PONTIFÍFICA UNIVERSIDADE ESTADUAL DE GOIÁS

PRÓ-REITORIA DE GRADUAÇÃO

CIÊNCIAS BIOLÓGICAS

BIO1230 - GENÉTICA

DOENÇAS MONOGÊNICAS

CONTRIBUIÇÃO MENDELIANA

Dr. Cláudio C. Silva

CONTRIBUIÇÃO MENDELIANA

- Albinismo REC
- Hemofilia REC
- Daltonismo REC
- Acromatopsia REC
- Fibrose Cística REC
- Ictiose Congênita REC
- Microcefalia Vera REC
- Hidrocefalia REC
- Fenilcetonúria (PKU) REC

- Acondroplasia DOM
- Polidactilia DOM
- Síndrome Orofaciodigital DOM
- Síndrome de Marfan DOM
- Ectrodactilia DOM
- Hipofosfatemia DOM
- Dentinogênese Imperfeita DOM
- Polipose Múltipla do Cólon DOM
- Prognatismo Mandibular DOM

DOENÇAS MONOGÊNICAS

OMIM – On line Mendelian Inheritance in Man

www3.ncbi.nlm.nhi.gov/Omim

> 14.000 características monogênicas

> 13.000 Autossômicas

~ 788 Ligadas ao Sexo (Cromossomo X)

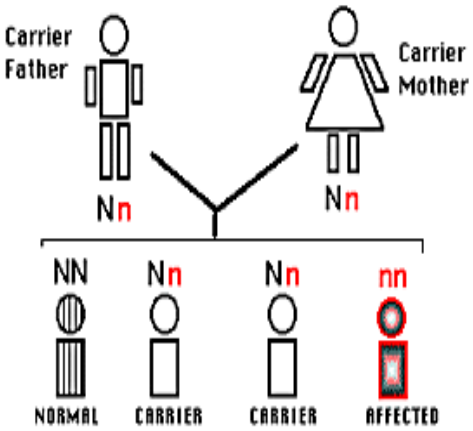
~ 43 Restritas ao Sexo (Cromossomo Y)

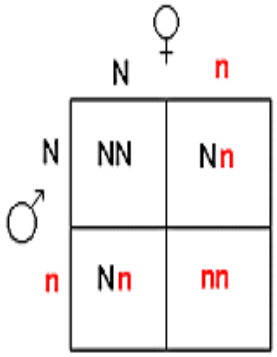
CONTRIBUIÇÃO MENDELIANA

The rules governing complex diseases are difficult to predict because they involve many factors, including life-style.

Monogenic Diseases	Complex Diseases
one gene	many genes
Inheritance Pattern (dominant or recessive)	Inheritance Pattern (complex)
100 / 0 with gene / without gene — Risk in Population	100 / 0 Risk in Population (includes lifestyle and environment)

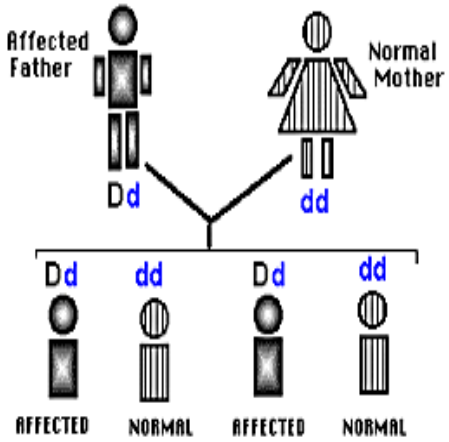
Herança Recessiva

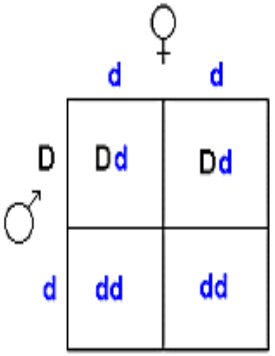




Normal: NN ou Nn
Afetado: nn

Herança Dominante





Normal: dd
Afetado: DD ou Dd

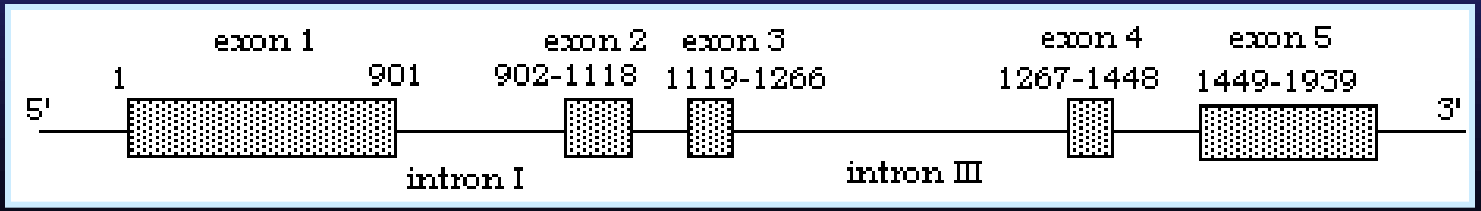
CONTRIBUIÇÃO MENDELIANA

DAR – Doença Autossômica Recessiva

Albinismo

Erro na enzima ***tirosinase,*** que transforma a tirosina em Melanina (proteína responsável pela pigmentação normal da pele humana).

Gene	**Tipos de Albinismo**
Tyrosinase gene	OCA1 (OCA1A and OCA1B)
P gene	OCA2
TRP1 gene	OCA3
HPS gene	Hermansky-Pudlak Syndrome
CHS gene	Chediak Higashi Syndrome
OA1 gene	X-linked ocular albinism



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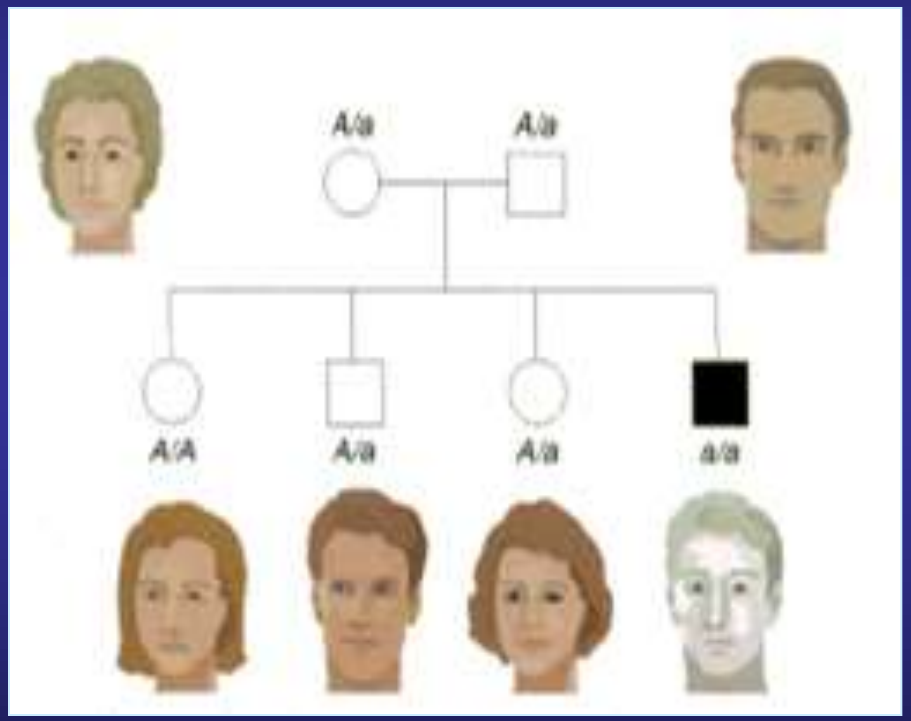

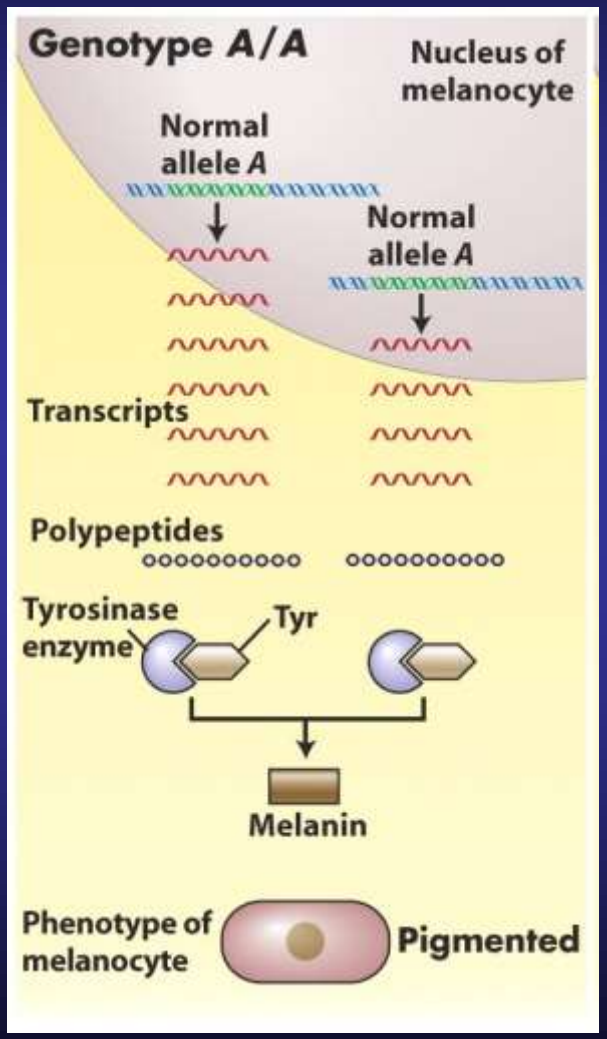

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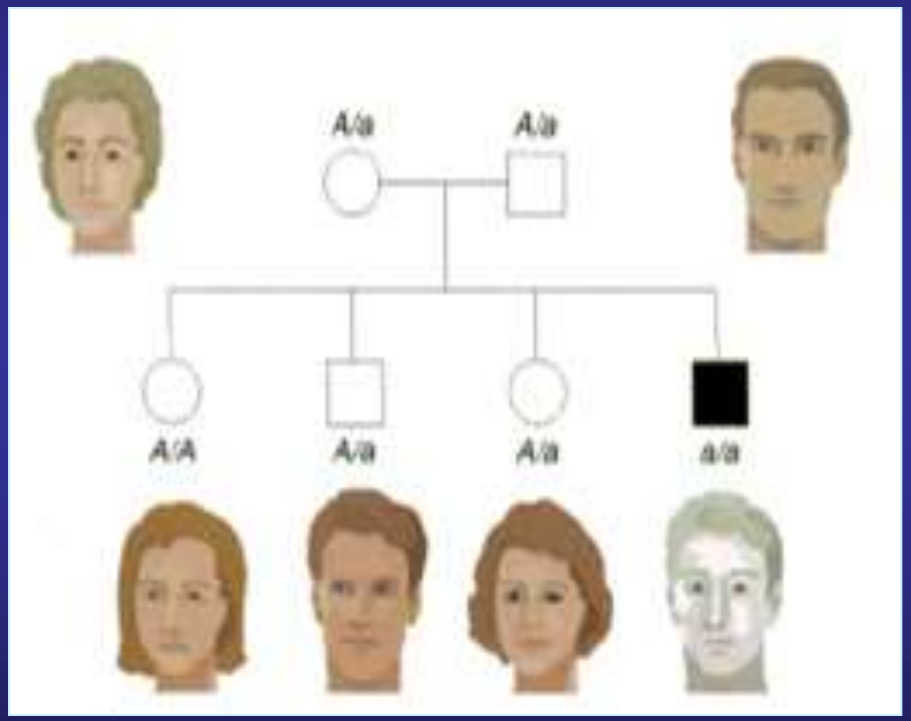

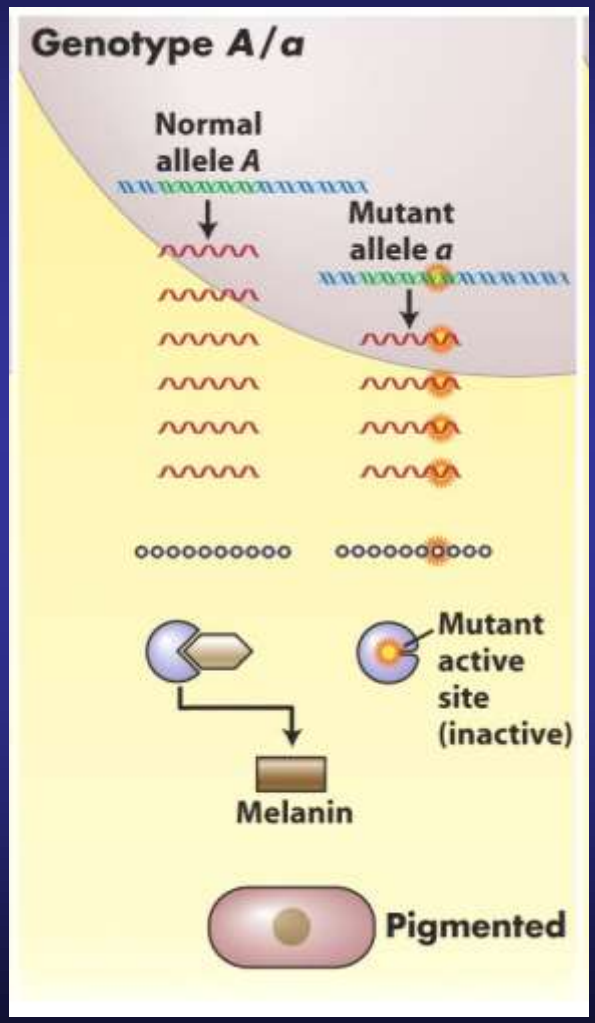

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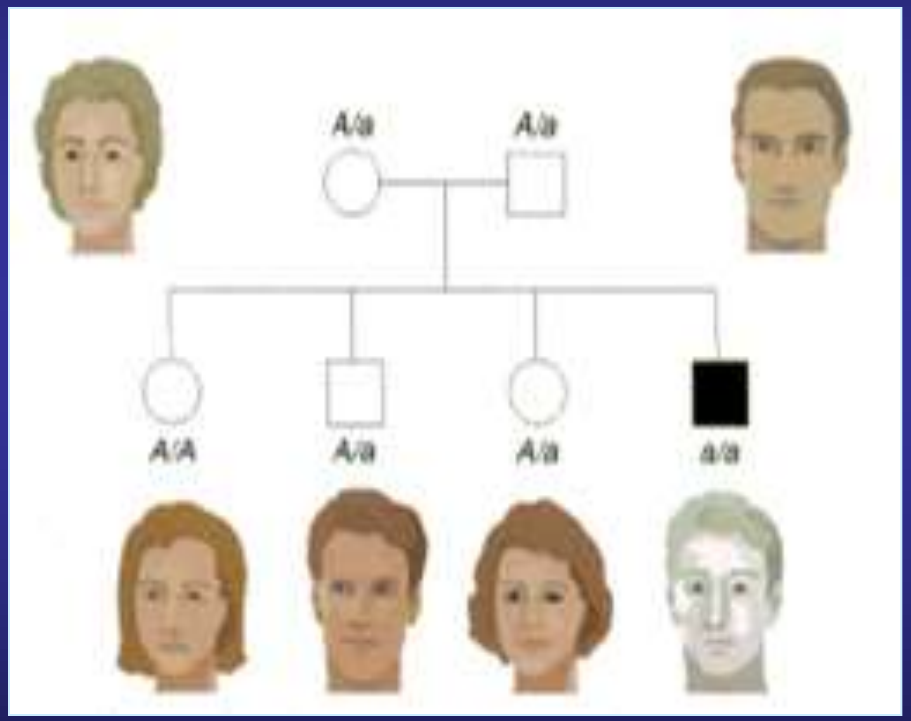
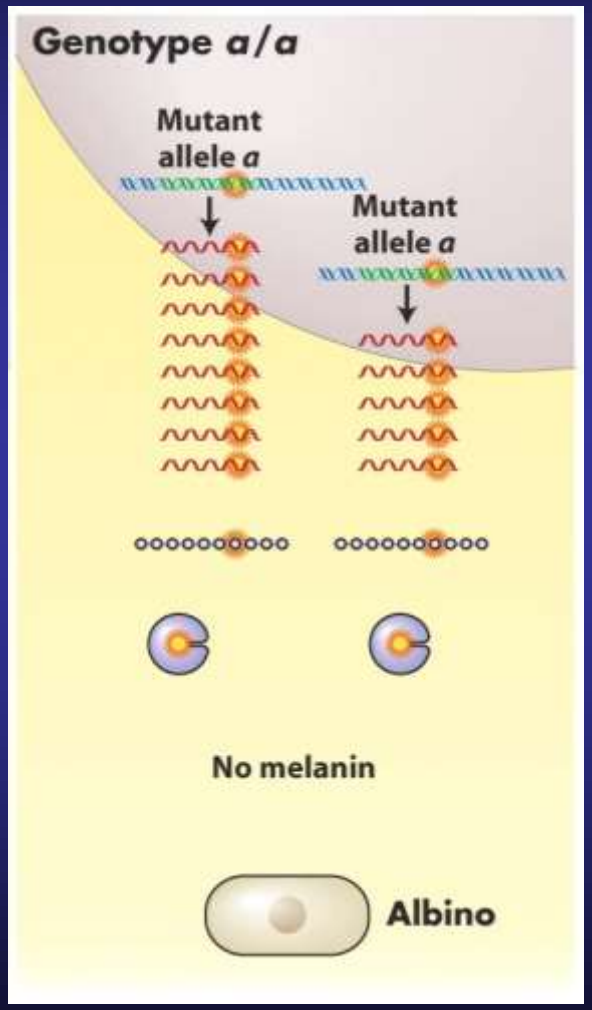
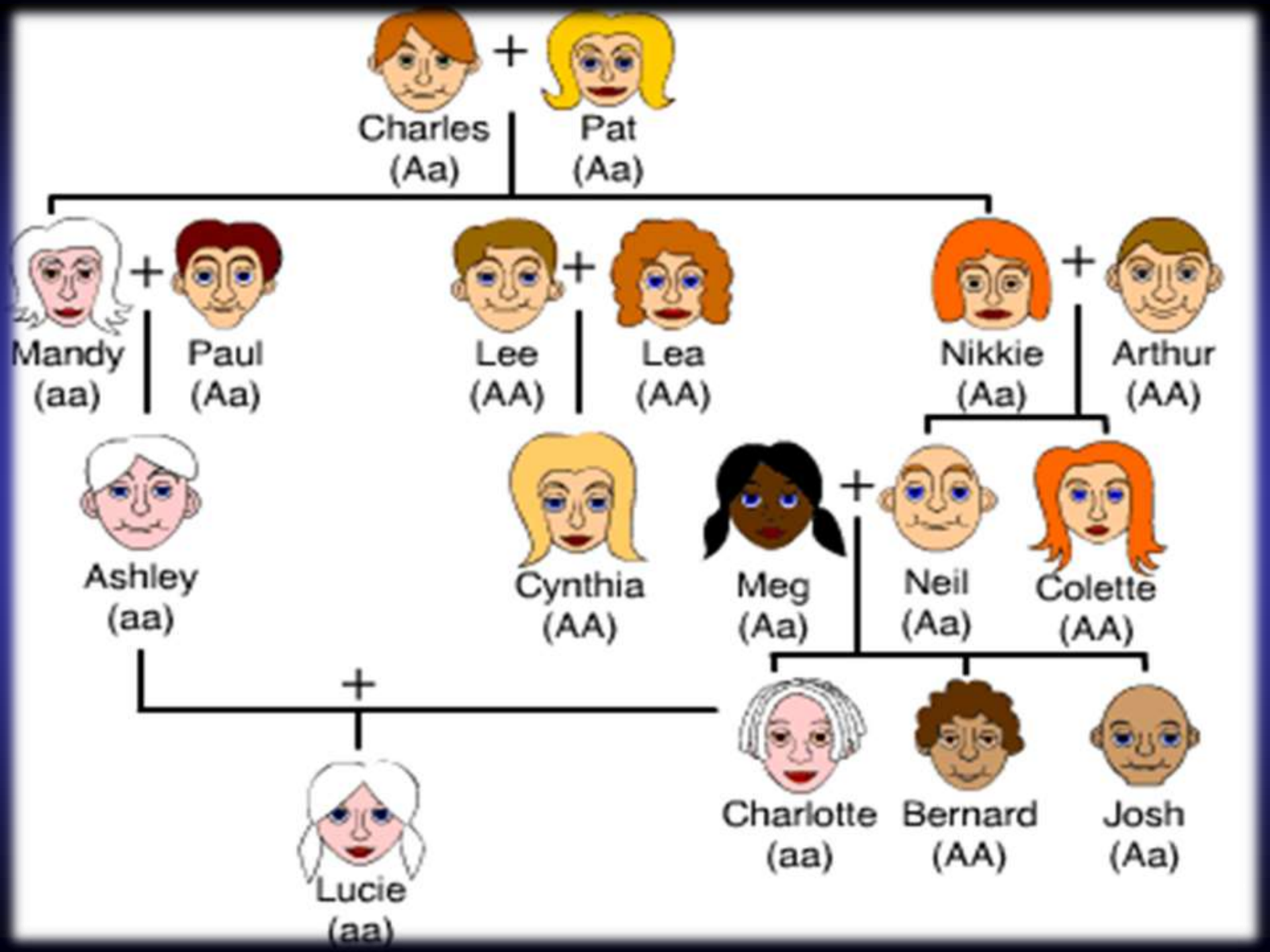





Charles
(Aa)
Pat
(Aa)
Mandy
(aa)
Paul
(Aa)
Lee
(AA)
Lea
(AA)
Nikkie
(Aa)
Arthur
(AA)
Ashley
(aa)
Cynthia
(AA)
Meg
(Aa)
Neil
(Aa)
Colette
(AA)
Lucie
(aa)
Charlotte
(aa)
Bernard
(AA)
Josh
(Aa)

CONTRIBUIÇÃO MENDELIANA

Acondroplasia – DAD (Doença Autossômica Dominante)

Nanismo acentuado, sem deficiência mental, cabeça grande e testa saliente

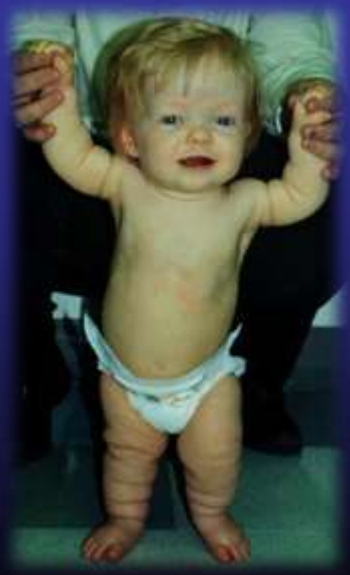
Em **homozigose** é letal.

Pode Ocorrer **Casos esporádicos**

CONTRIBUIÇÃO MENDELIANA

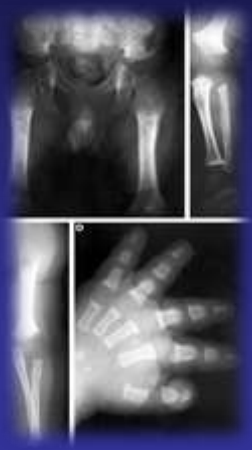
Aproximadamente 80% dos casos (a maioria) aparece como mutações espontâneas.

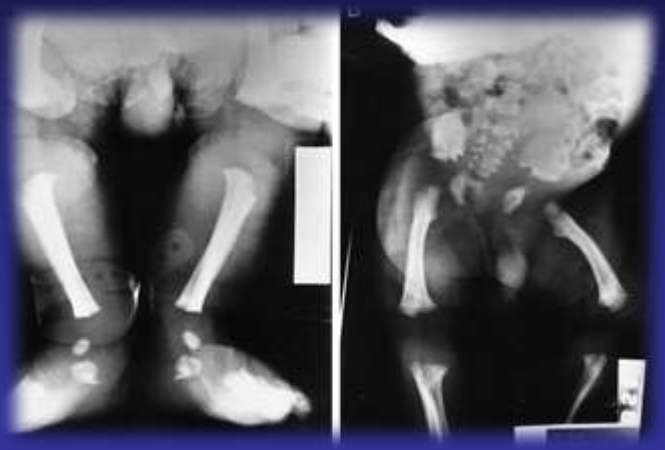
A aparência característica do nanismo por acondroplasia é visível desde o nascimento.

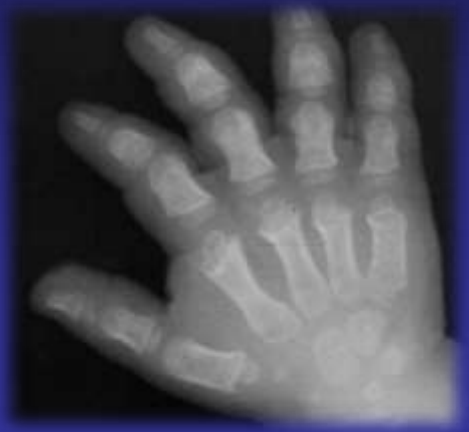


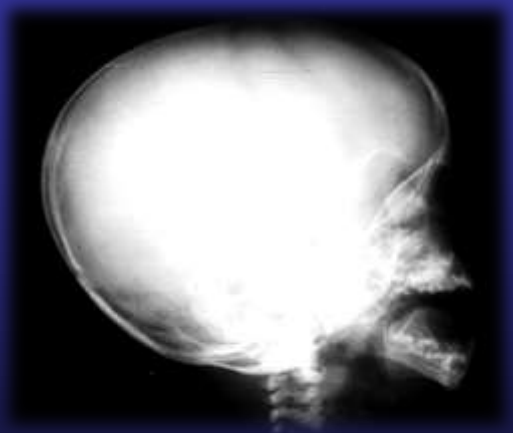
Baixa estatura, membros curtos (rizomelia); extremidade proximal (parte superior do braço e coxa), cabeça de aparência grande, pode estar associada a um pé torto e outras anormalidades esquelética dos membros.

CONTRIBUIÇÃO MENDELIANA

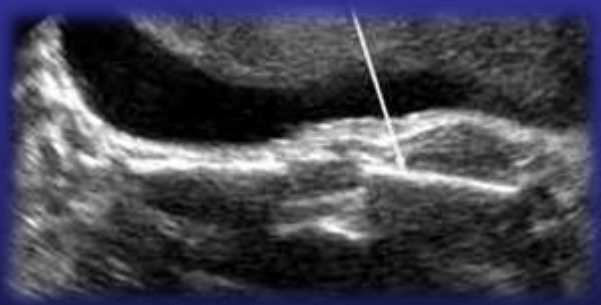


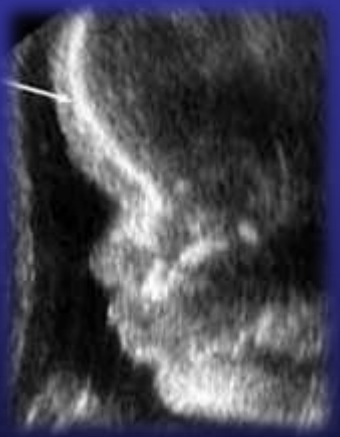






USG (32 semanas)





CONTRIBUIÇÃO MENDELIANA

DOENÇA: Acondroplasia

TIPOS DE ANÁLISES: DNA

TIPO DE DOENÇA: Dominante Autossômica

EXAMES: Gene FGFR3, análise de mutação

SIGLA: *aco*

SINONÍMIAS: Nanismo Acondroplásico

LOCUS: 4p16.3

GENE: FGFR3

OMIM: 100800 ACHONDROPLASIA; ACH134934 FIBROBLAST GROWT FACTOR RECEPTOR 3; FGFR3

CONTRIBUIÇÃO MENDELIANA

Mais de **97%** dos pacientes com acondroplasia apresentam a mesma mutação, **uma transição G à A no nucleotídeo 1138 do DNA (G1138A)**, levando à substituição de uma **glicina por arginina** no domínio transmembranar do receptor do fator de crescimento fibroblástico 3 (***FGFR3***).

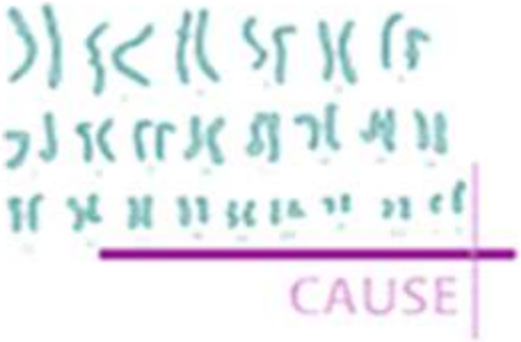
A segunda mutação, vista em aproximadamente **2,5%** dos casos, é uma **transversão G à C na mesma posição 1138 (G1138C)** levando à **mesma substituição de aminoácidos**.

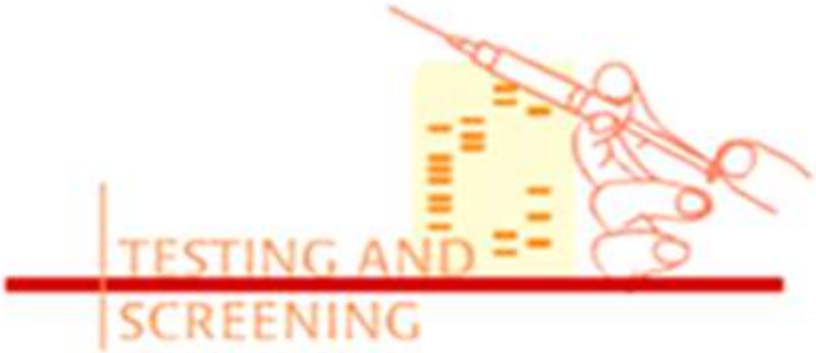
Hipocondroplasia: Rizomelia causada pela **mutação C1620A** também no gene ***FGFR3***.

CONTRIBUIÇÃO MENDELIANA

Fibrose Cística

(Mucoviscosidade)





CONTRIBUIÇÃO MENDELIANA

DAR – Doença Autossômica Recessiva

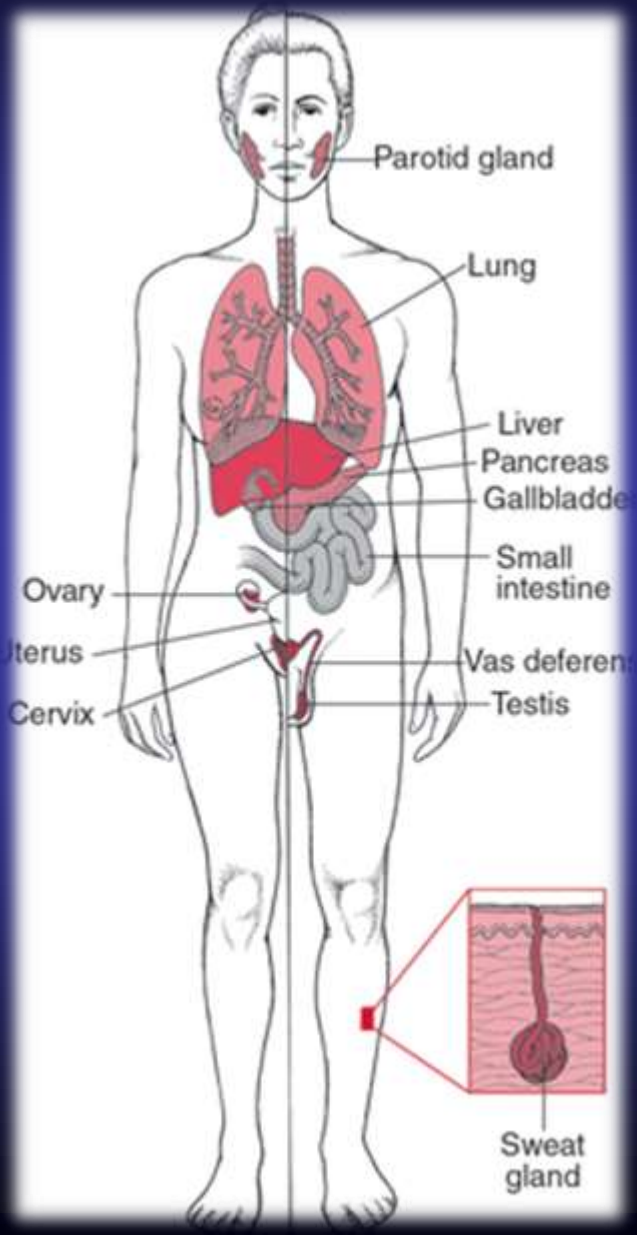
Distúrbio na secreção glandular (aumento na viscosidade da secreção)

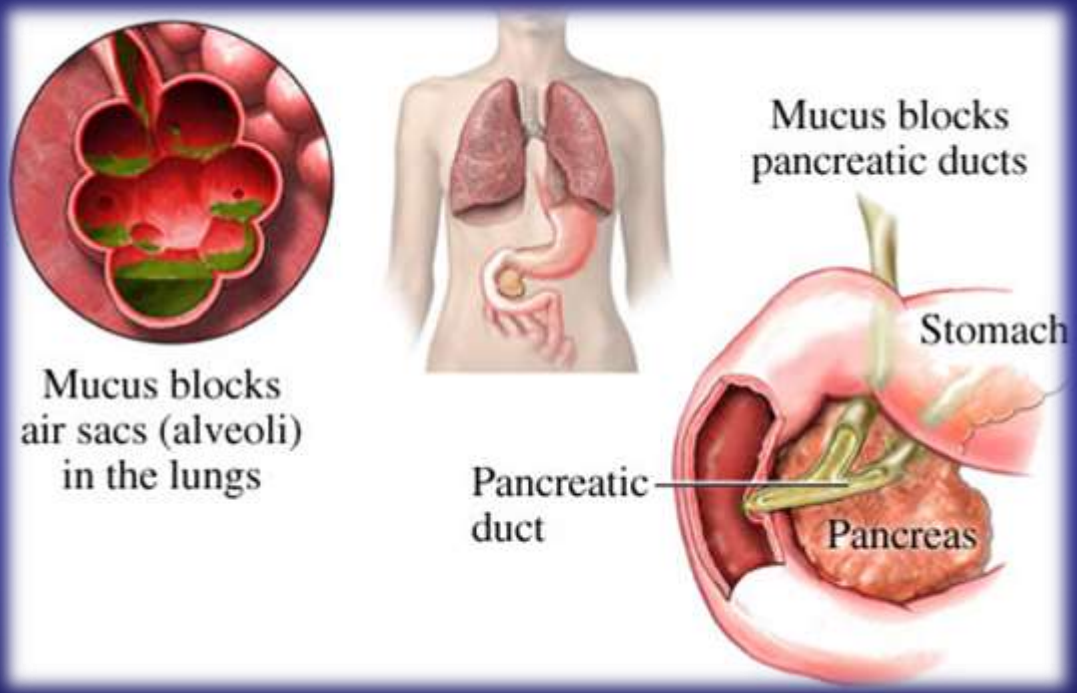
FIBROSE CÍSTICA
(Mucoviscosidade)

1:2000 (América do Norte)
1:4000 (Caucasóides)
1:15.000 (Negros)
1:40.000 (Asiáticos)

1:10.000 (Brasil)

CONTRIBUIÇÃO MENDELIANA





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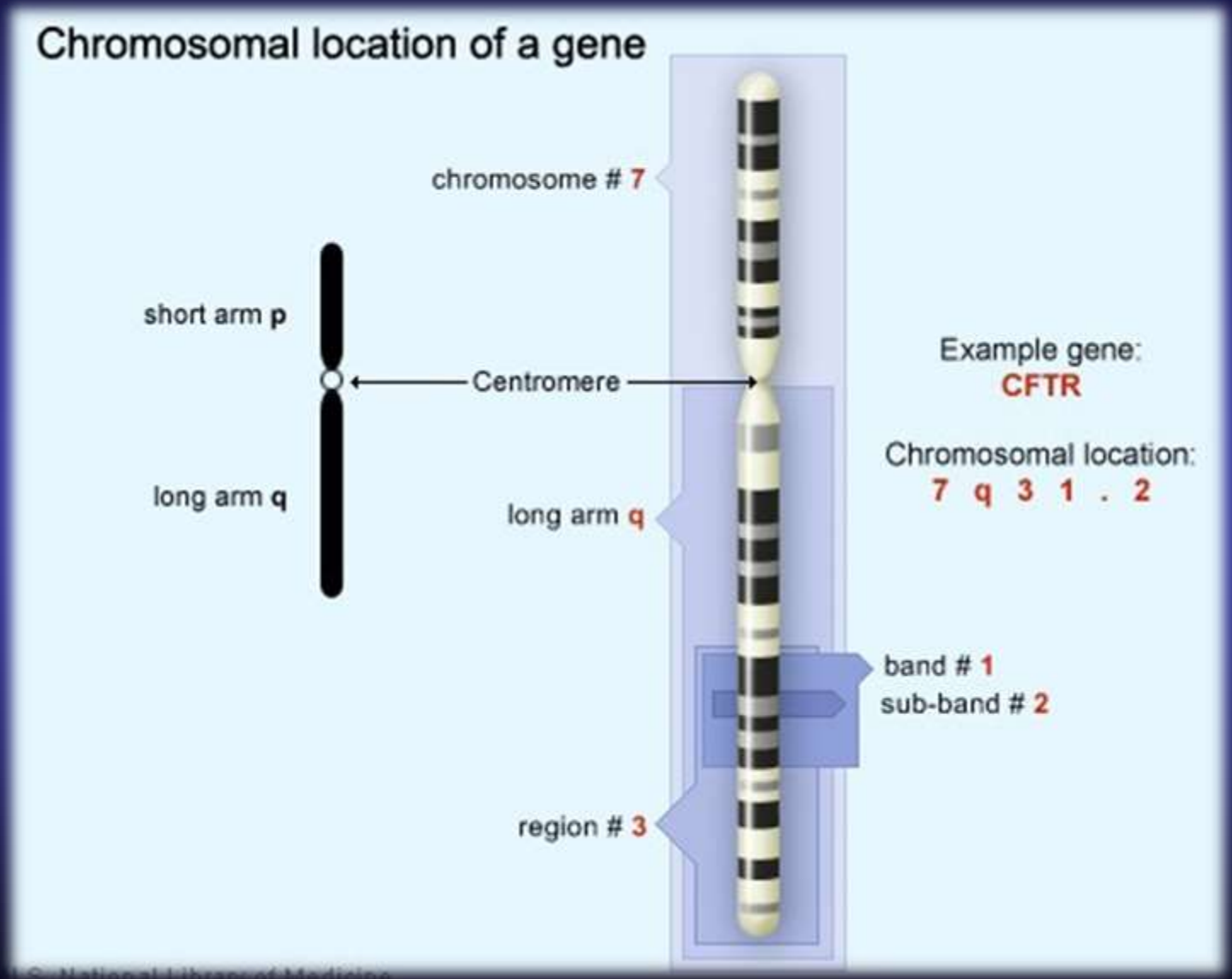

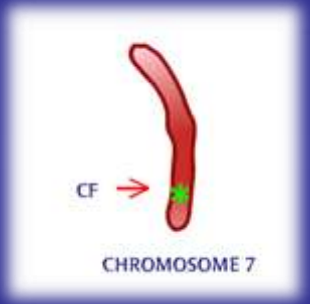

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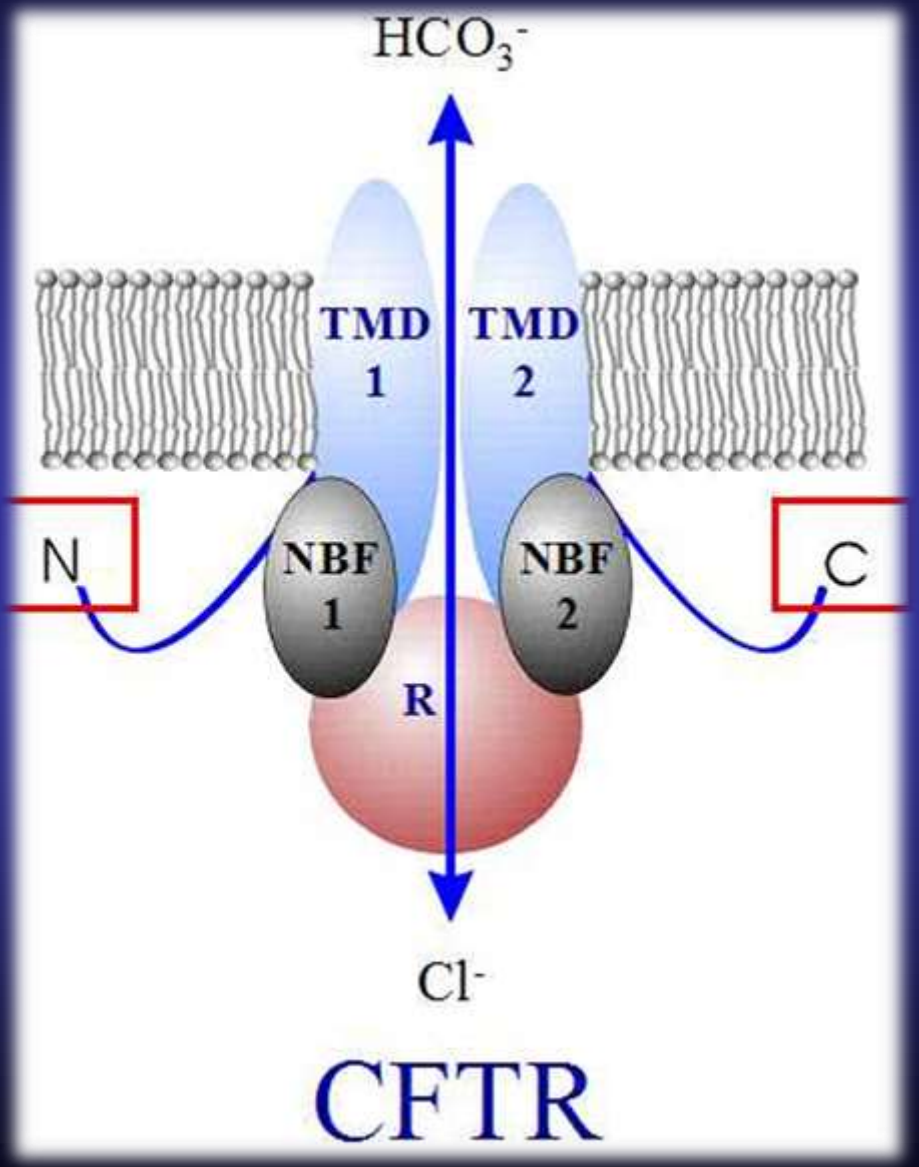
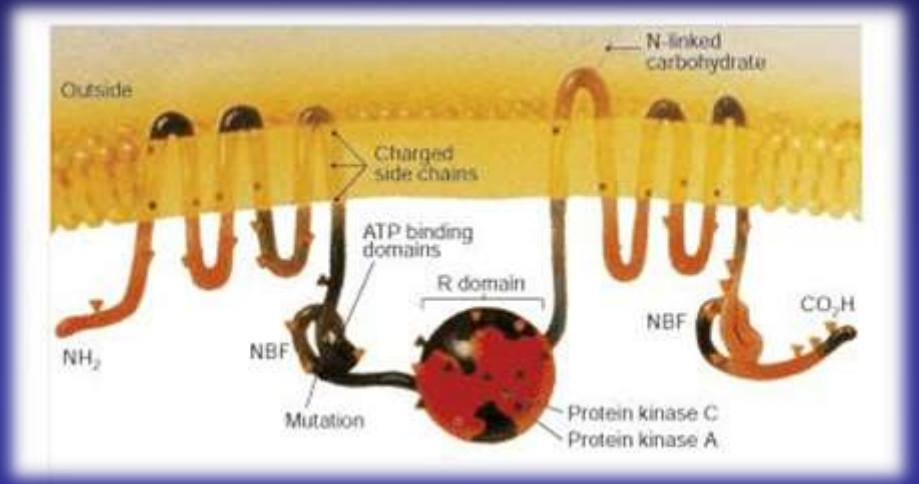
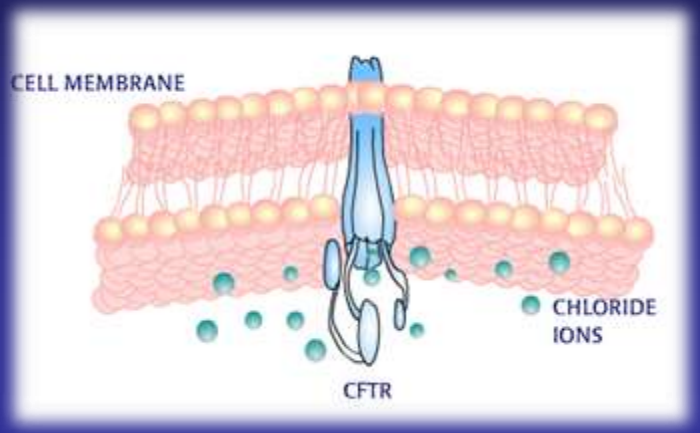


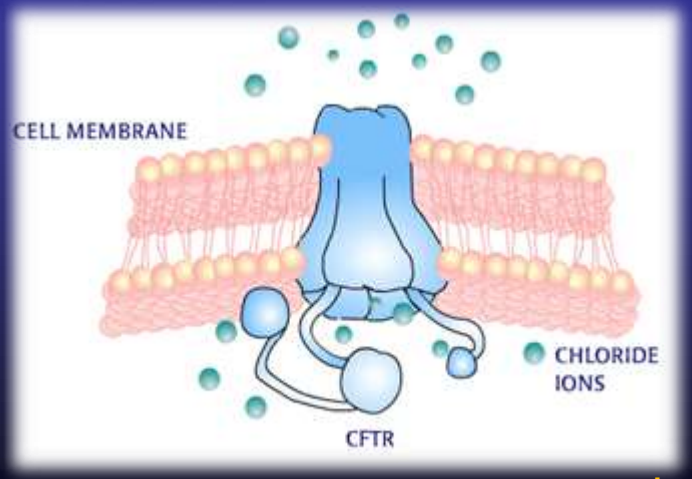


- Fator Transmembrânico de Regulação da Condutância (CFTR)
- Perfil mutacional populacional específico
- Mutação ΔF508

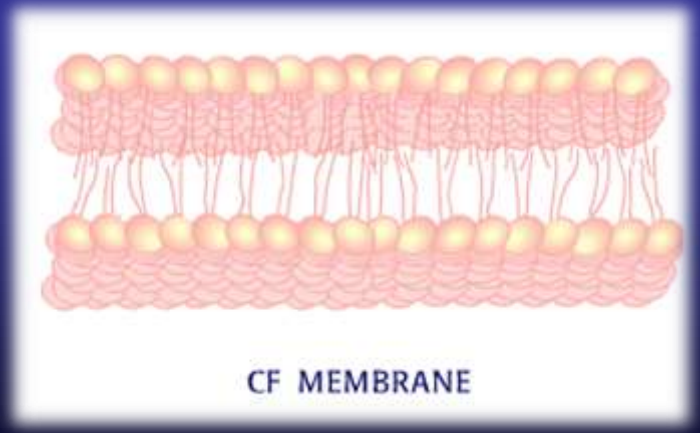
CONTRIBUIÇÃO MENDELIANA



Fibrose Cística



Normal



CHROMOSOME 7

isoleucine 506 →

isoleucine 507 →

phenylalanine 508 →

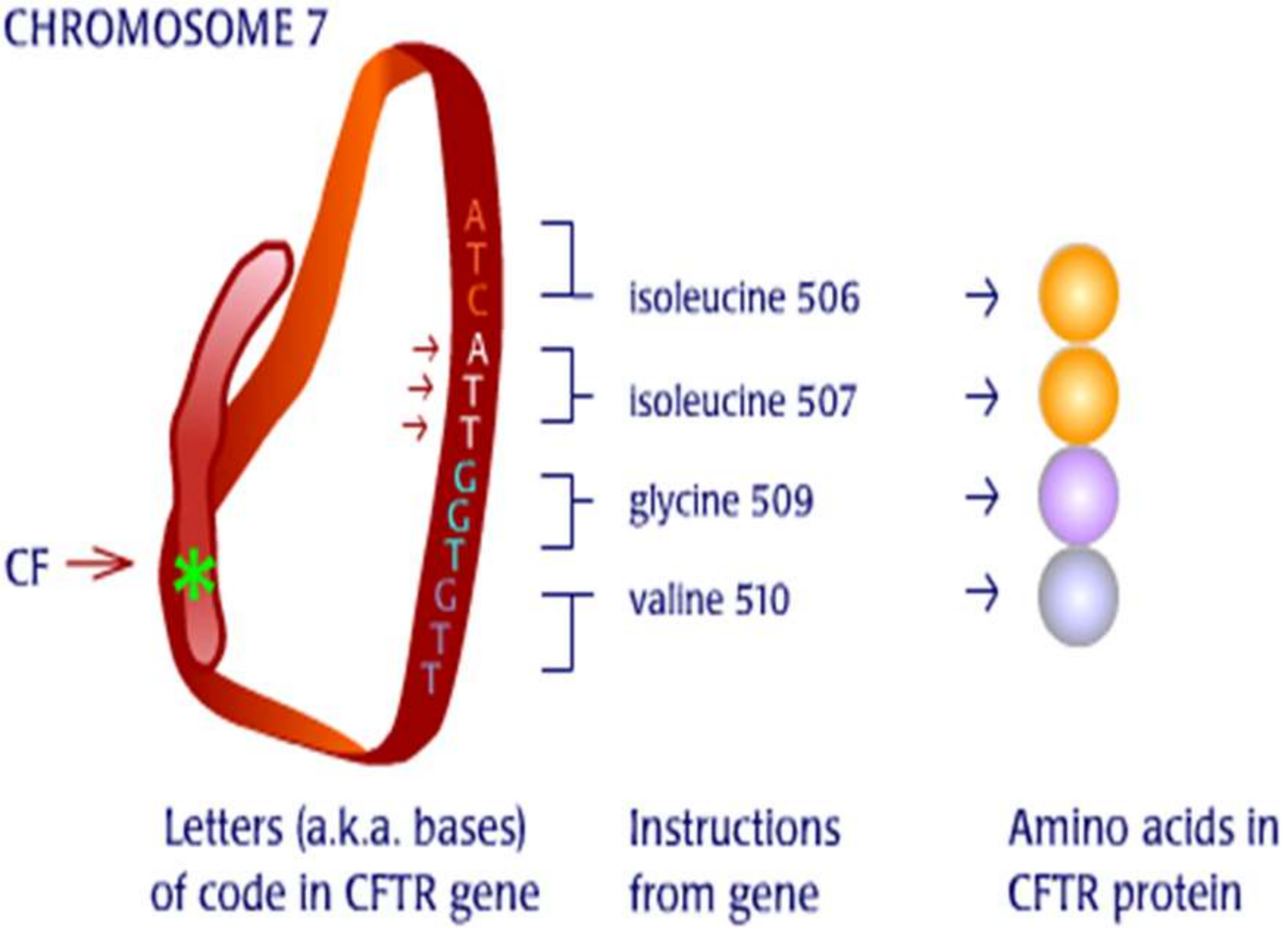
glycine 509 →

valine 510 →

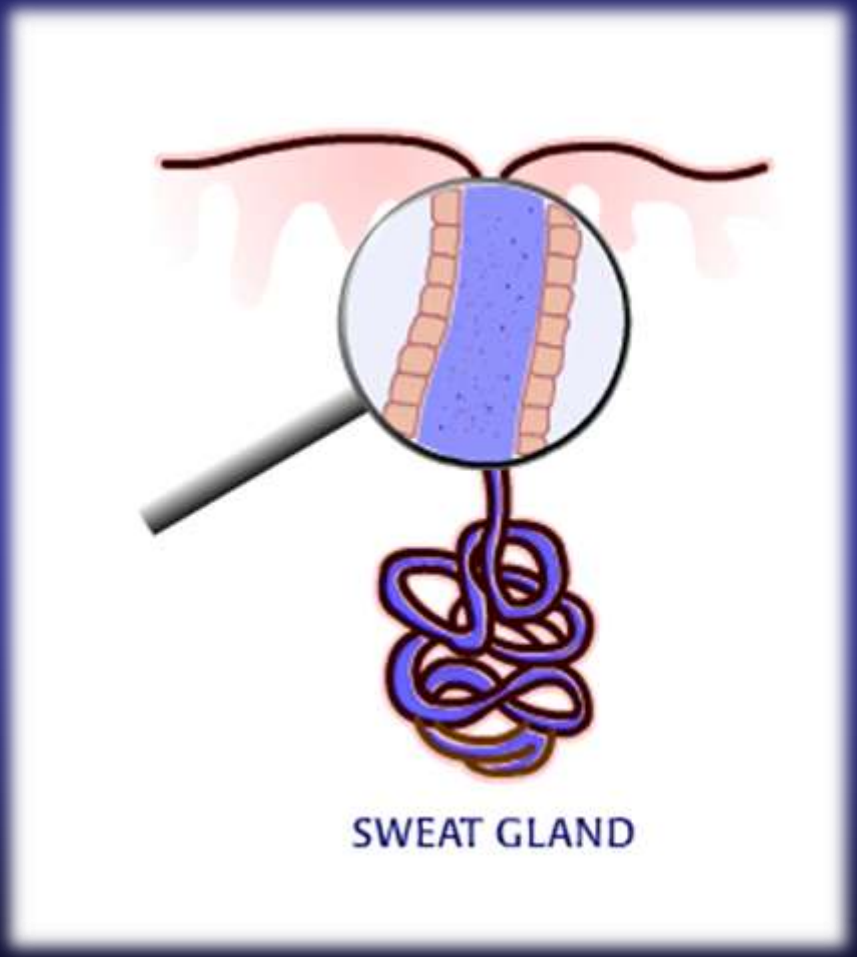
Letters (a.k.a. bases) of code in CFTR gene

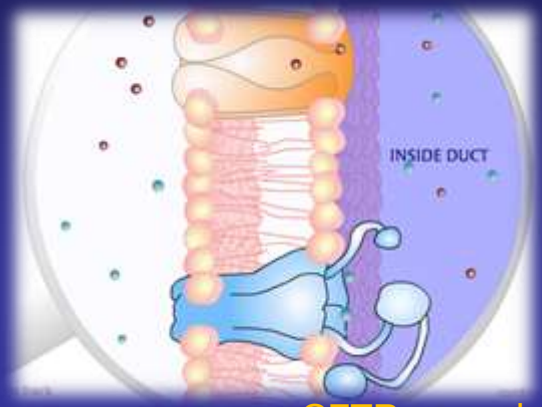
Instructions from gene

Amino acids in CFTR protein

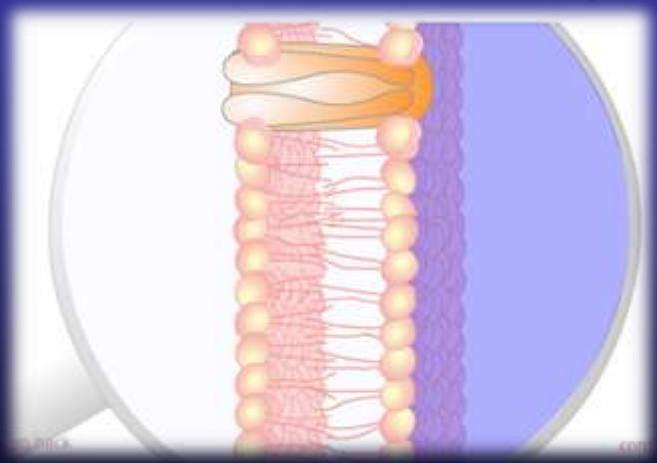

CHROMOSOME 7
CF
ATCATTGGTGTT
isoleucine 506
isoleucine 507
glycine 509
valine 510
Letters (a.k.a. bases) of code in CFTR gene
Instructions from gene
Amino acids in CFTR protein

CONTRIBUIÇÃO MENDELIANA



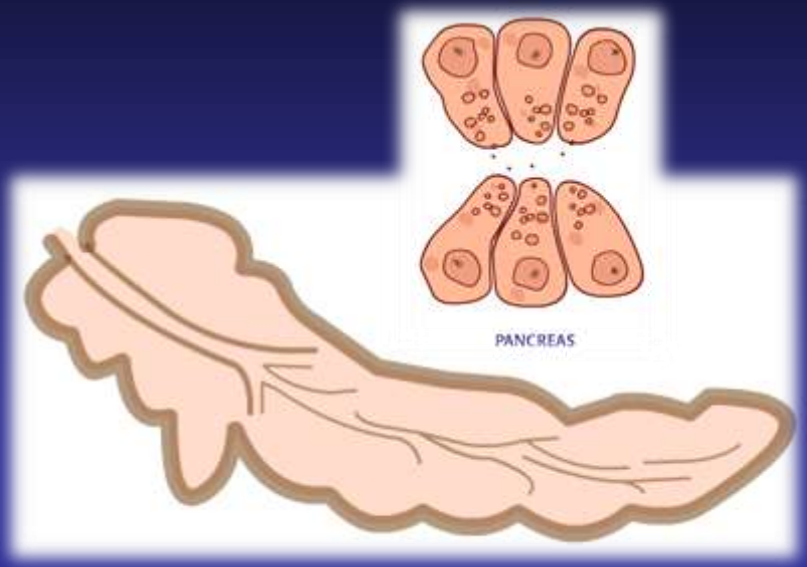


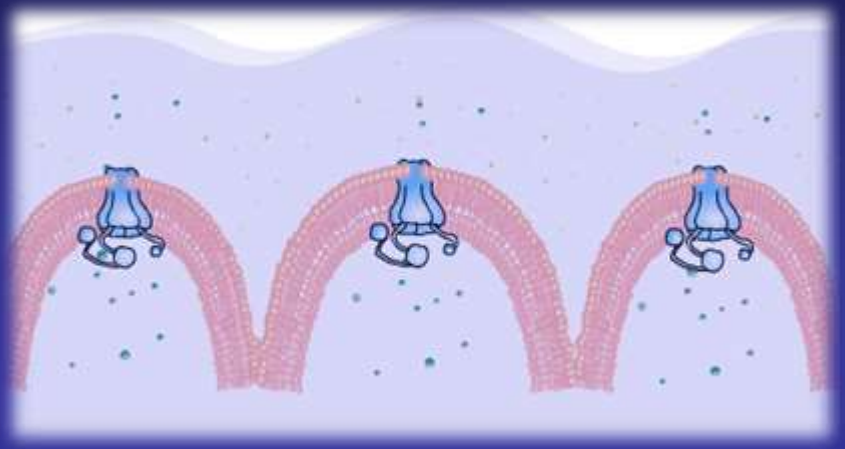
CFTR normal



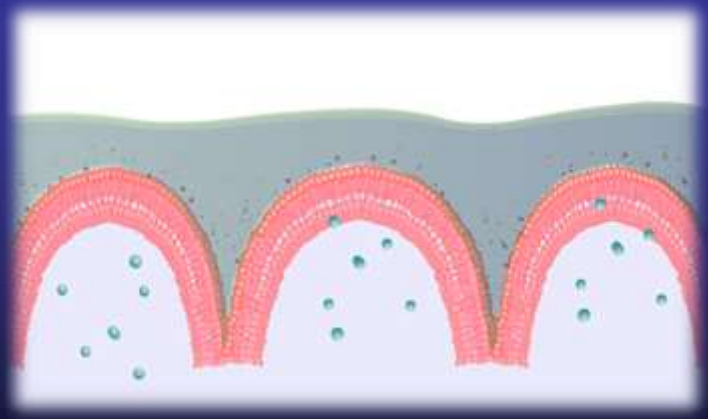
Ausência da CFTR
70 – 80%

CONTRIBUIÇÃO MENDELIANA



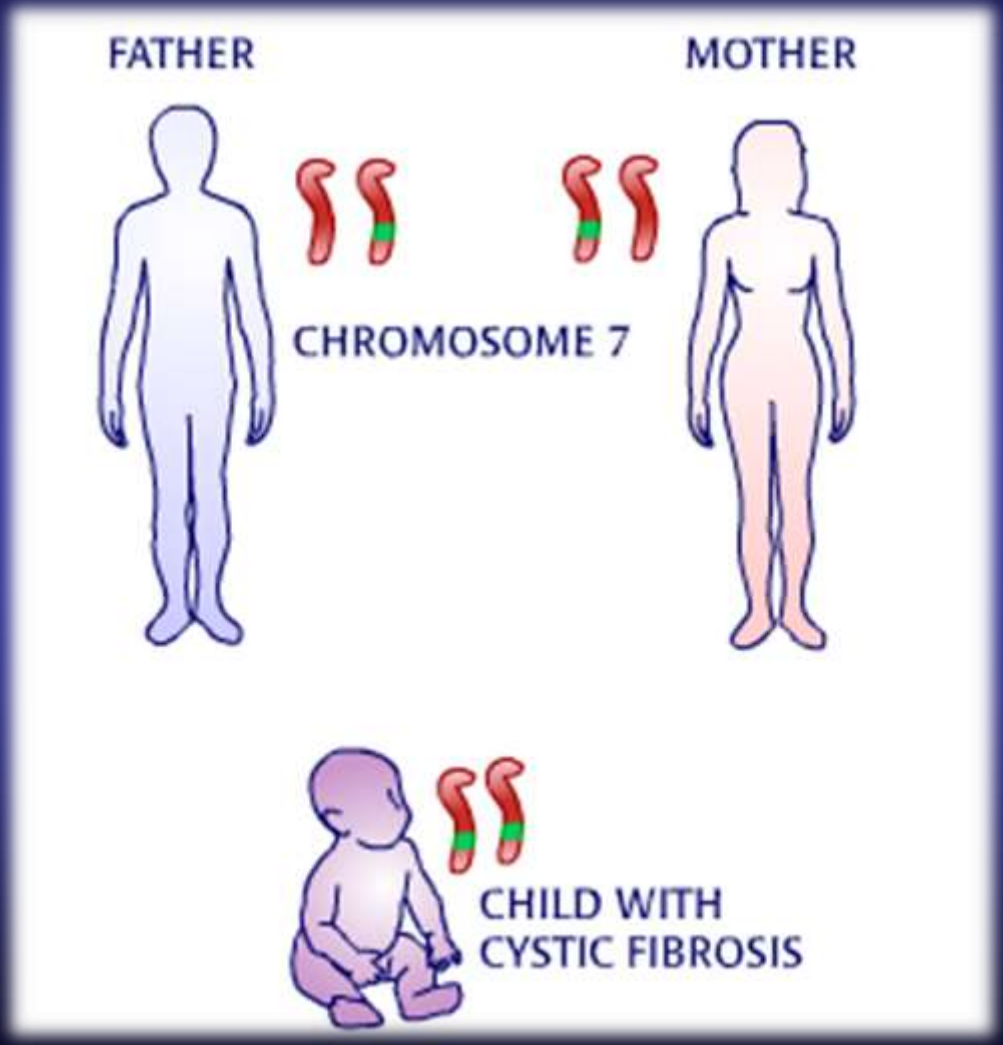


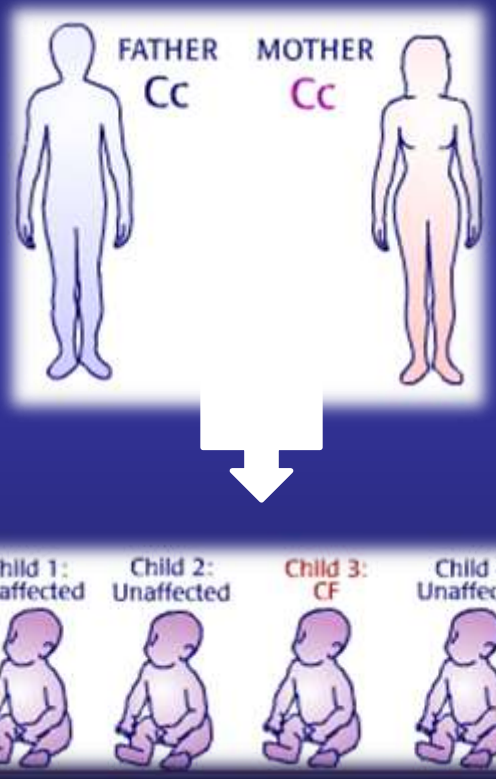
CFTR normal



Ausência da CFTR
70 – 80%

CONTRIBUIÇÃO MENDELIANA





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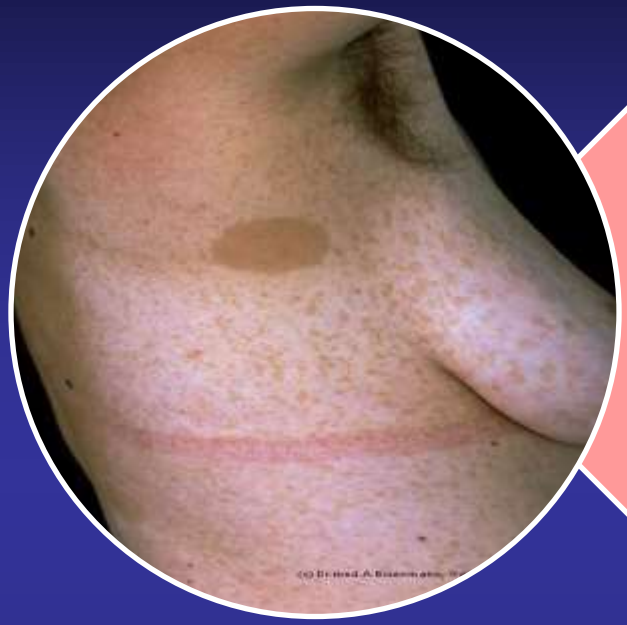


Neurofibromatose Tipo I

(Doença de Von Recklinghausen)

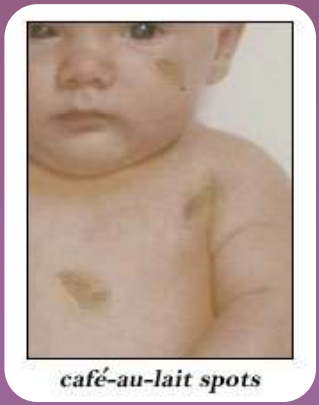
Incidência: 1:3500

DAD – Doença Autossômica Dominante

50% dos casos são esporádicos

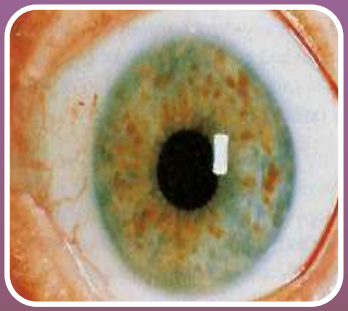
Expressão altamente variável

CONTRIBUIÇÃO MENDELIANA


café-au-lait spots

Manchas *café-au-lait*

Sinais hiperpigmentados na pele



Nódulos de Lisch

Tumores benignos na íris

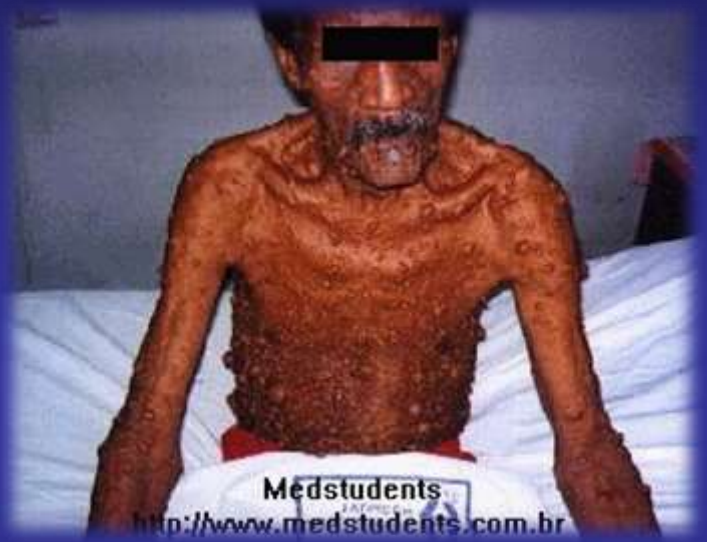
CONTRIBUIÇÃO MENDELIANA

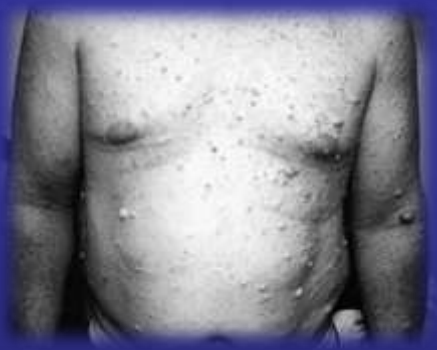
Neurofibromas

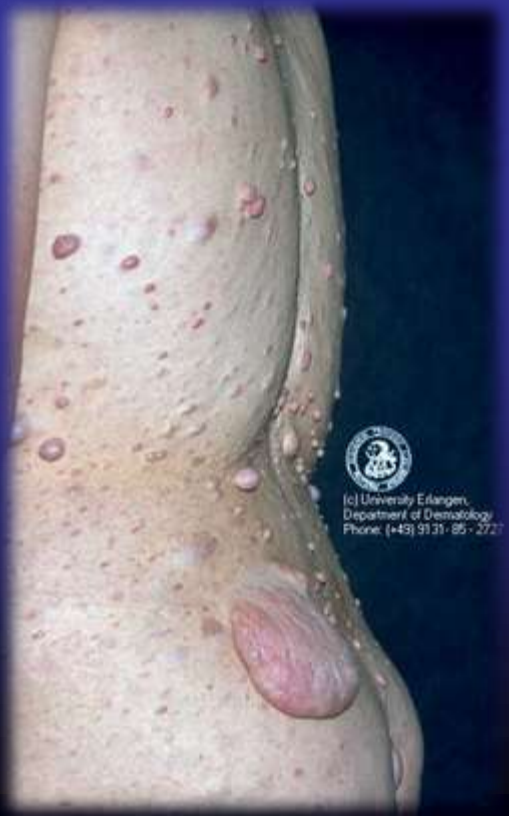
Células de Schwann

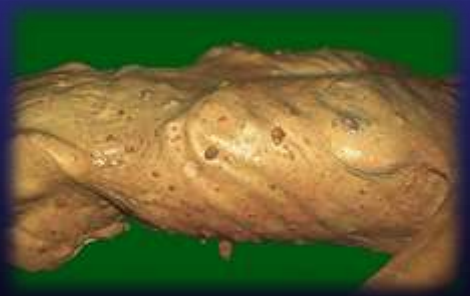
Células Perineurais

Fibroblastos









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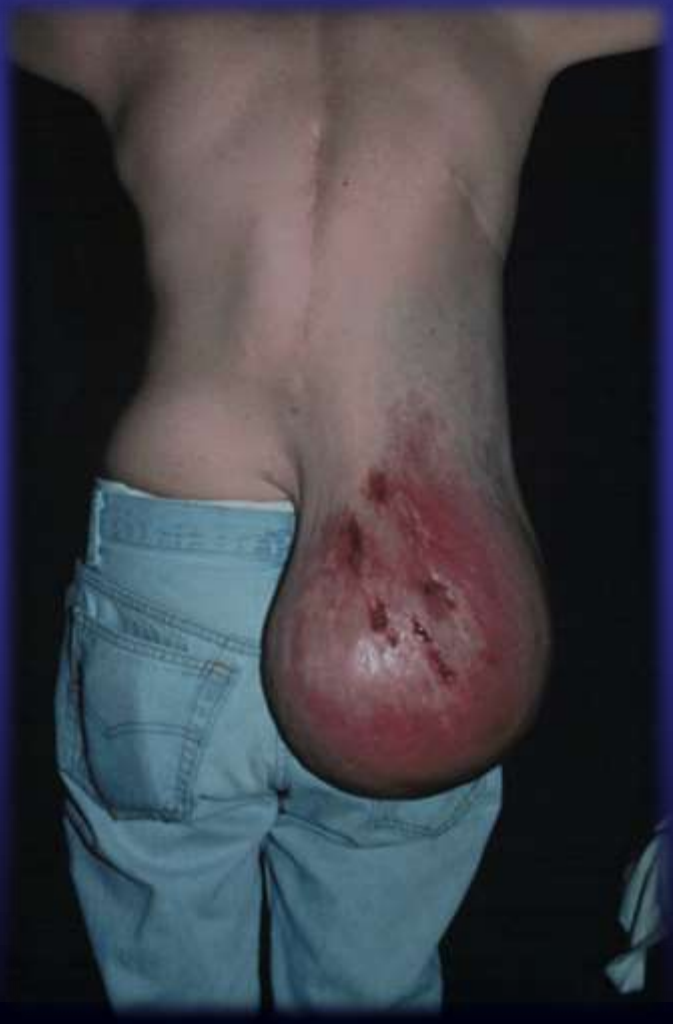
Neurofibromas



Plexiformes e outras variações

Arianto before

Arianto after


Ney Ket before

Ney Ket after


Eyerusalem before


Eyerusalem after

Martin Kelly & Norman Waterhouse

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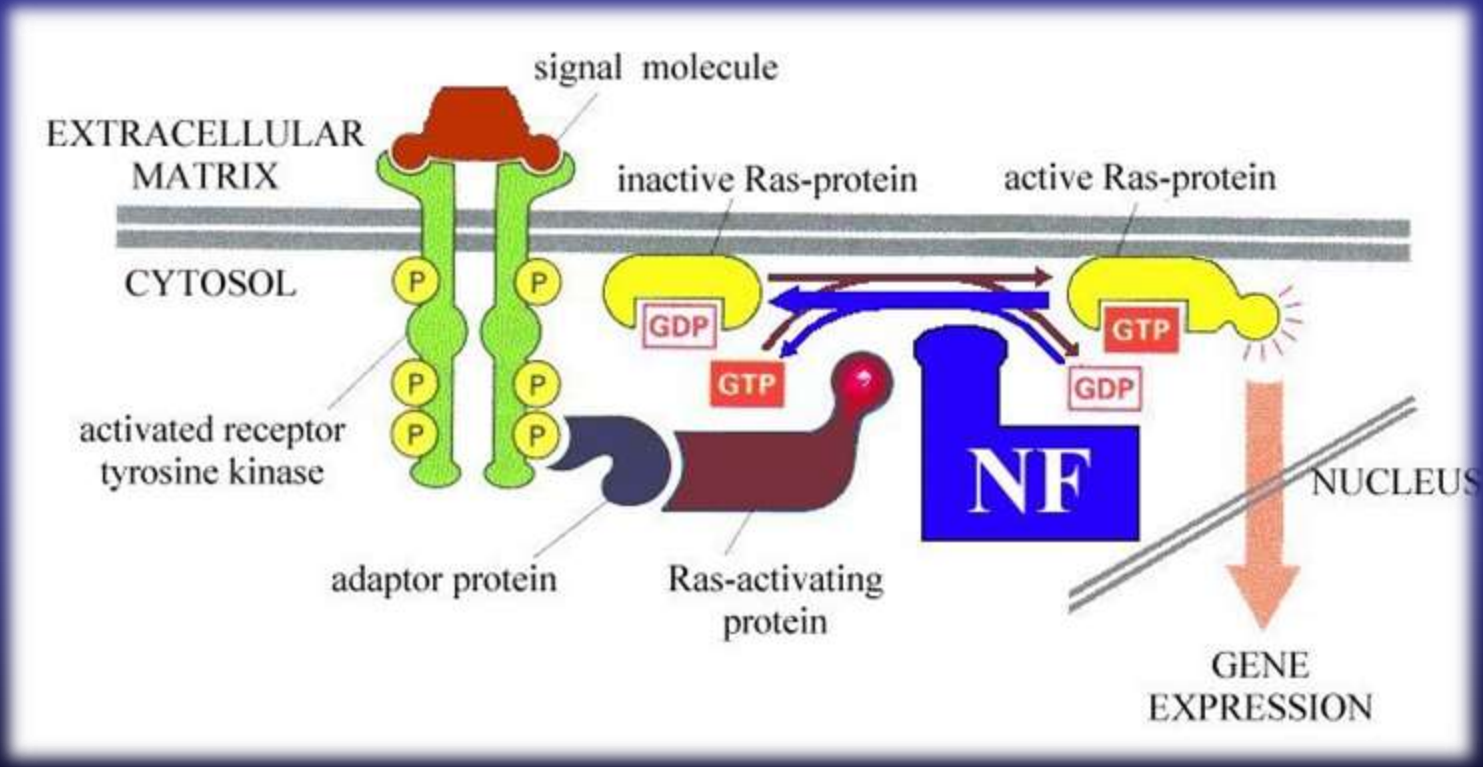
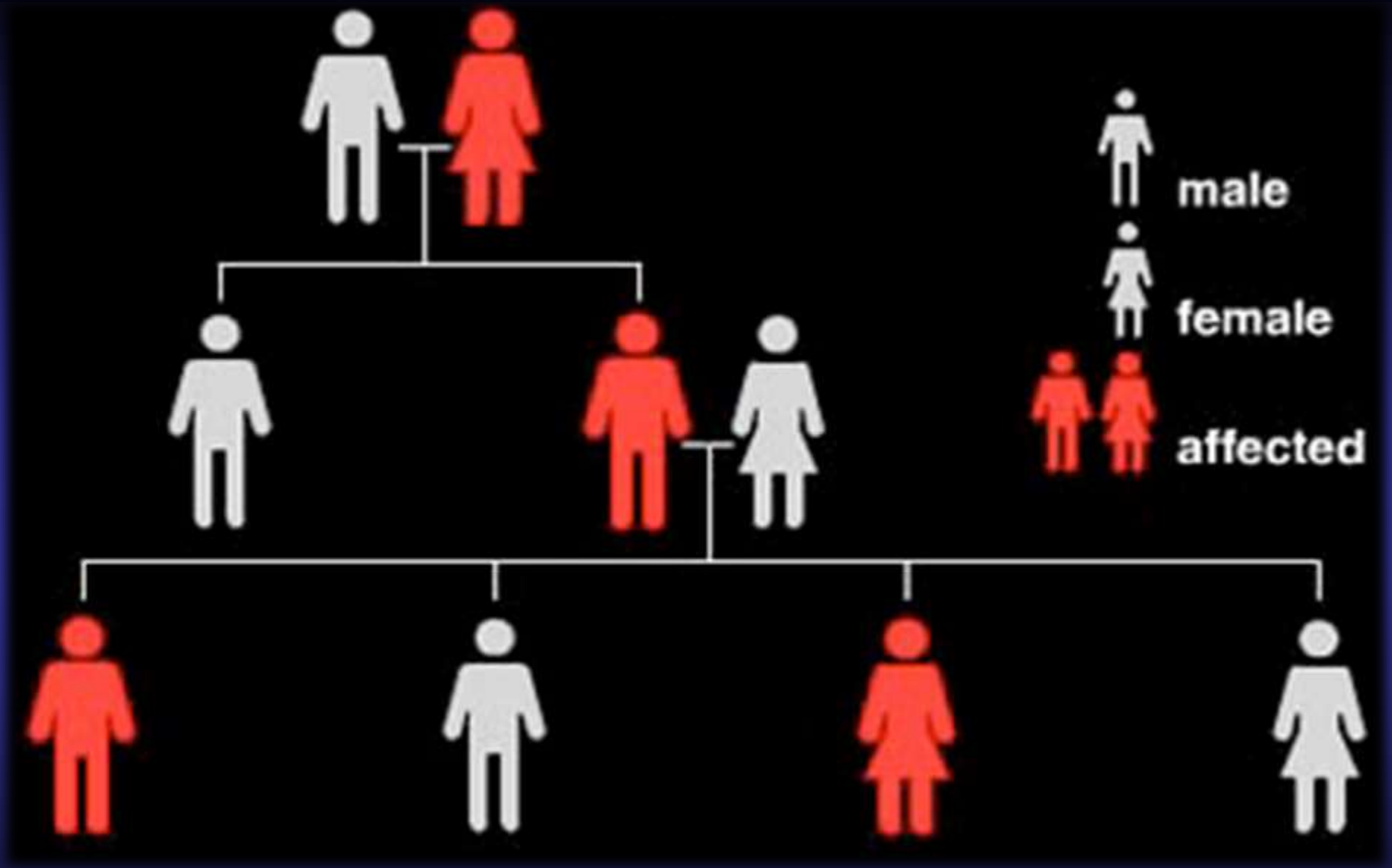
GENE NF1

17q → Proteína NF1 (2.818 aminoácidos) – Neurofibromina

(Proteína supressora de tumor)

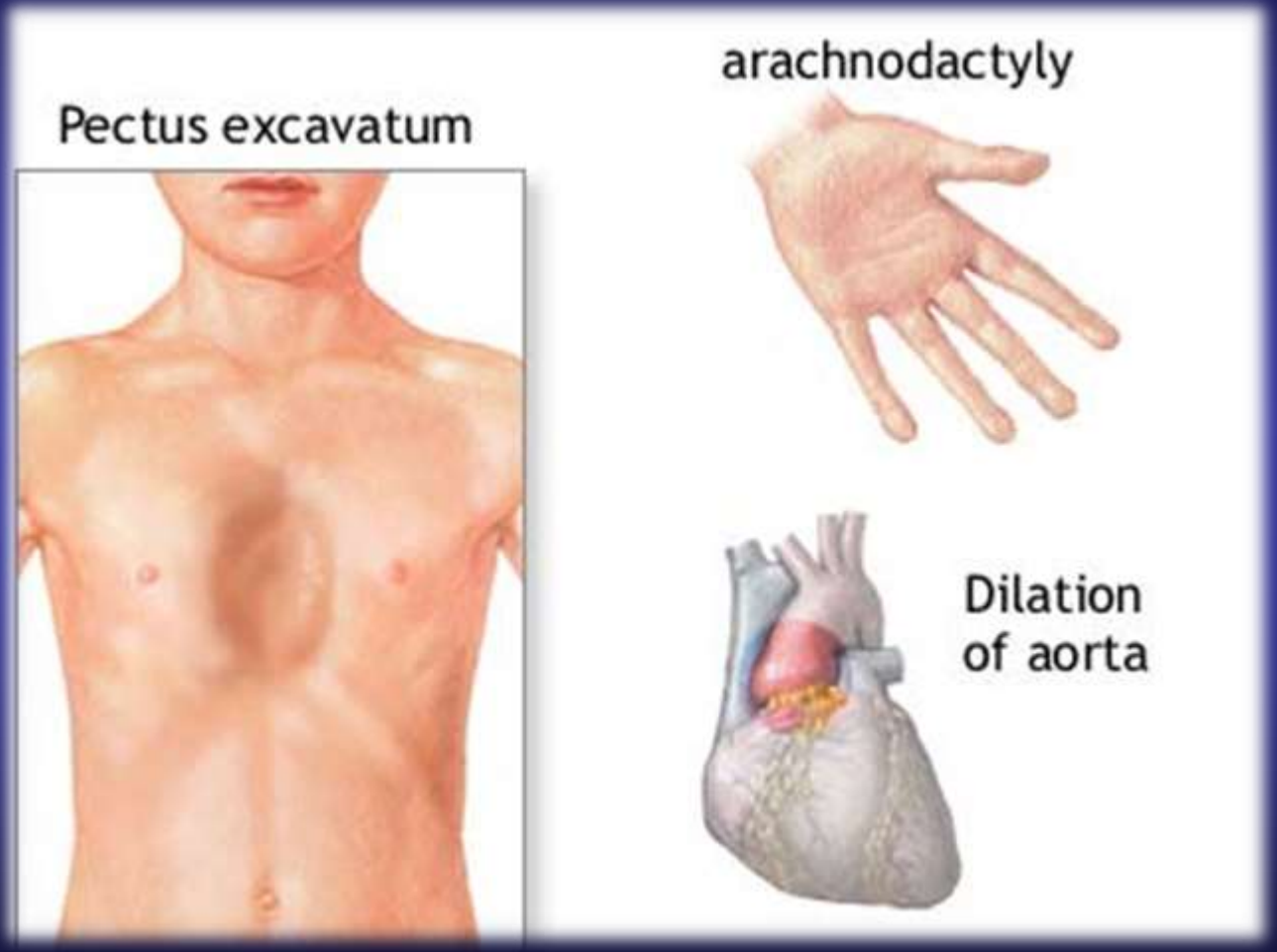


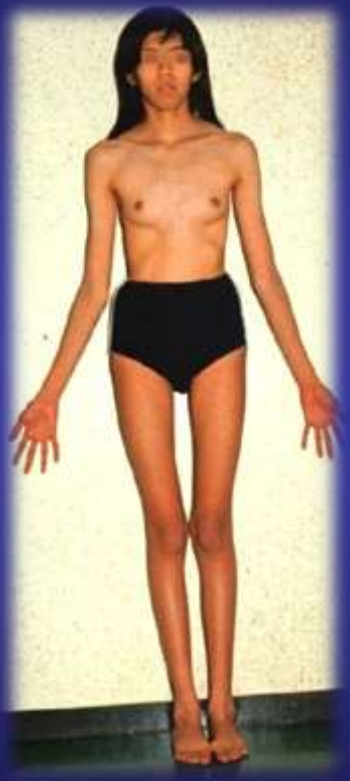


DAD – Doença autossômica Dominante

CONTRIBUIÇÃO MENDELIANA

DAD – Doença Autossômica Dominante





Incidência: 1:10.000

Síndrome de Marfan

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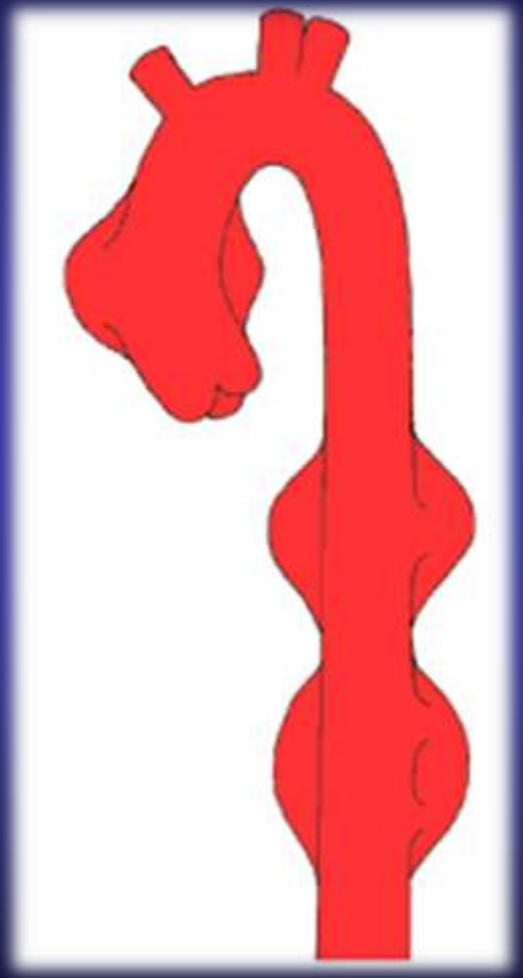

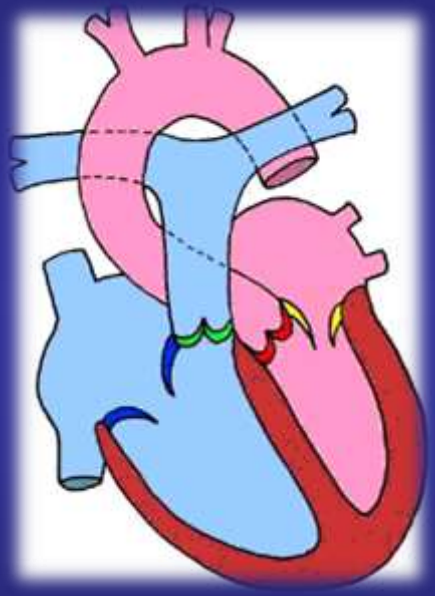

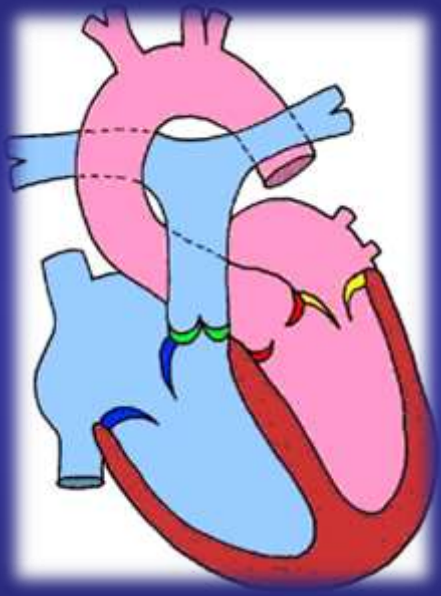

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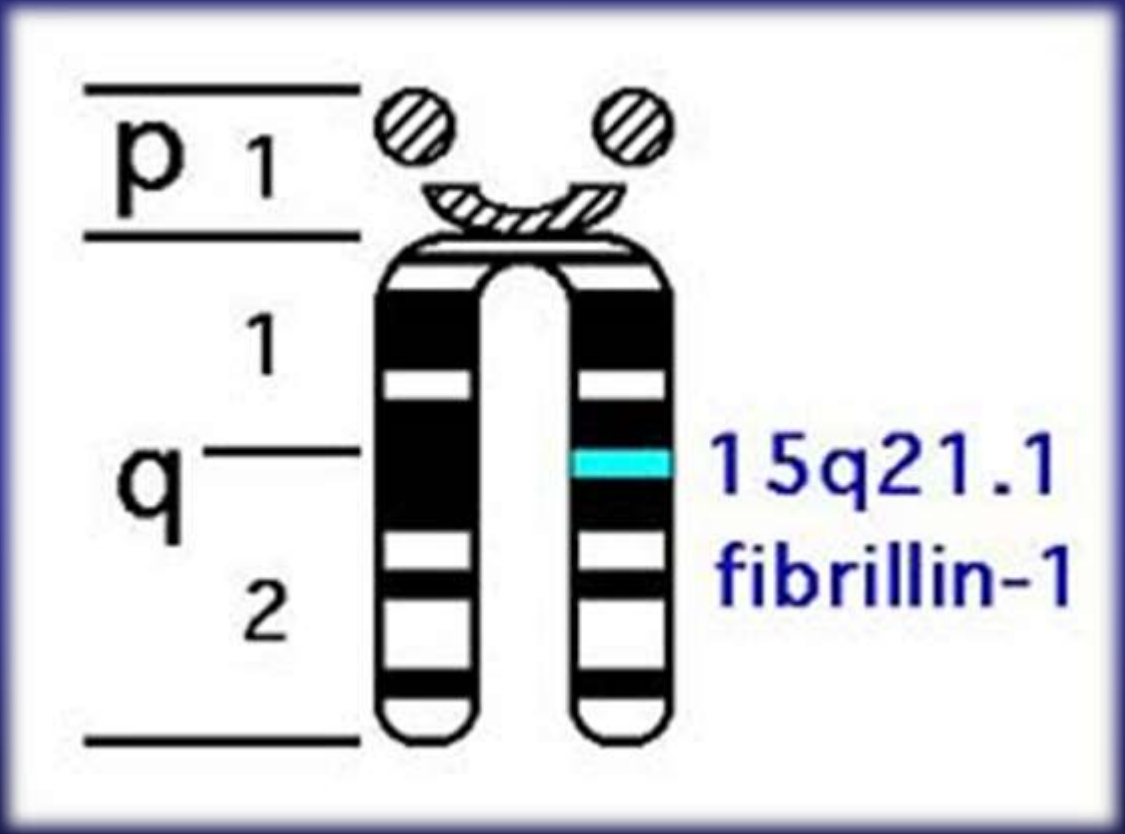
GENE FBN1



15q21.1 → Proteína Fibrilina 1 (presente em grande quantidade nos ligamentos e vasos sanguíneos)

Inheritance of Marfan Syndrome