia > 3 diopters	1
MVP	1

J Med Genet 2010;47:476e485.

Aortopathy

Medical Management

Prophylaxis of Aortic Dilatation

- **Beta Blocker** in maximally tolerated doses
- **ARB** in maximally tolerated doses

1	A	1. In patients with Marfan syndrome, treatment with either a beta blocker or an ARB, in maximally tolerated doses (unless contraindicated), is recommended to reduce the rate of aortic dilation.[1,2]	In patients with MFS, treatment with either a BB or an ARB, in maximally tolerated doses (unless contraindicated), is recommended to reduce the rate of aortic dilatation.[1461,1462]	I	A
2a	C-LD	2. In patients with Marfan syndrome, the use of both a beta blocker and an ARB, in maximally tolerated doses (unless contraindicated), is reasonable to reduce the rate of aortic dilation.[3,4]	In patients with MFS, the use of both a BB and an ARB, in maximally tolerated doses (unless contraindicated), should be considered to reduce the rate of aortic dilatation.[1463,1464]	IIa	A

Circulation. 2022;146:e334–e482.,European Heart Journal, Volume 45, Issue 36, 21 September 2024, Pages 3538–3700

Aortopathy

Surgical Management

Recommendation	Class	Level
In patients with Marfan syndrome and an aortic root diameter of **≥5.0 cm**, surgery to replace the aortic root and ascending aorta is recommended.	I	B-NR
In patients with Marfan syndrome, an aortic root diameter of **≥4.5 cm**, and features associated with an **increased risk of aortic dissection**, surgery to replace the aortic root and ascending aorta is reasonable, when performed by experienced surgeons in a Multidisciplinary Aortic Team	2a	B-NR

- Family history of aortic dissection
- Rapid aortic growth (≥0.3 cm/y)
- Diffuse aortic root and ascending aortic dilation[14]
- Marked vertebral arterial tortuosity[15]

Circulation. 2022;146:e334–e482.

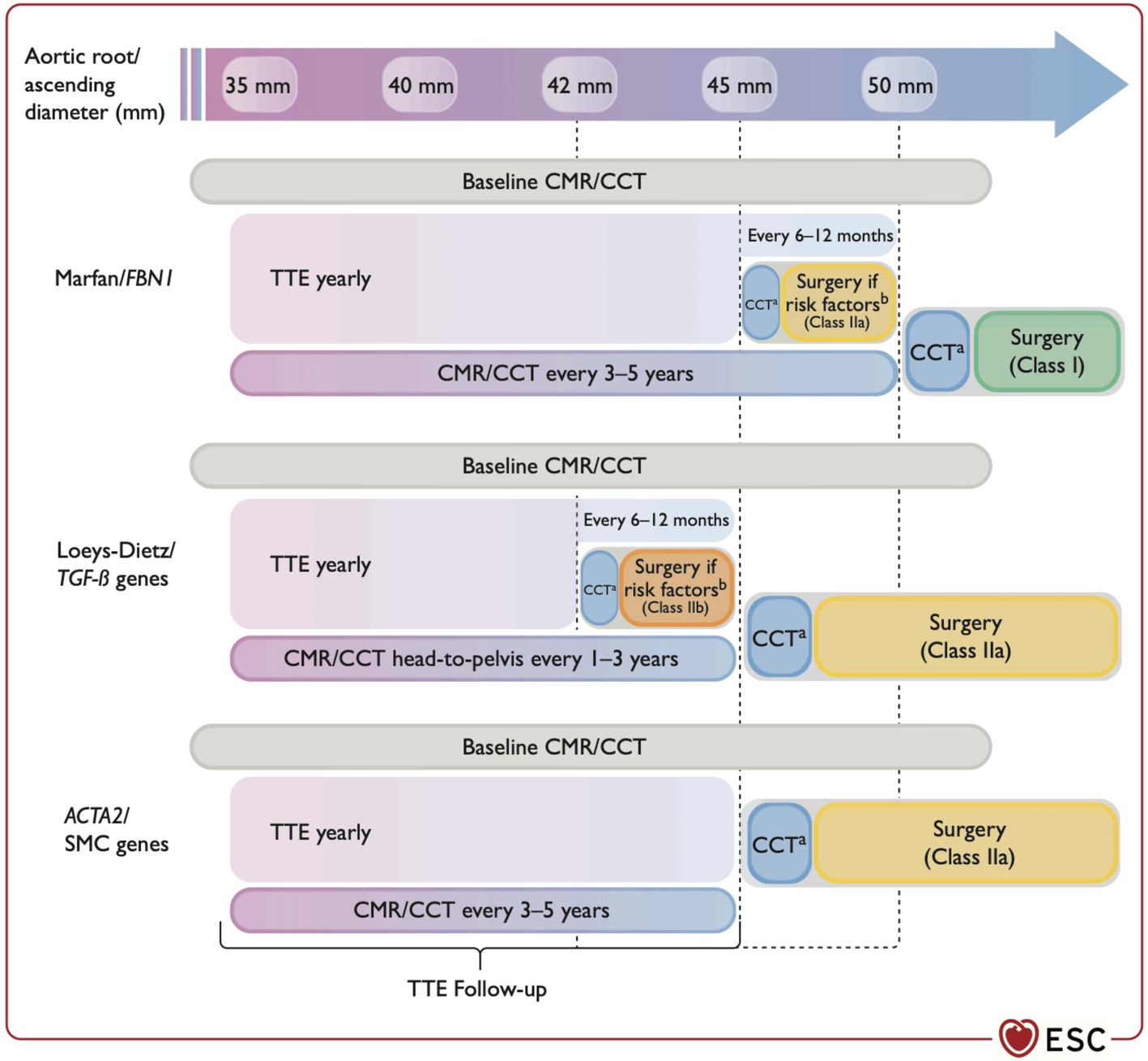
Aortopathy

Surgical Management

Recommendation	Class	Level
In asymptomatic patients with aneurysms of the aortic root or ascending aorta with nsHTAD and no identified genetic cause but no information on aortic diameters at the time of dissection or aneurysm repair in affected family members and who have no high-risk features for adverse aortic events, it is recommended to repair the aorta when the maximal diameter reaches **≥5.0 cm**	I	C-LD
In patients with aneurysms of the aortic root or ascending aorta with nsHTAD and no identified genetic cause and a maximal aortic diameter of **≥4.5 cm**, who have **high-risk features** for adverse aortic events, or who are undergoing cardiac surgery for other indications, aortic repair is reasonable when performed by experienced surgeons in a Multidisciplinary Aortic Team	2a	C-LD

Heritable Thoracic Aortic Aneurysms and No Identified Genetic Cause
Family history of aortic dissection at an aortic diameter <5.0 cm
Family history of unexplained sudden death at age <50 y
Rapid aortic growth (≥0.5 cm in 1 y or ≥0.3 cm/y in 2 consecutive y)

Circulation. 2022;146:e334–e482.

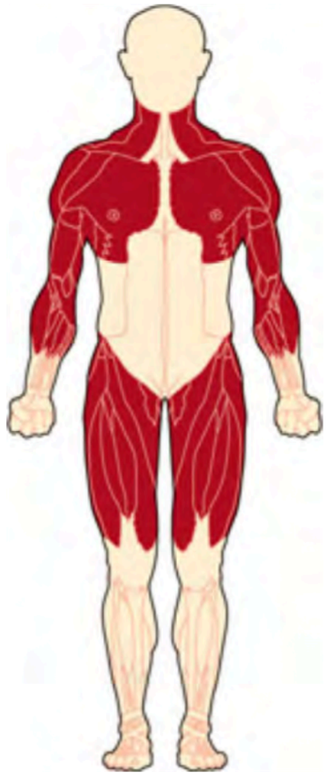


European Heart Journal, Volume 45, Issue 36, 21 September 2024, Pages 3538–3700

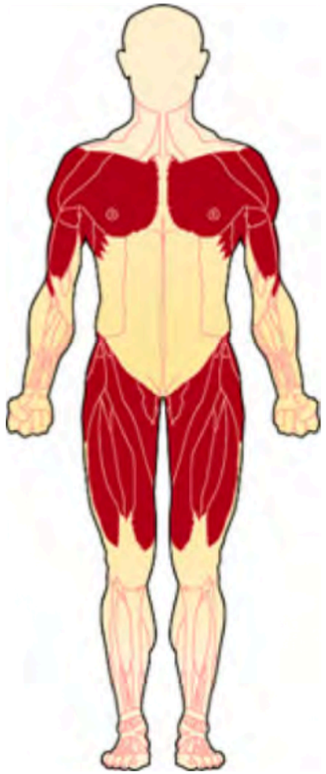
Muscular Dystrophy

Affected group of muscles

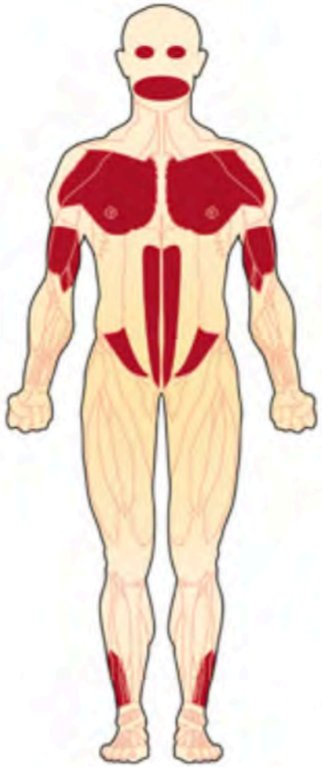
Dystrophinopathy



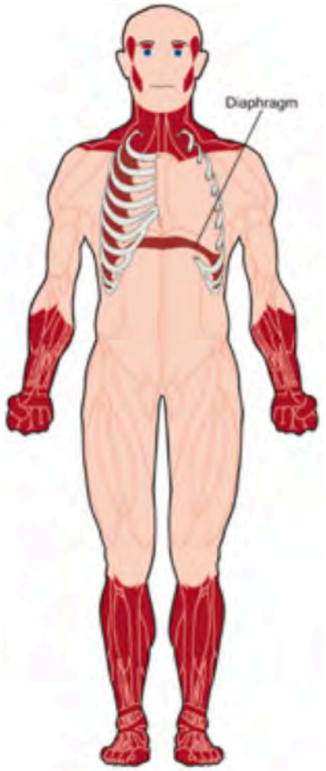
Limb-Girdle



Facioscpulohumeral



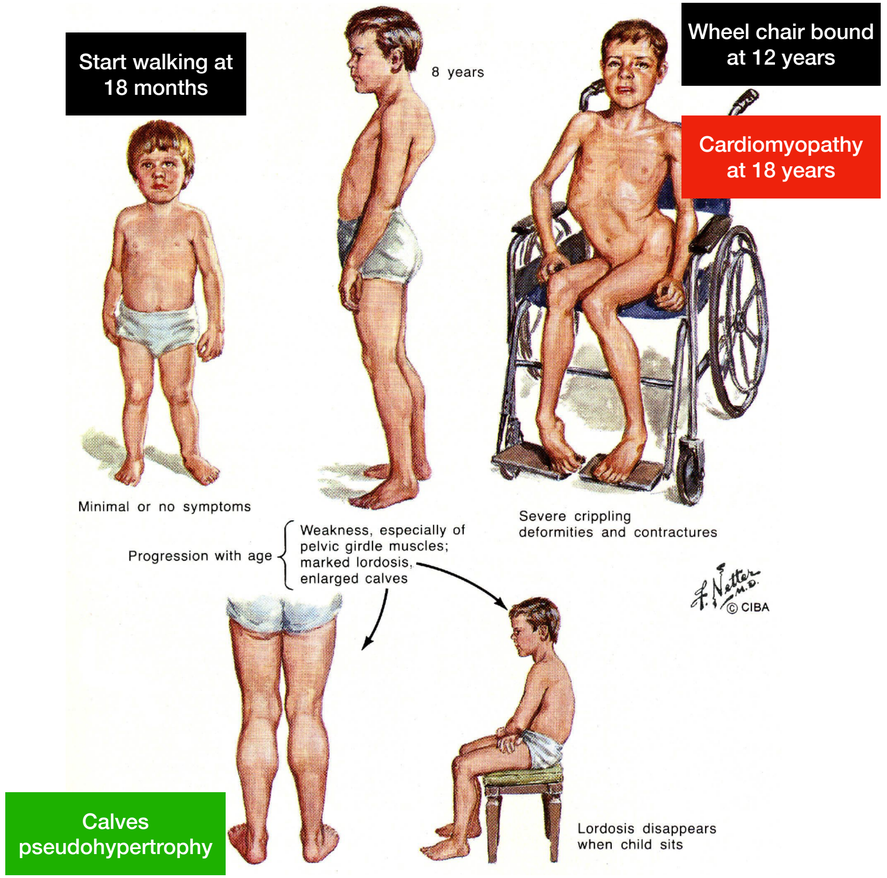
Myotonic



Dystrophinopathy

Duchenne & Becker Muscular Dystrophy

- **Onset**: DMD at preschool
  BMD at 1st decade of life
- **Incidence** = 1:3,500 male birth
  (most common form of MDs in children)
- **Dystrophin gene (X-linked Recessive)**
- **Symmetrical proximal muscle weakness** with **pseudohypertrophy of calves** followed by pelvis, upper arms, heart and respiratory muscles.
- Life expectancy < 30 years, death from **respiratory failure** and **cardiomyopathy**



Dystrophinopathy

Duchenne & Becker Muscular Dystrophy

Becker Muscular Dystrophy

In-frame errors can occur when a deletion mutation takes out "three-letter" chunks without disrupting the "words" on either side. This allows a shorter — but still readable — sentence to be produced. In-frame mutations in the dystrophin gene allow shorter but still functional dystrophin to be made, as in BMD.

The mad cat ate the ~~fat rat and the~~ big bat.

deletion

The mad cat ate the big bat.

Duchenne Muscular Dystrophy

Out-of-frame errors occur when the deletion disrupts the "three-letter" reading pattern, creating "words" that don't make sense. This leads to an unreadable sentence, just as an out-of-frame mutation leads to nonfunctional dystrophin in DMD.

The mad cat ate the ~~fa~~t rat and the big bat.

deletion

The mad cat ate the tra tan dth ebi gba t.

Exon Skipping Therapy

Exon skipping converts an out-of-frame error into an in-frame error by causing the cell to skip not only the deleted section but also a nearby section (exon), restoring the reading frame and creating a readable sentence:

The mad cat ate the ~~tra tan dth e~~bi gba t.

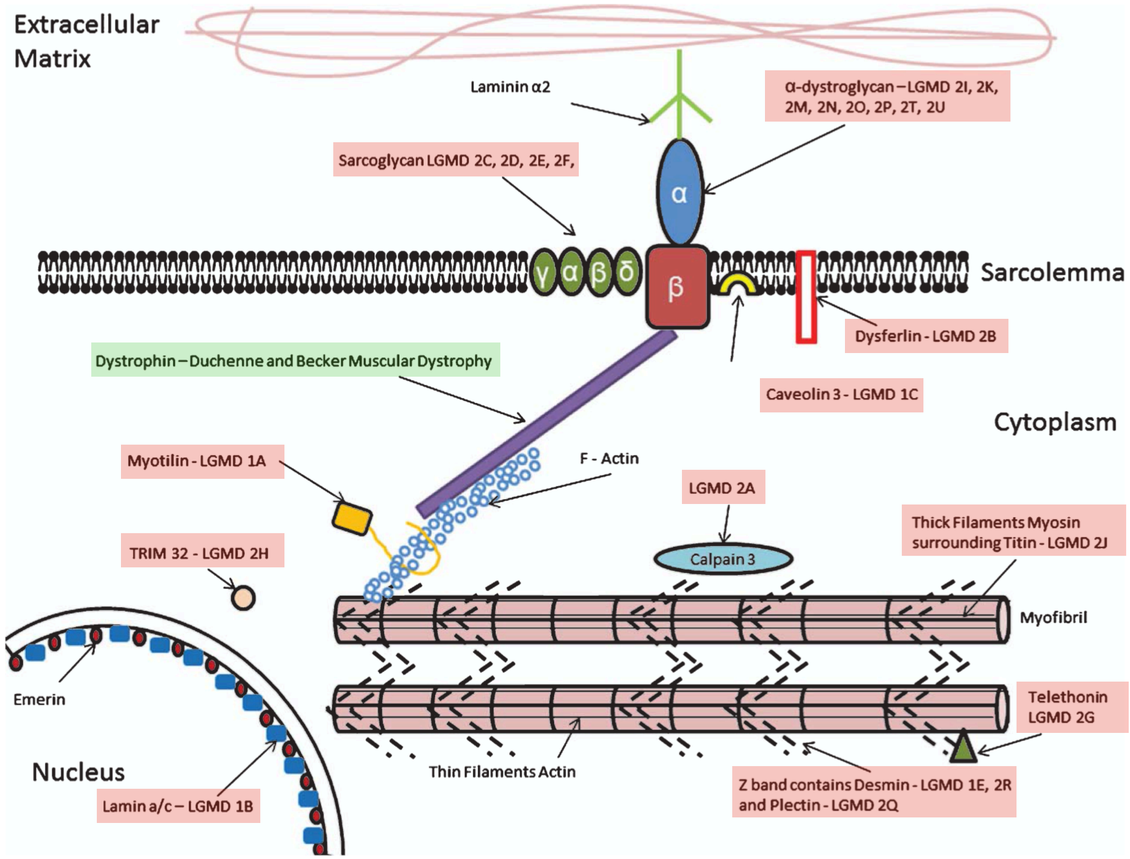
skipped exon

The mad cat ate the big bat.

Muscular Dystrophy

Limb Girdle Muscular Dystrophy

- **Multiple** sarcoglycan-dystroglycan complex **subunits**
- Autosomal Dominant, Autosomal Recessive, rarely X-linked
- Genetic heterogeneity
- **Various** manifestations and onset
- **Clinical Manifestations**: Proximal muscle atrophy of limbs and girdles
- Mortality due to Respiratory failure and cardiomyopathy



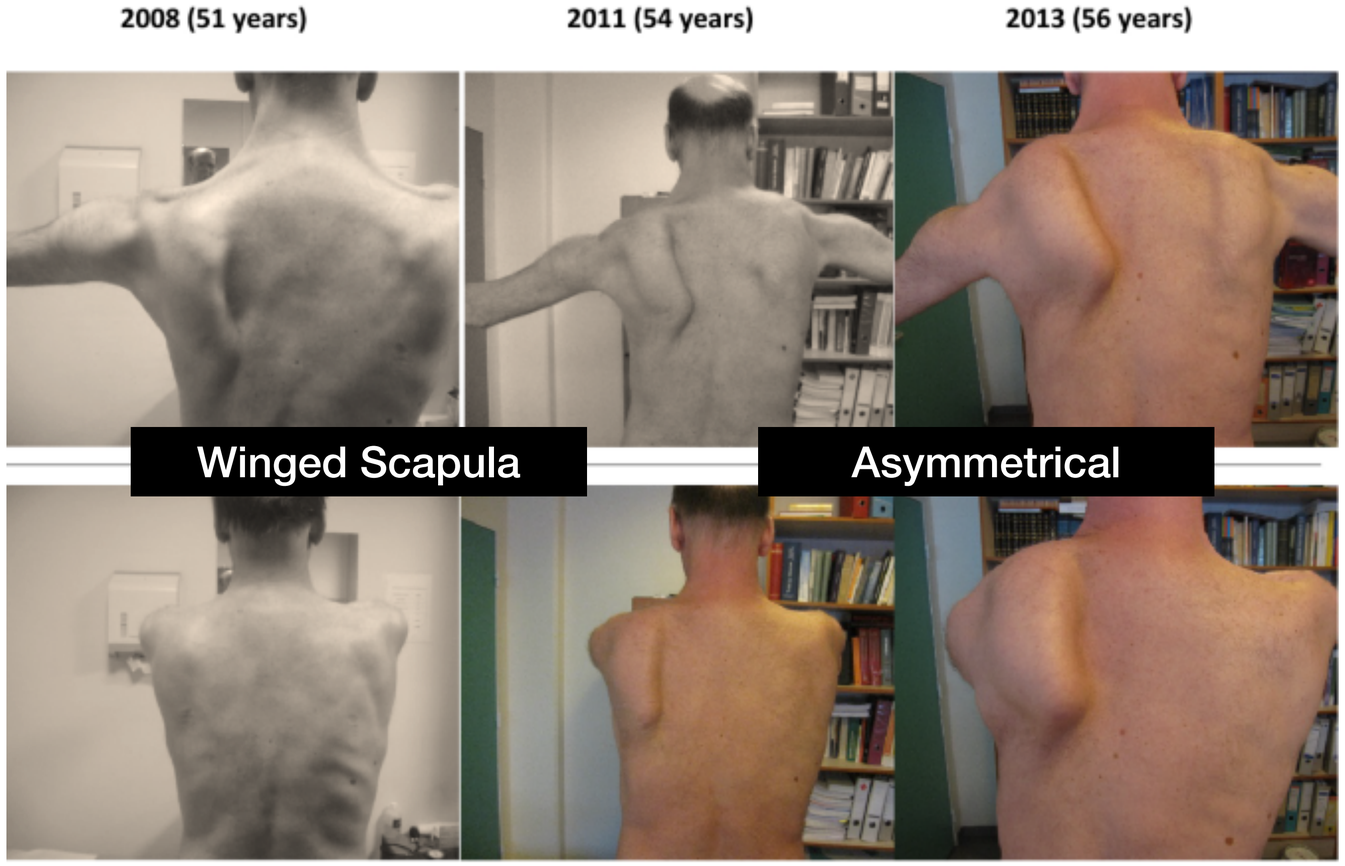
Clinical Colorectal Cancer 2018, Vol. 17, No. 2, e293-305

Muscular Dystrophy

Facioscapulohumeral Muscular Dystrophy

- Deletion within **D4Z4 gene** repeat region on chromosome 4q35.2
- Autosomal Dominant
- **Clinical Manifestation**:
  - Asymmetrical face
  - defects in blowing and whistling

  (Circular muscle defect)
- **Uncommon cardiac involvement**

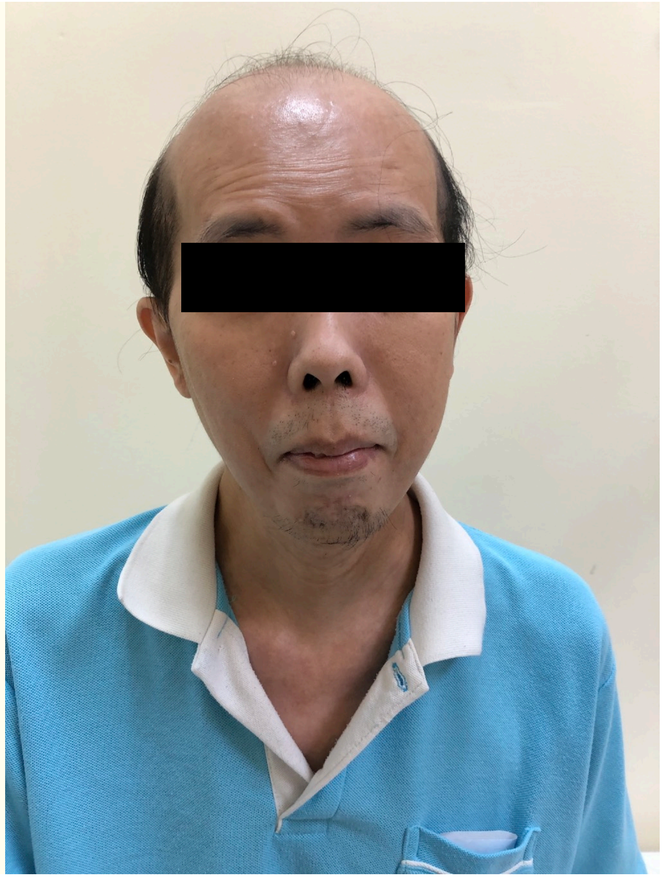


Journal of Neurology volume 266, pages 2987–2996(2019)

Muscular Dystrophy

Myotonic Dystrophy

- **Onset**: vary up to CTG repeat size (Classic 10-30 years)
- **Incidence** = 1:8,000 (most common form of MDs in adult)
- **DMPK gene** on chromosome 19
- **Autosomal Dominant with Anticipation**
- **Slowly pregressive muscle weakness with myotonia** (prolong relaxation)
- **Characteristics**: Frontal baldness, cataract, diabetes, impair GI function, testicular atrophy
- **Life expectancy**: vary up to CTG repeat size (Classic 48-55 years),
- **cardiac conductive defect (complex AV block)**

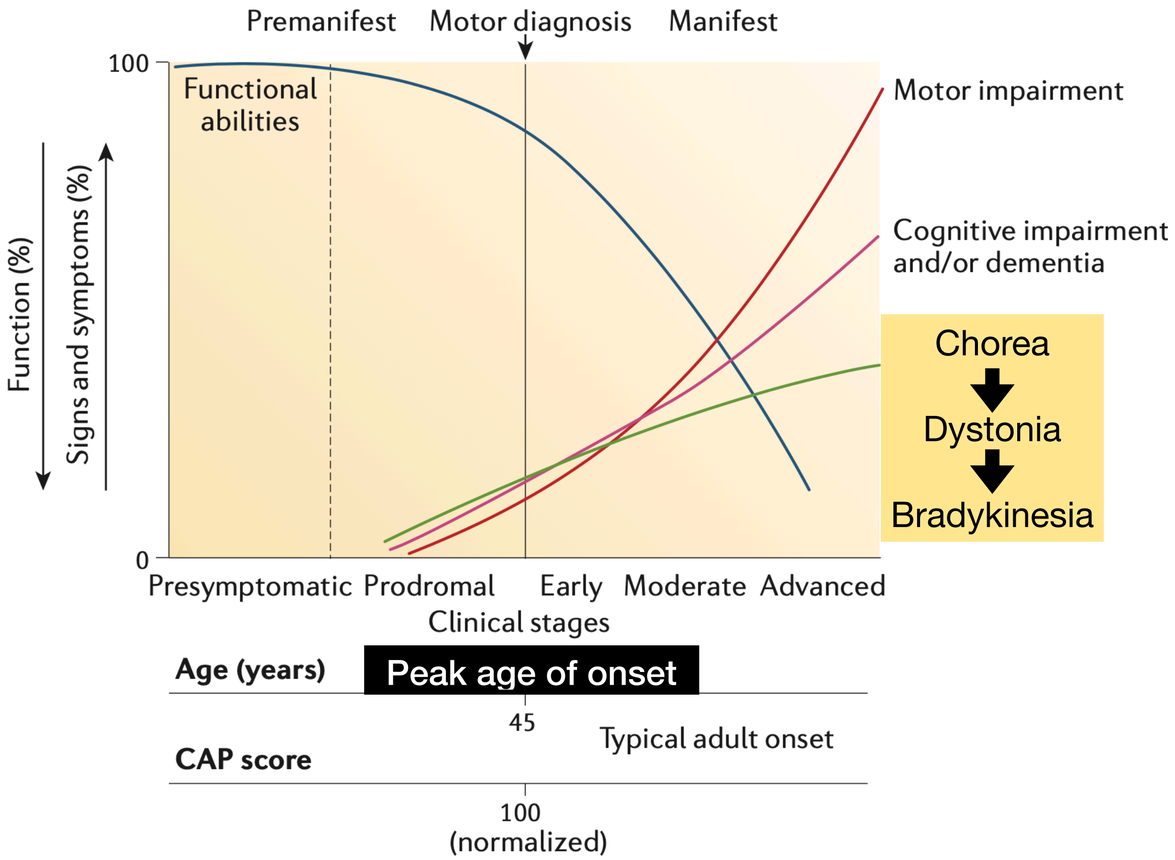


Huntington Disease

- Progressive neurodegenration
- **Prevalence** = 1:10,000
- Increase CAG repeat within **HD gene** on chromosome 4p16
- Autosomal Dominant with Anticipation

Classical Triads

- Involuntary movement disorder
- Psychiatric disturbance
- Dementia



Nature Reviews Disease Primers volume 1, Article number: 15005 (2015).

For individuals **at-risk** for Huntington disease,

Do they **want to know** their carrier status ?

Principles of Biomedical Ethics

Autonomy

Beneficence

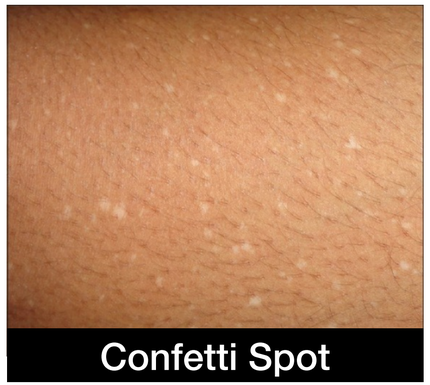
Avoidance of Maleficence

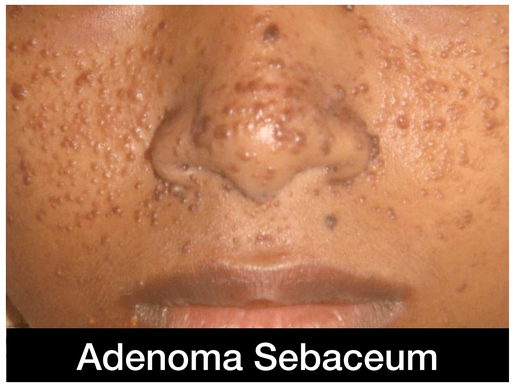
Justice

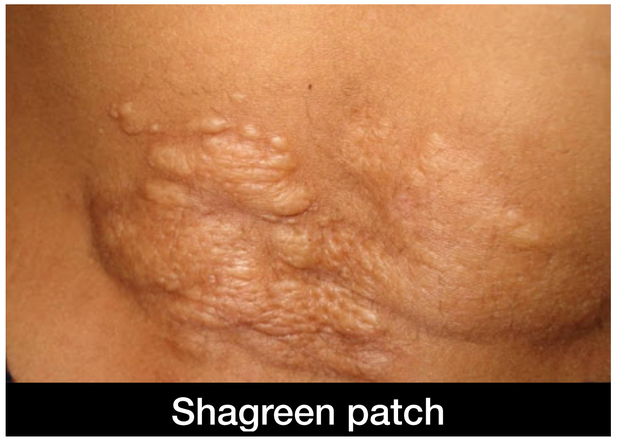
Thompson & Thompson Genetics in Medicine 8th Edition

Tuberous Sclerosis

- Autosomal Dominant
- **TSC1 gene** on chromosome 9q34.13
- **TSC2 gene** on chromosome 16p13.3
- **Prevalence** = 1:15,000
- **Complications**:
  - Subependymal giant cell astrocytoma: 10–15%[200]
  - Renal (bleeding or chronic kidney disease): 21–40%[58,143]
  - Symptomatic lymphangioleiomyomatosis: 5–48% (in women)[40]
  - Resistant epilepsy: up to 33%[126]
  - Disfiguring facial rash: 75%[3]
  - Tuberous sclerosis complex (TSC)-associated neuropsychiatric disorders: 90%[36]

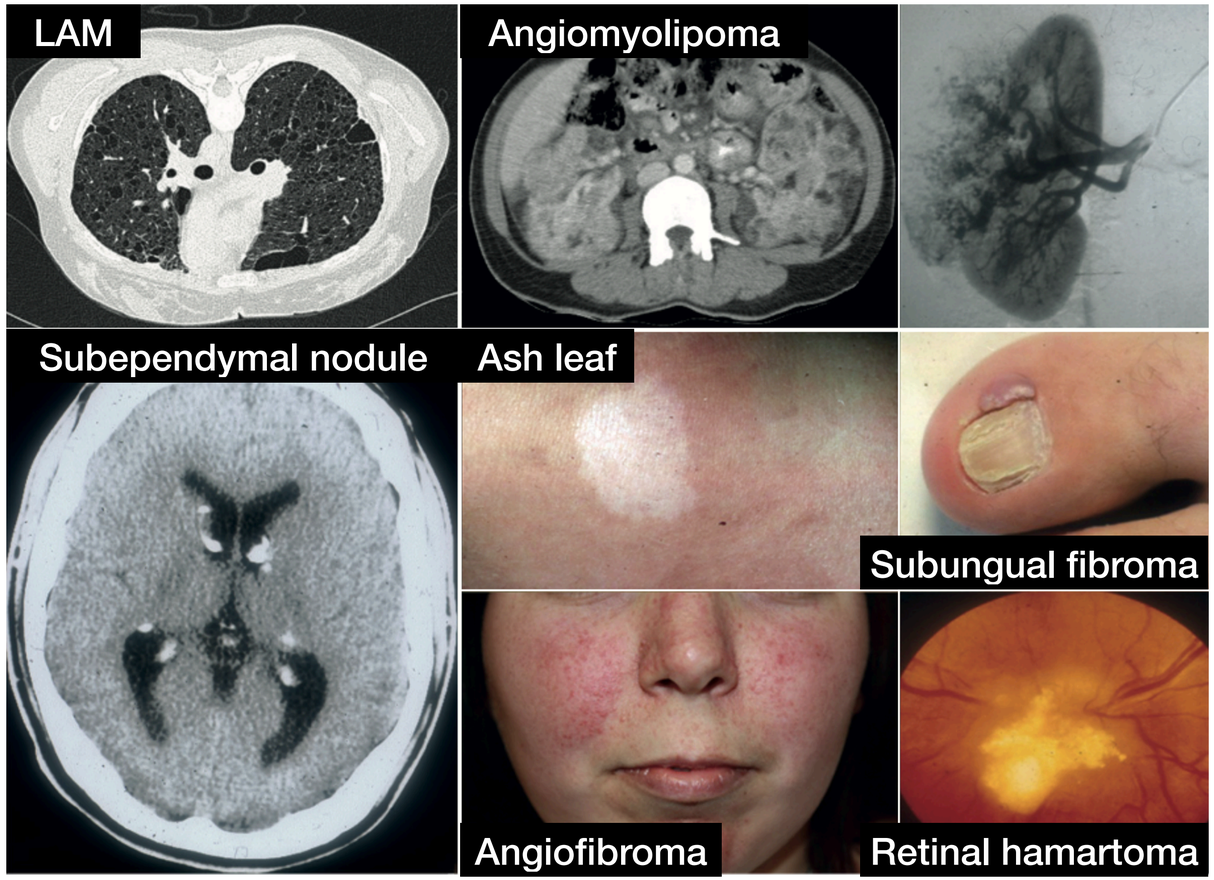

Confetti Spot

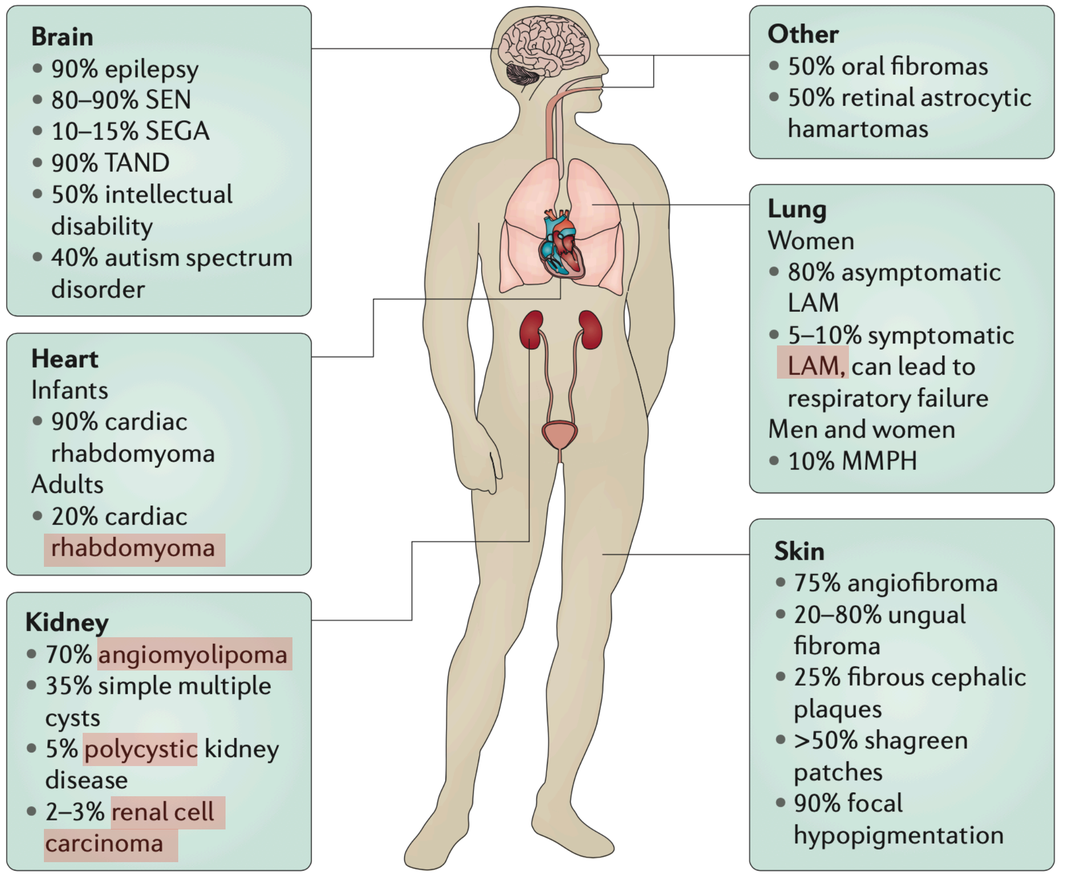

Adenoma Sebaceum


Shagreen patch

Tuberous Sclerosis

Clinical Manifestations

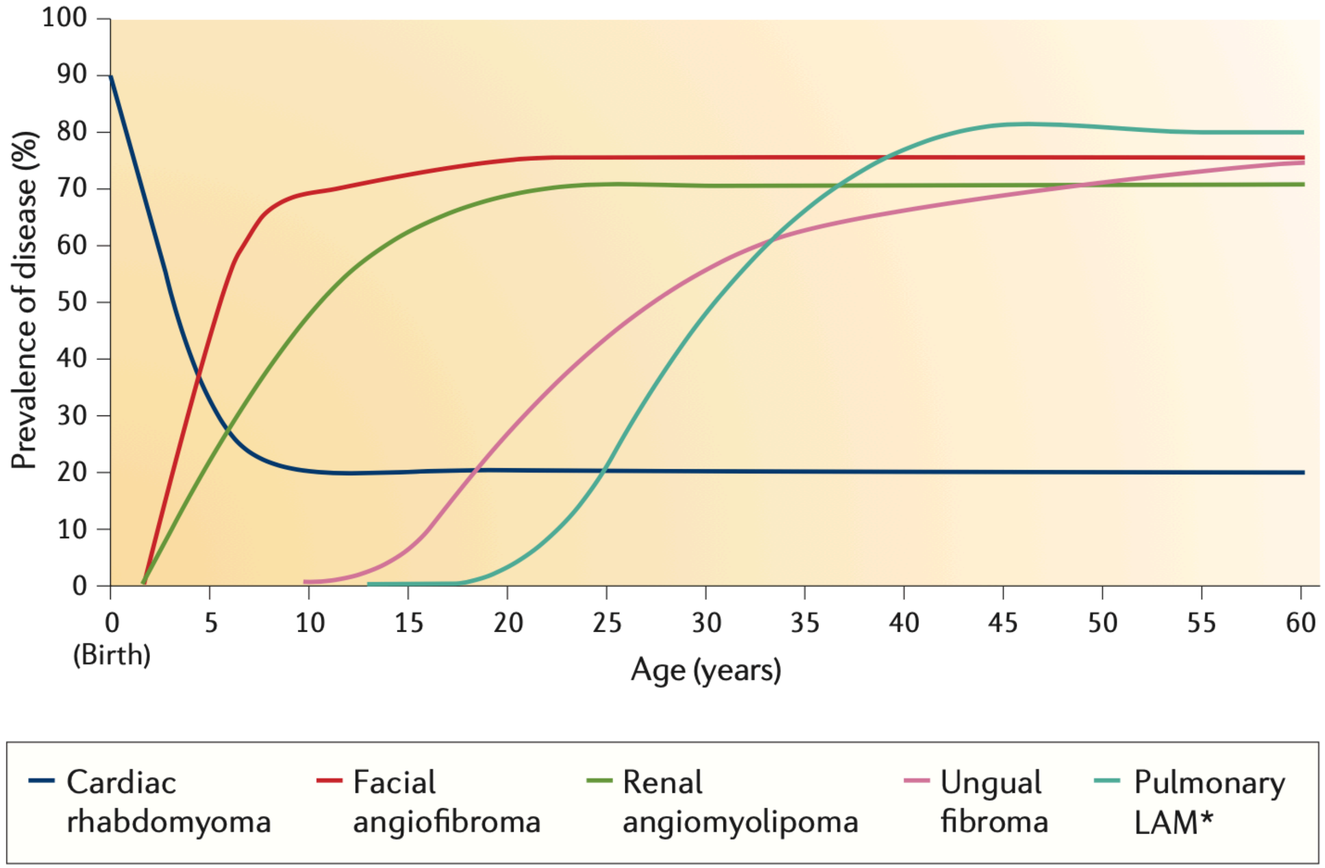




Nat Rev Dis Primers **2,** 16035 (2016).

Tuberous Sclerosis

Age-dependent Manifestations



Nat Rev Dis Primers **2,** 16035 (2016).

Tuberous Sclerosis

2012 TSC Consensus Criteria

Genetic Diagnostic Criteria: Identify either TSC1 or TSC2 pathogenic mutation

Clinical Diagnostic Criteria: **definite**: 2 major or 1 major + 2 minor, **possible**: 1 major or 2 minor

Major features

- ≥ 3 Hypomelanotic macule
- (≥5 mm in diameter)
- ≥ 3 Angiofibroma
- ≥ 2 Ungual fibroma
- Shagreen patch
- Multiple retinal hamartomas
- Cortical dysplasia
- Subependymal nodules
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyomas
- Lymphangioleiomyomatosis (LAM)
- ≥ 2 Angiomyolipomas

Minor features

- Confetti skin lesions
- Dental Enamel pits > 3
- Intraoral fibromas ≥ 2
- Retinal achromatic patch
- Multiple renal cysts
- Non-renal hamartomas

Nat Rev Dis Primers 2, 16035 (2016).

Tuberous Sclerosis

Surveillance

Clinical Manifestations	Procedures	Management
Infantile spasms & seizures	EEG	Steroids, anticonvulsants, ketogenic diet, Vagal nerve stimulation, resection
Subependymal giant cell astrocytomas	MRI	Everolimus Surgical resection
Neuropsychiatric disorder	Periodic screening	Special education programmes, Psychiatric evaluation & treatment
Lymphangioleiomyomatosis	HRCT, PFT, Diffusion Capacity, Oxygen monitoring during exercise	Sirolimus
Angiomyolipoma	MRI, Renal function tests, CT scan	Percutaneous embolisation, Everolimus, Nephron-sparing resection
Skin lesions	Periodic examination	Ablation, Laser, Sun protection, Topical rapamycin

Nat Rev Dis Primers **2,** 16035 (2016).

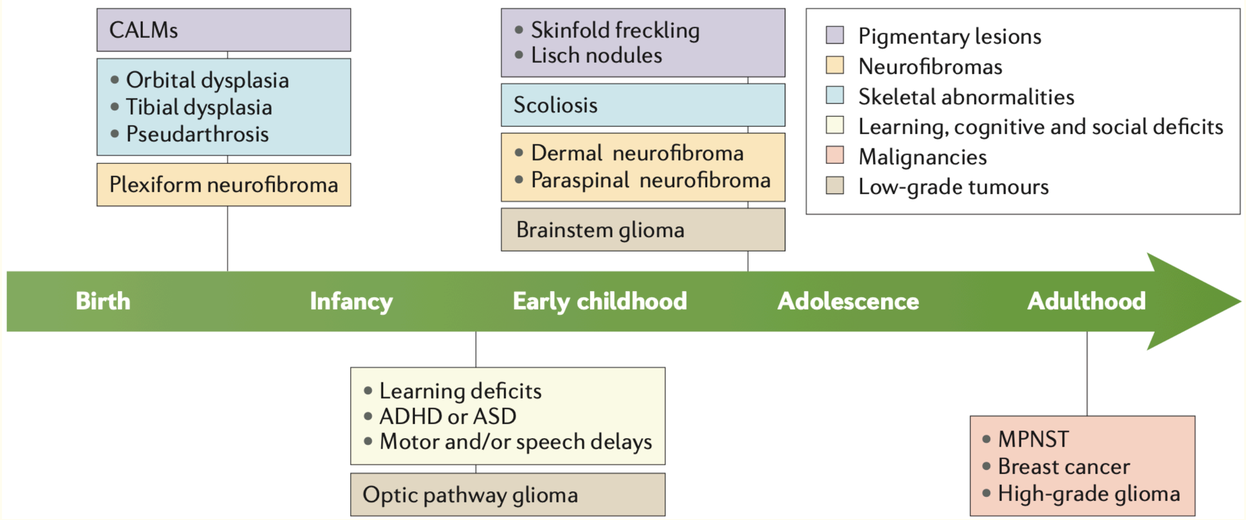
Neurofibromatosis I (von Recklinghausen)

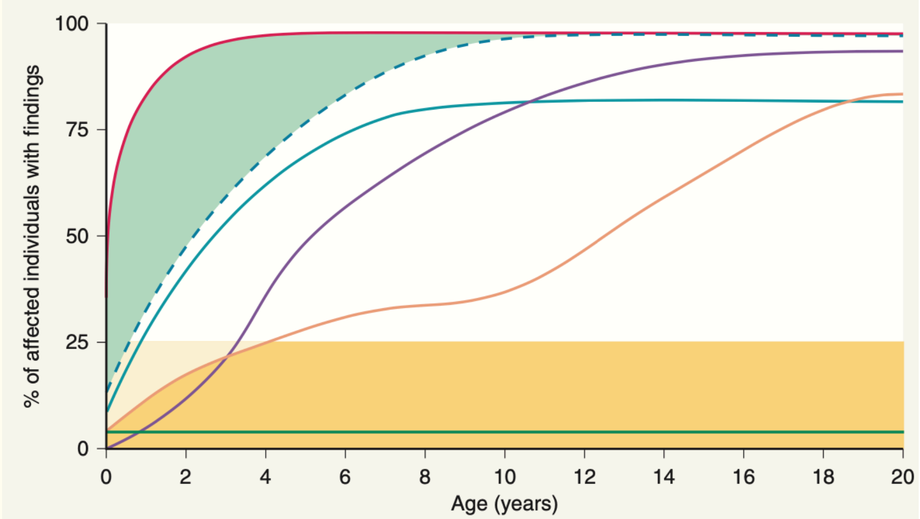
Key Features

Inheritance: Autosomal dominant **Penetrance:** 100%

Incidence: 1:3,000 live births (de novo rate 50%)

Gene: *NF1* (**N**eurof**i**bromin **1** Gene) (OMIM: 613113)





Nat Rev Dis Primers vol 3, Article number:17004.2017., Jean L. Bolognia Dermatology 4th Edition

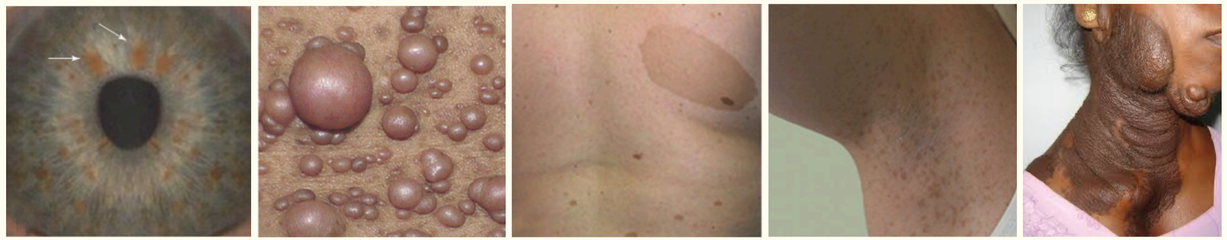
Neurofibromatosis I (von Recklinghausen)

NIH Diagnostic Criteria 1988

- ≥ 6 **café-au-lait** patches > 15 mm in adults, > 5 mm in children
- ≥ 2 **neurofibromas** or ≥ 1 **plexiform neurofibroma**

≥ 2 of following

- Axillary or groin **freckling**
- **Lisch nodules** (Iris hamartomas)
- **Optic glioma** (via MRI)



- A **distinctive osseous lesion** such as sphenoid wing dysplasia or thinning of the long bone cortex with or without pseudoarthorsis
- A **first-degree** relative with NF1 by above criteria

Arch Neurol 1988;45:575-578.

Neurofibromatosis

Risk of Malignancy and Others Disorders

- **Nerve sheath tumour (9,043 folds)** ****most common ~15% of NF1 patients
- Brain tumor eg. Meningioma (0.6%; 56.7 folds)
- Pheochromocytoma (1.2%; 126 folds)
- Neurofibrosarcoma, Soft tissue sarcoma
- Early onset breast cancer (2.9%; 4 folds)
- Gastrointestinal stromal tumour (GIST) (1.2%; 272 folds)
- Acute leukemia (0.6%; 28.2 folds)
- **Other**: Neuropathy, **Stroke**, **Renal artery stenosis**, DM, MS, epilepsy, **learning disabilities**, sleep disorder, craniofacial & dental abnormalities

JAMA Netw Open. 2021;4(3):e210945.

Neoplasm type	NF1 group (N = 1607)			General population estimates[a]			
	Prevalence, No. (%)	Age at diagnosis, median (range), y[b]	5-y DSS, No. (%)	Prevalence, %	Age at diagnosis, median (range), y[b]	5-y DSS, No. (%)	OR (95% CI)
Nonneurofibroma neoplasms	666 (41.4)	NA	NA	NA	NA	NA	NA
Single neoplasm	550 (34.2)	NA	NA	5.5[22]	NA	NA	9.5 (8.5-10.5)[c]
Multiple neoplasms	116 (7.2)	NA	NA	NA	NA	NA	NA
Glioma							
Low grade	267 (16.6)	11.0 (0.1-56.8)	118 (98.1)	0.003	9.0 (0-19.0)	4040 (92.0-94.0)[14]	5473.0 (4782.0-6263.0)[c]
Optic pathway[d]	178 (11.1)	8.0 (0.1-56.8)	75 (99.8)	<0.001	7.0 (1.0-85.0)	445 (96.0);[15]	31 060.0 (25 907.0-37 237.0)[c]
High grade	28 (1.7)	25.9 (9.7-60.6)	8 (23.1)	0.04	58.0 (0-85.0)	77 454 (34.9);[16]	82.2 (56.6-119.5)[c]
Glioblastoma multiform[e]	18 (1.1)	25.2 (7.0-60.6)	4 (18.8)	0.01	64.0 (0-85.0)	33,951 (5.5)[16]	59.9 (37.6-95.3)[c]
Other[e]	10 (0.6)	30.2 (0.3-38.6)	4 (30.0)	NA	NA	NA	NA
Sarcoma[f]							
MPNST	243 (15.1)	33.3 (1.0-74.6)	72 (31.6)	0.003	46.0 (0-85.0)	2186 (43.4-71.9)[11]	9043.0 (7840.0-10 431.0)[c]
GIST	20 (1.2)	43.7 (24.9-68.6)	9 (80.0)	0.004	62.0 (18.0-101.0)	5138 (65.0-81.0)[12]	272.2 (175.0-423.4)[c]
ERMS	13 (0.8)	2.6 (1.0-61.4)	6 (63.6)	0.002	15.0 (0-85.0)	2831 (15.0-71.6);[11]	319.7 (185.0-552.4)[c]
UPS	5 (0.3)	36.8 (13.0-57.4)	1 (20.0)	0.01	57.0 (0-85.0)	14 599 (61.8-98.6)[11]	23.7 (9.9-57.1)[c]
Osteosarcoma	4 (0.2)	29.0 (17.4-44.0)	1 (50.0)	0.004	42.0 (0.1-78.8)	3482 (24.2-61.6)[13]	407.2 (152.2-1089.0)[c]
Breast carcinoma	47 (2.9)	44.2 (23.4-70.9)	27 (85.1)	0.78	62.0 (20.0-85.0)	3 597 331 (90.0)	3.8 (2.9-5.1)[c]
Endocrine neoplasia[g]							
Pheochromocytoma	20 (1.2)	44.9 (26.0-72.0)	8 (77.8)	0.01	47.1 (13.5-80.7)	107 (44.0-96.0)[19]	126.0 (81.0-195.9)[c]
Neuroendocrine tumor	9 (0.6)	56.6 (30.1-65.4)	7 (75.0)	0.04	63.0 (0-85.0)	35 618 (35.0-82.0)[20]	14.1 (7.3-21.1)[c]
Papillary thyroid carcinoma	7 (0.4)	49.4 (11.1-66.2)	4 (100)	0.17	51.0 (<20.0-85.0)	765 547 (98.0)	2.6 (1.2-5.4)
Skin cancer							
Melanoma	15 (0.9)	51.8 (34.3-82.5)	8 (66.7)	0.24	64.0 (<20.0-85.0)	1 245 276 (92.0)	3.9 (2.4-6.5)[c]
Nonmelanoma	14 (0.9)	68.6 (36.8-84.5)	4 (100)	NA	NA	NA	NA
Leukemia							
ALL	9 (0.6)	8.5 (2.1-38.3)	9 (100)	0.02	15.0 (<20.0-85.0)	100 012 (68.0)	28.2 (14.6-54.2)[c]
Other[h]	5 (0.3)	58.1 (3.8-73.8)	4 (100)	NA	NA	NA	NA
Genitourinary Neoplasia							
Ovarian serous carcinoma	8 (0.5)	48.8 (30.1-57.7)	4 (57.1)	0.09	63.0 (<20.0-85.0)	233 364 (47.0)	5.6 (2.8-11.1)[c]
Prostate adenocarcinoma	6 (0.4)	67.7 (31.8-77.9)	2 (100)	1.78	66.0 (35.0-85.0)	3 170 339 (98.0)	0.2 (0.1-0.5)[c]
Uterine adenocarcinoma	4 (0.2)	39.0 (31.6-54.6)	3 (100)	0.29	62.0 (20.0-85.0)	291 704 (81.0)	0.9 (0.3-2.3)
Lymphoma							
Hodgkin lymphoma	4 (0.2)	29.8 (23.2-44.2)	2 (100)	0.04	39.5 (<20.0-85.0)	215 531 (87.0)	6.2 (2.3-16.6)[c]
Non-Hodgkin lymphoma	2 (0.1)	48.9 (26.1-71.8)	2 (100)	0.16	67.0 (<20.0-85.0)	719 831 (71.0)	0.8 (0.2-3.1)
Other							
Meningioma	9 (0.6)	43.9 (27.3-57.8)	5 (100)	0.01	65.0 (7.0-87.0)	9000 (70.0)[21]	56.7 (29.4-109.1)[c]
Lung squamous cell carcinoma	6 (0.4)	68.8 (40.1-83.0)	2 (40.0)	0.13	71.0 (20.0-85.0)	248 102 (19.0)	2.9 (1.3-6.4)

20-39% cumulative risk of malignancy by 50 years of age

2-5 folds relative to general population

60% life time cancer risk

50 fold of high grade tumour

JAMA Netw Open. 2021;4(3):e210945.

Neurofibromatosis I (von Recklinghausen)

ACMG Surveillance Guideline 2018

- Annual ophthalmologic examination
- Regular developmental assessment

} Children

- Annual physical examination
- Regular Blood Pressure monitoring

Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

Douglas R. Stewart, MD[1], Bruce R. Korf, MD, Ph.D[2], Katherine L. Nathanson, MD[3,4], David A. Stevenson, MD[5] and Kaleb Yohay, MD[6]

ACMG PRACTICE GUIDELINE | Genetics inMedicine

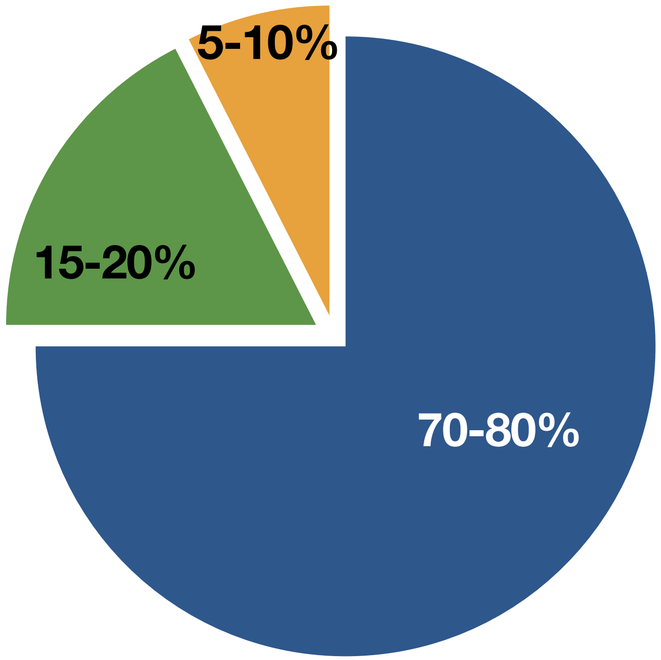
- Hypertension age < 30; **renovascular** cause should be 1st evaluated
- Pheochromocytoma screening is **not recommended** in asymptomatic patients
- **NCCN** Guidelines recommend **mammography annually** start at **30 years** and consideration of **breast MRI** at **30-50 years** (cost-effectiveness not demonstrated)
- Other studies (eg. MRI) only as indicated on the basis of clinically apparent signs

ACMG Practice Guidelines, Volume 20, Issue 7, Page 671-682, 2018

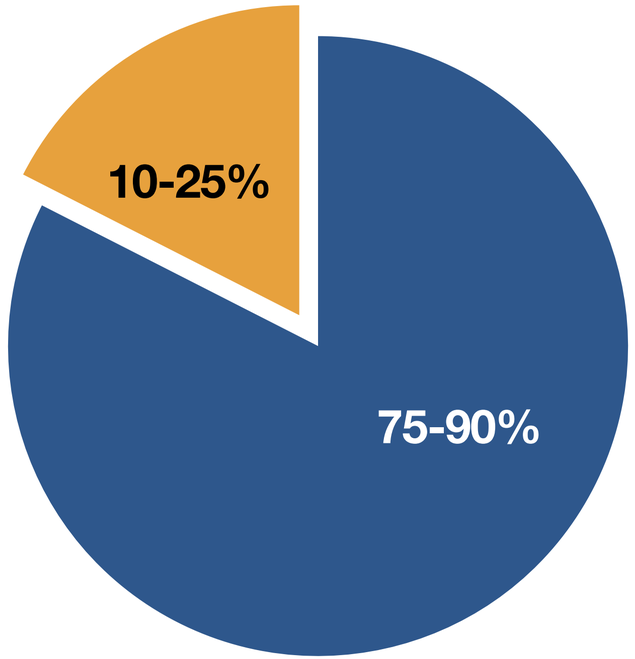
Proportion of Inherited Cancer

Sporadic VS Familial VS Inherited Cancer

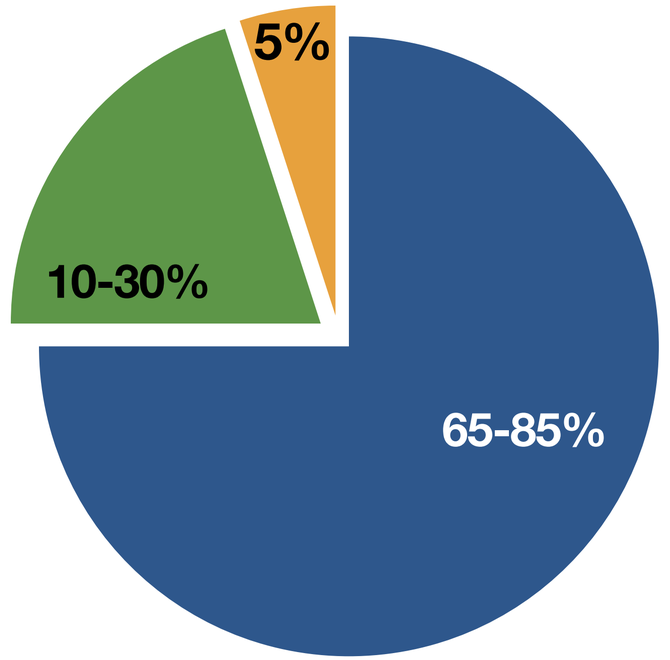
Breast Cancer



Ovarian Cancer



Colorectal Cancer



Sporadic Cancer Familial Cancer Inherited Cancer

Adapted from NIH NATIONAL CANCER INSTITUTE

Common Cancer

Common Hereditary & Non-Hereditary Cancer

Common Hereditary Cancer

Breast Cancer

Ovarian Cancer

Endometrial Cancer

Colorectal Cancer

Thyroid Cancer

Common Non-Hereditary Cancer

Hepatobilliary Cancer

Lung Cancer

Cervical Cancer

Head & Neck Cancer

Germ Cell Tumor

Leukemia

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Woman Screening Recommendation:

- Clinical breast exam every 6 - 12 months; starting at 25 years
- Breast Cancer Screening **Individualized based on family history if CA breast diagnosed before age of 30**
  - Age 25-29 years: Annual breast **MRI with contrast** **Days 7-15 of menstrual cycle**

    (or **Mammogram** only if MRI unavailable)
  - Age 30-75 years: Annual Mammogram & Breast MRI with contrast
  - Age > 75 years: consider on individual basis
  - BRCA P/LP variant: annual mammogram & Breast MRI with contrast

NCCN Guideline Version 1.2023

Hereditary Breast and Ovarian Cancer

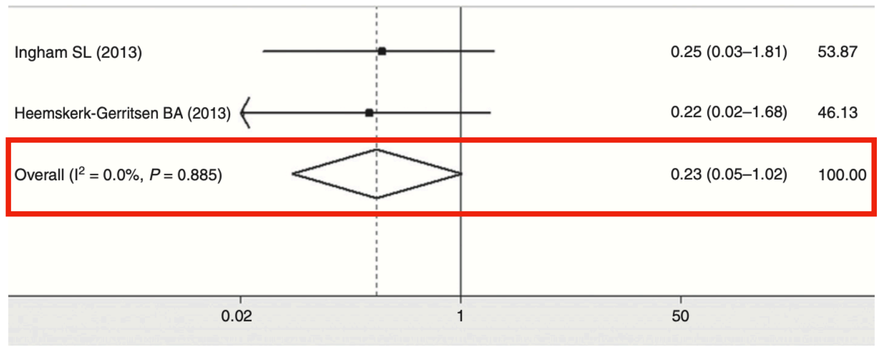
BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

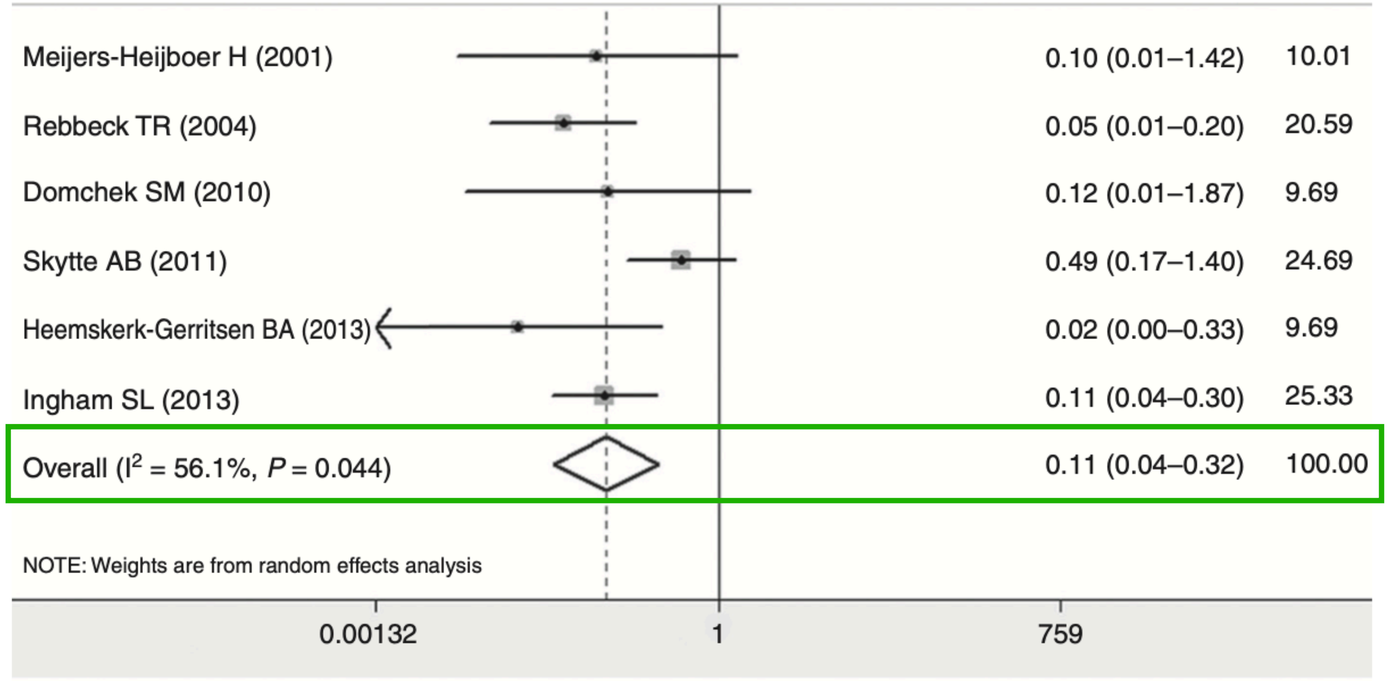
- **Bilateral Total Mastectomy**

Meta-analysis (n = 2,555)

All-Cause Mortality



Breast Cancer Risk



Clin Cancer Res 2016;22:3971-3981.

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

- **Bilateral Salpingo-oophorectomy**

Association between Oophorectomy and All-cause mortality

Variable	No. of Patients	*BRCA1*			*BRCA2*			All Patients		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age group at study entry, years										
≤ 40	2,104	0.27	0.15 to 0.48	< .001	0.44	0.17 to 1.09	.08	0.30	0.19 to 0.49	< .001
41-50	1,906	0.23	0.16 to 0.33	< .001	0.29	0.14 to 0.59	< .001	0.24	0.17 to 0.33	< .001
51-60	1,189	0.28	0.19 to 0.43	< .001	0.19	0.08 to 0.43	< .001	0.27	0.18 to 0.38	< .001
≥ 61	584	0.43	0.25 to 0.71	.001	0.89	0.33 to 2.43	.84	0.49	0.31 to 0.76	.002
Total	5,783	0.30	0.24 to 0.38	< .001	0.33	0.22 to 0.50	< .001	0.31	0.26 to 0.38	< .001
Previous breast cancer										
Yes	2,561	0.31	0.24 to 0.39	< .001	0.34	0.22 to 0.52	< .001	0.32	0.26 to 0.39	< .001
No	2,633	0.21	0.12 to 0.37	< .001	0.67	0.08 to 5.35	.70	0.23	0.13 to 0.39	< .001

J Clin Oncol 2014;32:1547-1553.

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

- **Bilateral Salpingo-oophorectomy**

NCCN Guidelines Panel Recommendation for women with known BRCA1/2 pathogenic/likely pathogenic variant

- Age 35-40 years for BRCA1
- Age 40-45 years for BRCA2
- Unless age of diagnosis in family

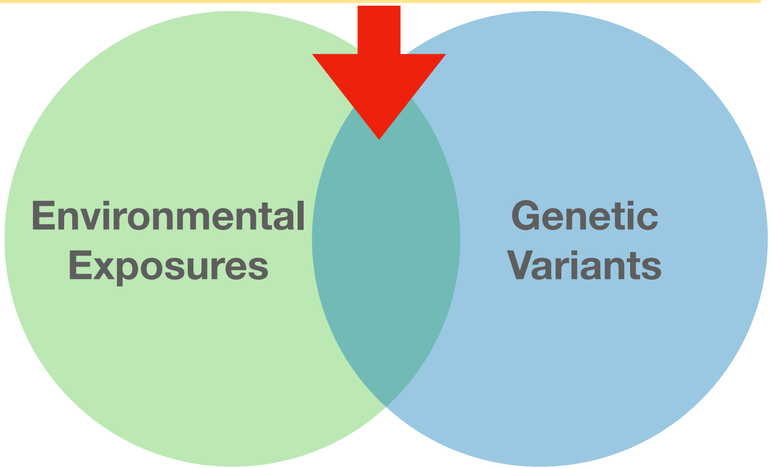
Salpingectomy alone is not the standard of care for risk reduction.

Clinical Significance of **Concurrent Hysterectomy** at the time of RRSO is unclear. (Limited data about serous uterine cancer in *BRCA1*)

NCCN Guideline Version 1.2022

Multifactorial Disease with Complex Inheritance

Complex Interaction



Incidence at Birth = 5% in pediatric

Prevalence = 60% of entire population

KEY: Genetic **increase risk** for disease compared to normal population

Qualitative Traits

Distinguish between individual who either have a disease or not

eg. Congenital Malformation, Alzheimer, Diabetes Mellitus, Cardiovascular Disease

Quantitative Traits

Measurable physiological or biochemical quantity

eg. Blood Pressure, Body Height, Body Mass Index, Cholesterol level

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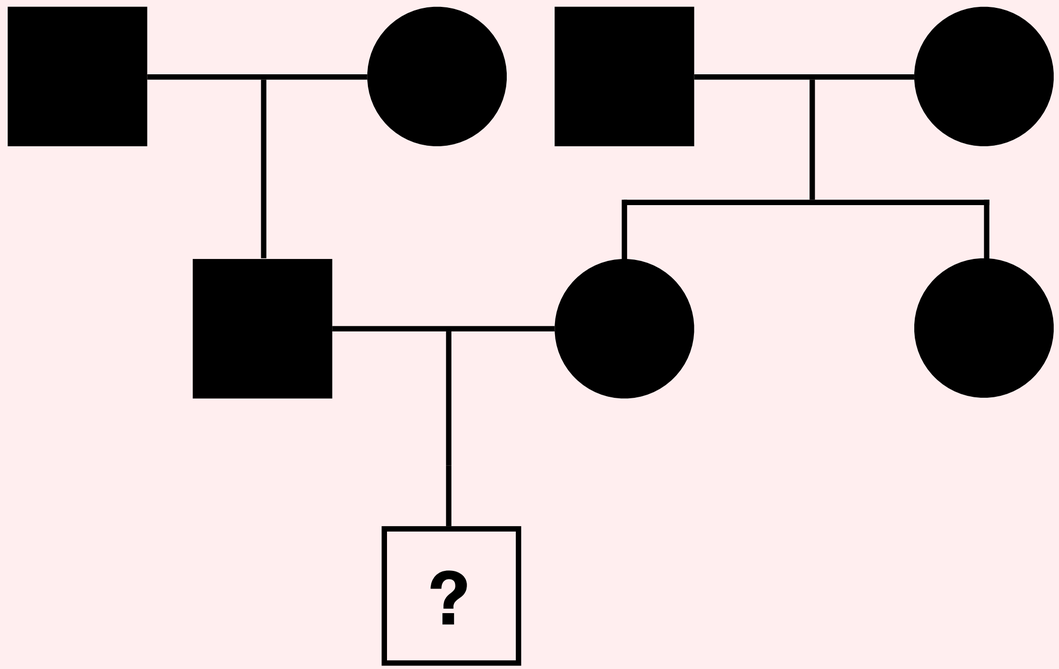
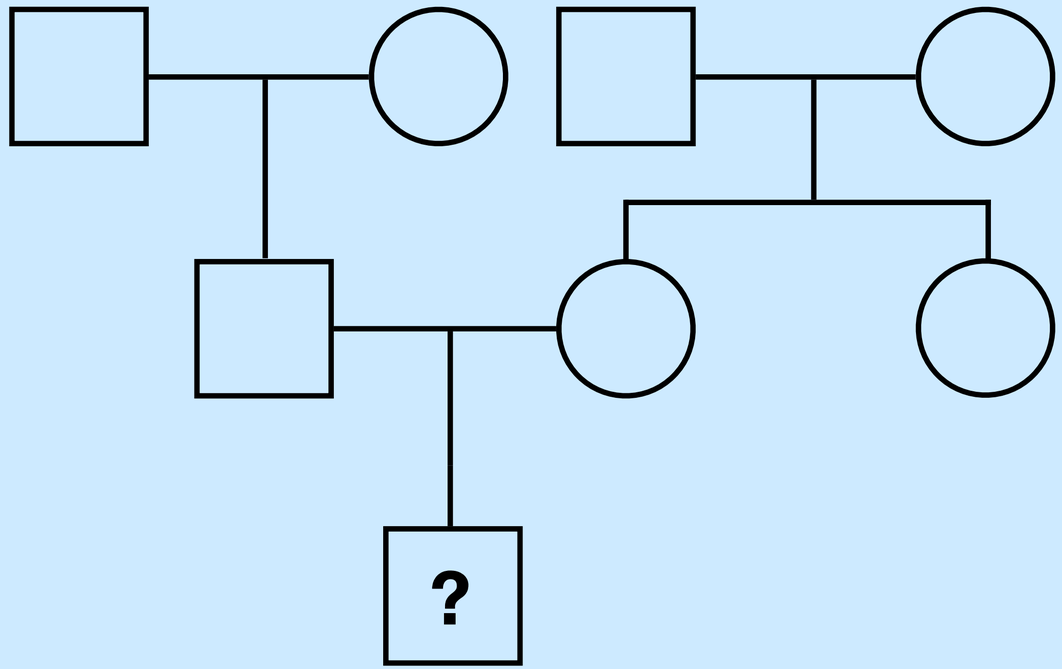
Multifactorial Disease with Complex Inheritance

First Family



VS

Second Family



The relatives of an affected individual are more likely to experience the same **gene-gene** and **gene-environment** interaction.

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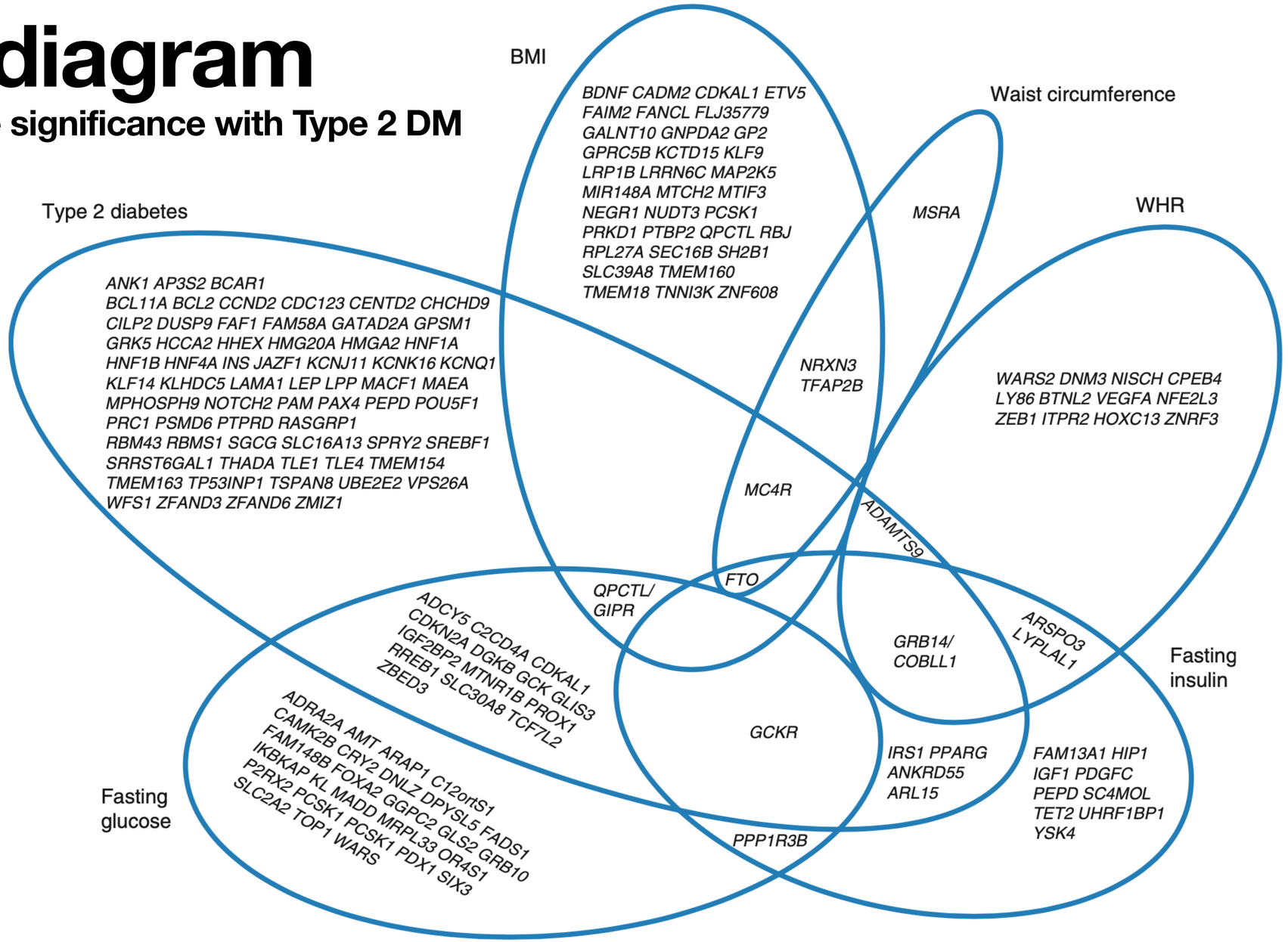
Venn diagram

Genome-wide significance with Type 2 DM



Emery's Elements of Medical Genetics 15th Edition.

Polygenic Risk Score

What is a polygenic risk score ?

A score reflecting the risk of developing a disease,

calculated as the weighted sum of risk alleles:

$$PRS = \sum_{i=1}^{N} \beta_i * SNP_i$$

β_i = the effect size of an individual SNP_i on a certain phenotype

SNP_i = the allelic dosage counts

*Generally used in complex disease, but could also be using in predicting the penetrance of traditional genetic diseases.

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Polygenic Risk Score

What is a polygenic risk score ?

Single-nucleotide polymorphism
(SNP)

Effect allele

A

Reference allele

G

AA - 2
AG - 1
GG - 0

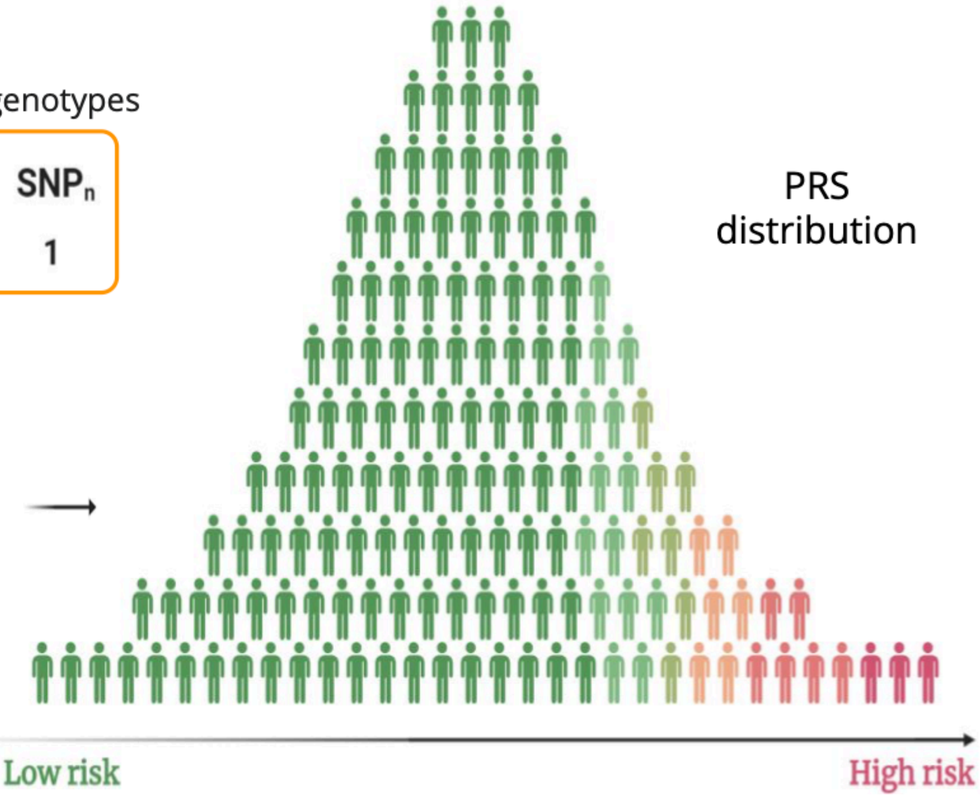
X - vector of the individual's marker genotypes

SNP_1	SNP_2	SNP_3	SNP_4	.....	SNP_n
0	2	0	1		1

$$PRS = \sum_{i=1}^{n} X_i \beta_i$$

β - vector of the weights of SNPs for a trait of interest

SNP_1	SNP_2	SNP_3	SNP_4	.....	SNP_n
β_1	β_2	β_3	β_4		β_n



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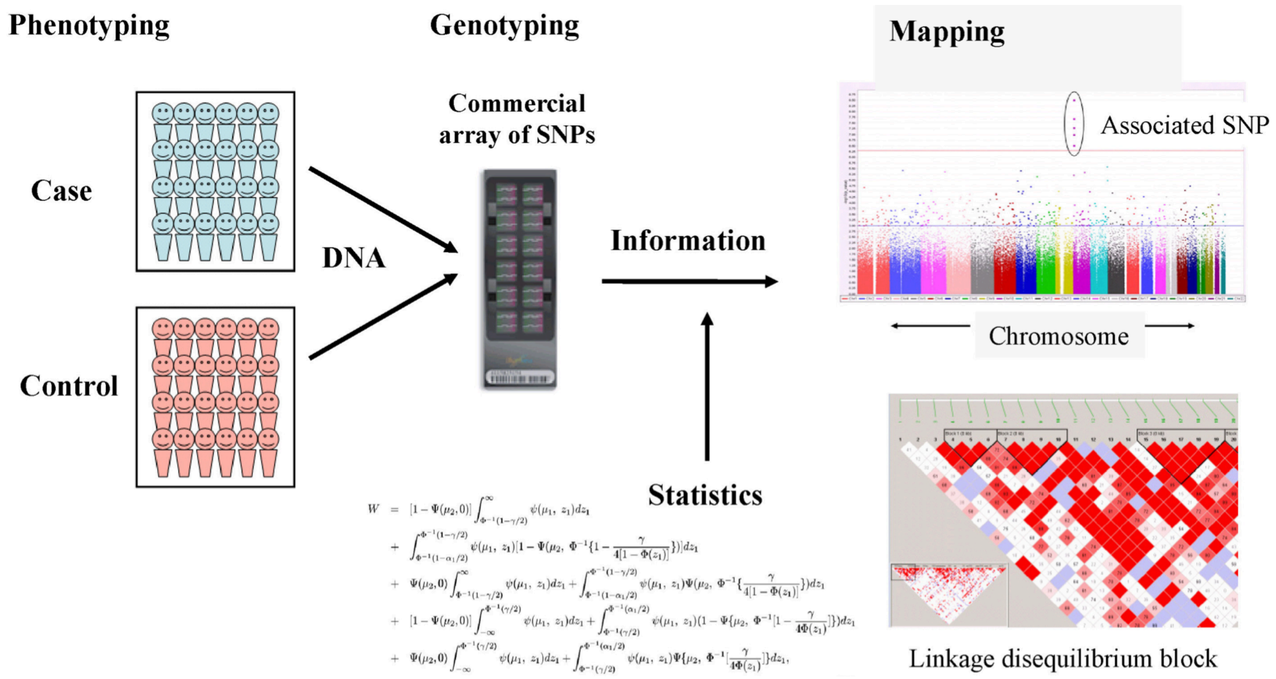
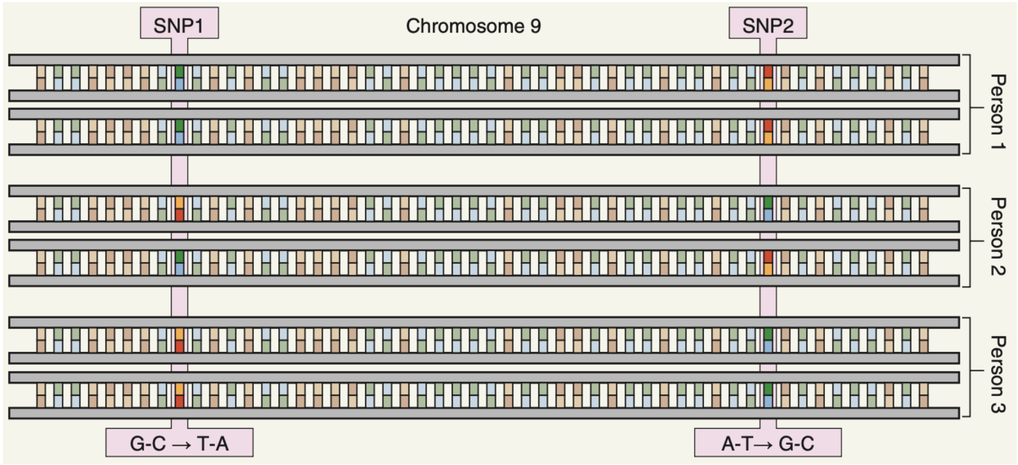
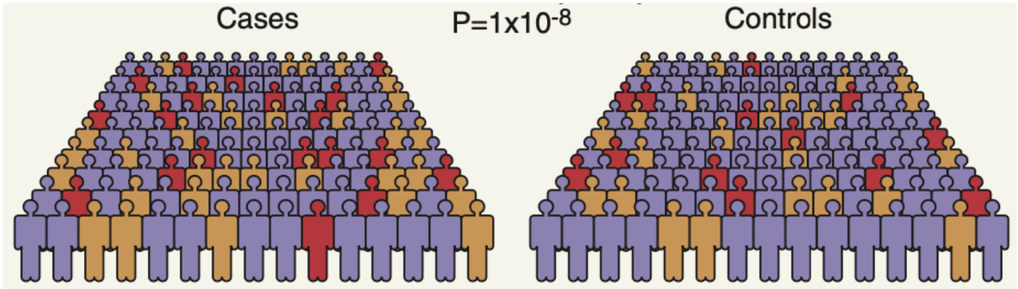
Polygenic Risk Score

Genome Wide Association Study



$$
\begin{aligned}
W &= [1-\Psi(\mu_2,0)]\int_{\Phi^{-1}(1-\gamma/2)}^{\infty}\psi(\mu_1,z_1)dz_1 \\
&+ \int_{\Phi^{-1}(1-\alpha_1/2)}^{\Phi^{-1}(1-\gamma/2)}\psi(\mu_1,z_1)[1-\Psi(\mu_2,\Phi^{-1}\{1-\frac{\gamma}{4[1-\Phi(z_1)]}\})]dz_1 \\
&+ \Psi(\mu_2,0)\int_{\Phi^{-1}(1-\gamma/2)}^{\infty}\psi(\mu_1,z_1)dz_1 + \int_{\Phi^{-1}(1-\alpha_1/2)}^{\Phi^{-1}(1-\gamma/2)}\psi(\mu_1,z_1)\Psi(\mu_2,\Phi^{-1}\{\frac{\gamma}{4[1-\Phi(z_1)]}\})dz_1 \\
&+ [1-\Psi(\mu_2,0)]\int_{-\infty}^{\Phi^{-1}(\gamma/2)}\psi(\mu_1,z_1)dz_1 + \int_{\Phi^{-1}(\gamma/2)}^{\Phi^{-1}(\alpha_1/2)}\psi(\mu_1,z_1)(1-\Psi\{\mu_2,\Phi^{-1}[1-\frac{\gamma}{4\Phi(z_1)}]\})dz_1 \\
&+ \Psi(\mu_2,0)\int_{-\infty}^{\Phi^{-1}(\gamma/2)}\psi(\mu_1,z_1)dz_1 + \int_{\Phi^{-1}(\gamma/2)}^{\Phi^{-1}(\alpha_1/2)}\psi(\mu_1,z_1)\Psi\{\mu_2,\Phi^{-1}[\frac{\gamma}{4\Phi(z_1)}]\}dz_1,
\end{aligned}
$$





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Polygenic Risk Score

Current Issues

Accuracy of GWAS

Sample Size

Number of Variants Included

Uncertainty in Individual Level

(Especially in high risk individuals)

Common VS Rare Variants

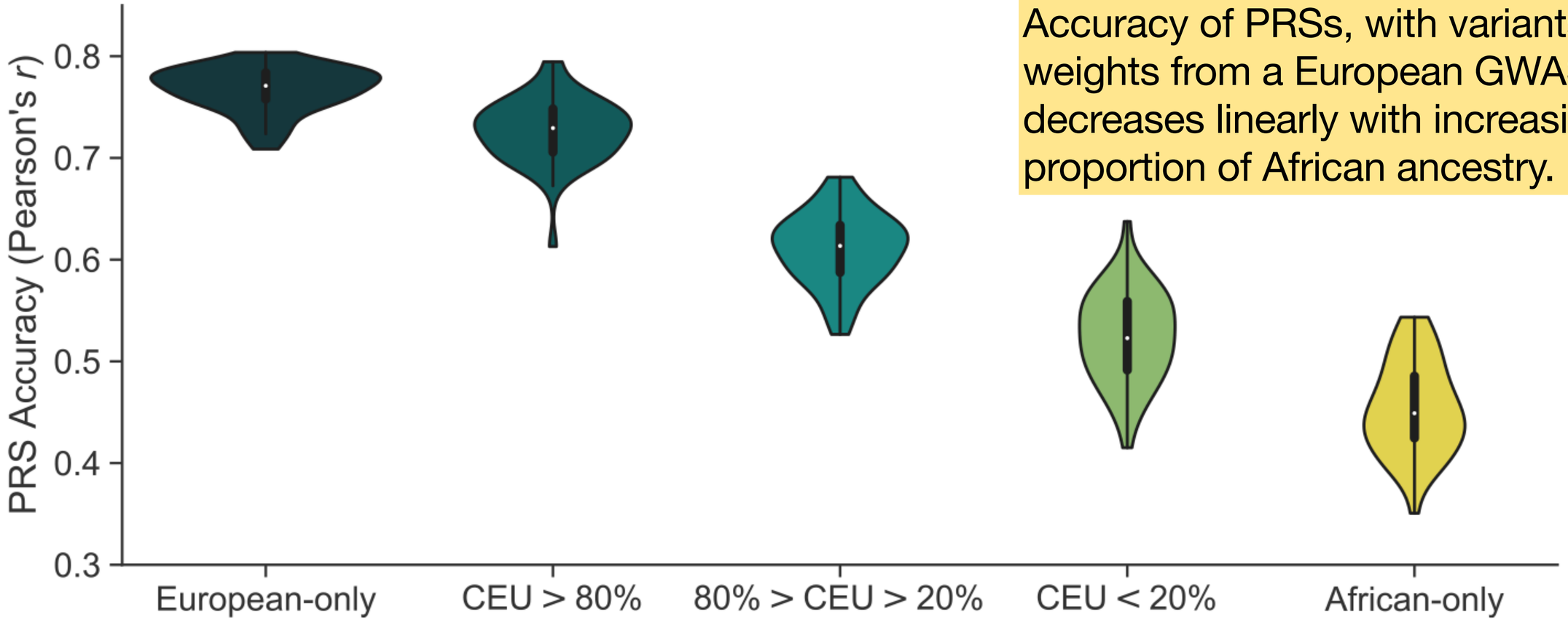
Interpretation of Results

Linkage Disequilibrium

Transferability

Polygenic Risk Score

Accuracy in distant population



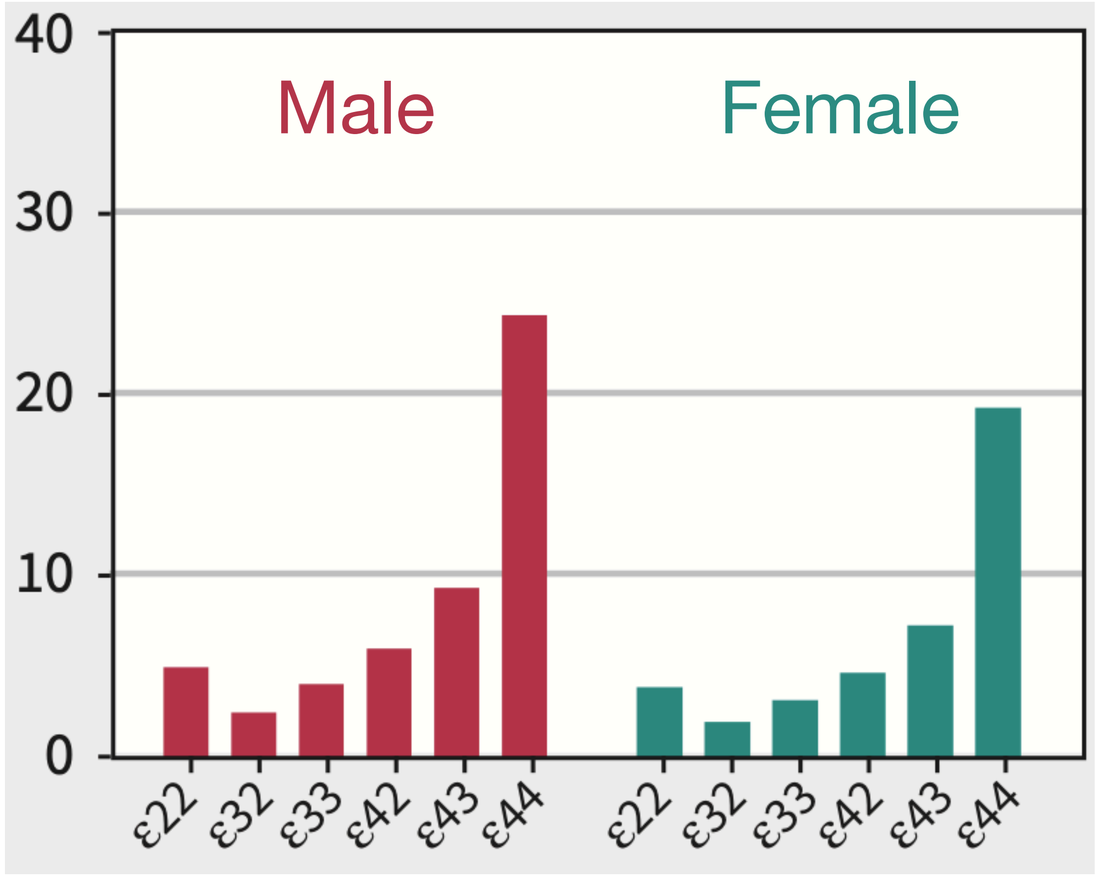
Accuracy of PRSs, with variants and weights from a European GWAS, decreases linearly with increasing proportion of African ancestry.

HGG Adv. 2021 Jan 14;2(1):100017.

Absolute 10-year risk of Alzheimer disease

At age ≥ 80

APOE genotype	*n* total	*n* events	HR (95% CI)
Alzheimer disease			
ε22	715	6	1.30 (0.58–2.91)
ε32	12 994	59	0.62 (0.47–0.82)
ε33	58 172	405	1.00 (Ref.)
ε42	3013	28	1.48 (1.01–2.16)
ε43	26 626	398	2.47 (2.15–2.84)
ε44	3017	112	8.74 (7.08–10.79)



CMAJ September 04, 2018 190 (35) E1033-E1041.

GEN Genetic Engineering & Biotechnology News

Mary Ann Liebert, Inc. publishers

Personality & Talent

Nutrigenomics

Multifactorial Disease

Ancestry

Take Home Message