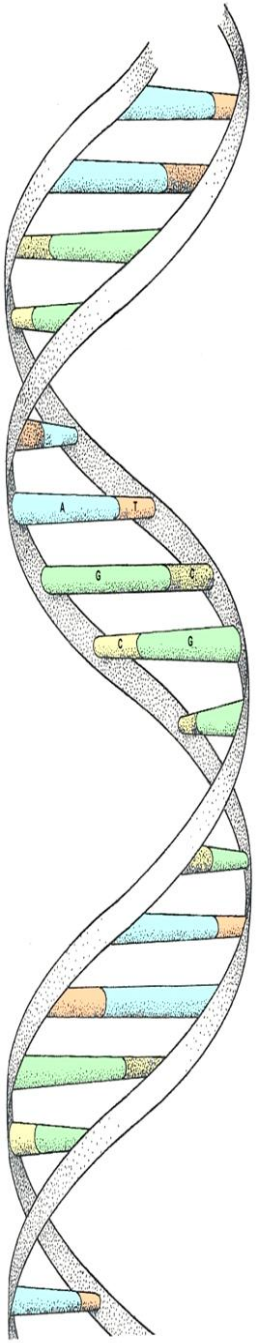

Genetics of Congenital Heart Diseases

by

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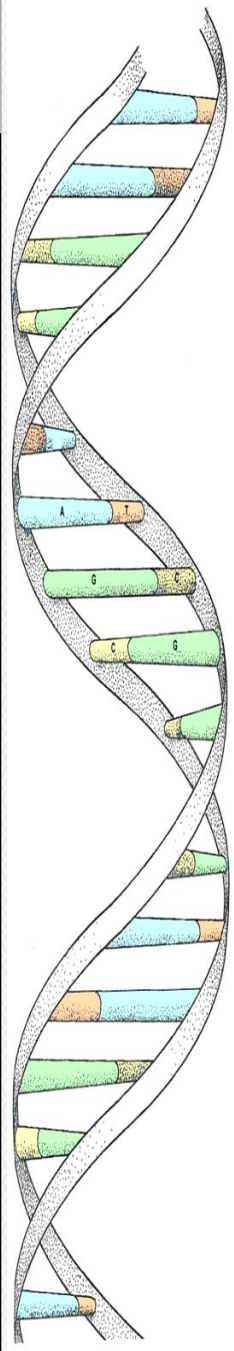
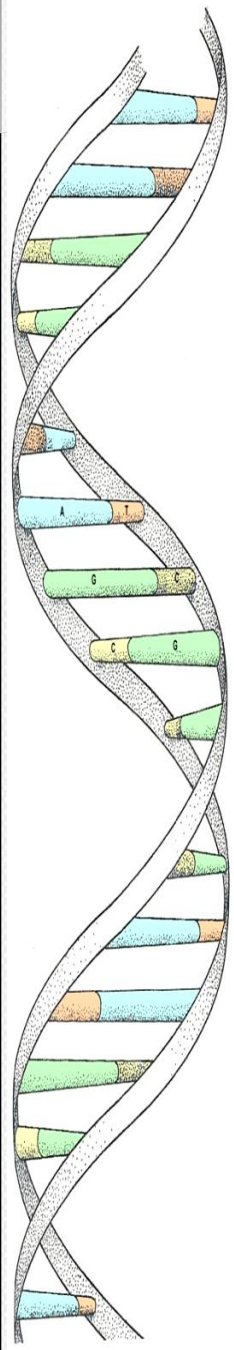
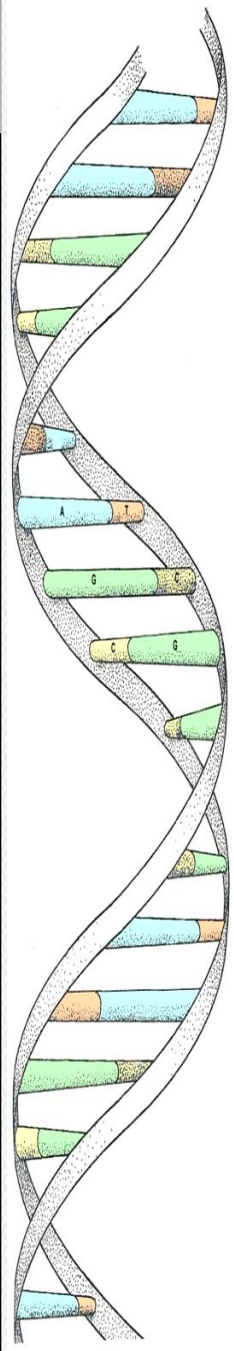


- Introduction
- Embryology in brief
- General genetics approach to CHD
- Chromosomal disorders
- Microdeletion/ duplication disorders
- Single gene disorders
- Pathway disorders



Introduction

- CHD: 1/3rd of all major congenital abnormalities
- Affects 2 to 3 children per 100 live births
- Polygenic: Environmental and genetic
- Knowledge about genetics is essential in reproductive counseling of patients with CHD



Evidence for genetic basis of CHD

- Specific type of CHDs are more common in specific chromosomal abnormalities
- Multiple family members affected
- Increased RR in a family with an affected member

Timeline of genetic CHD discoveries

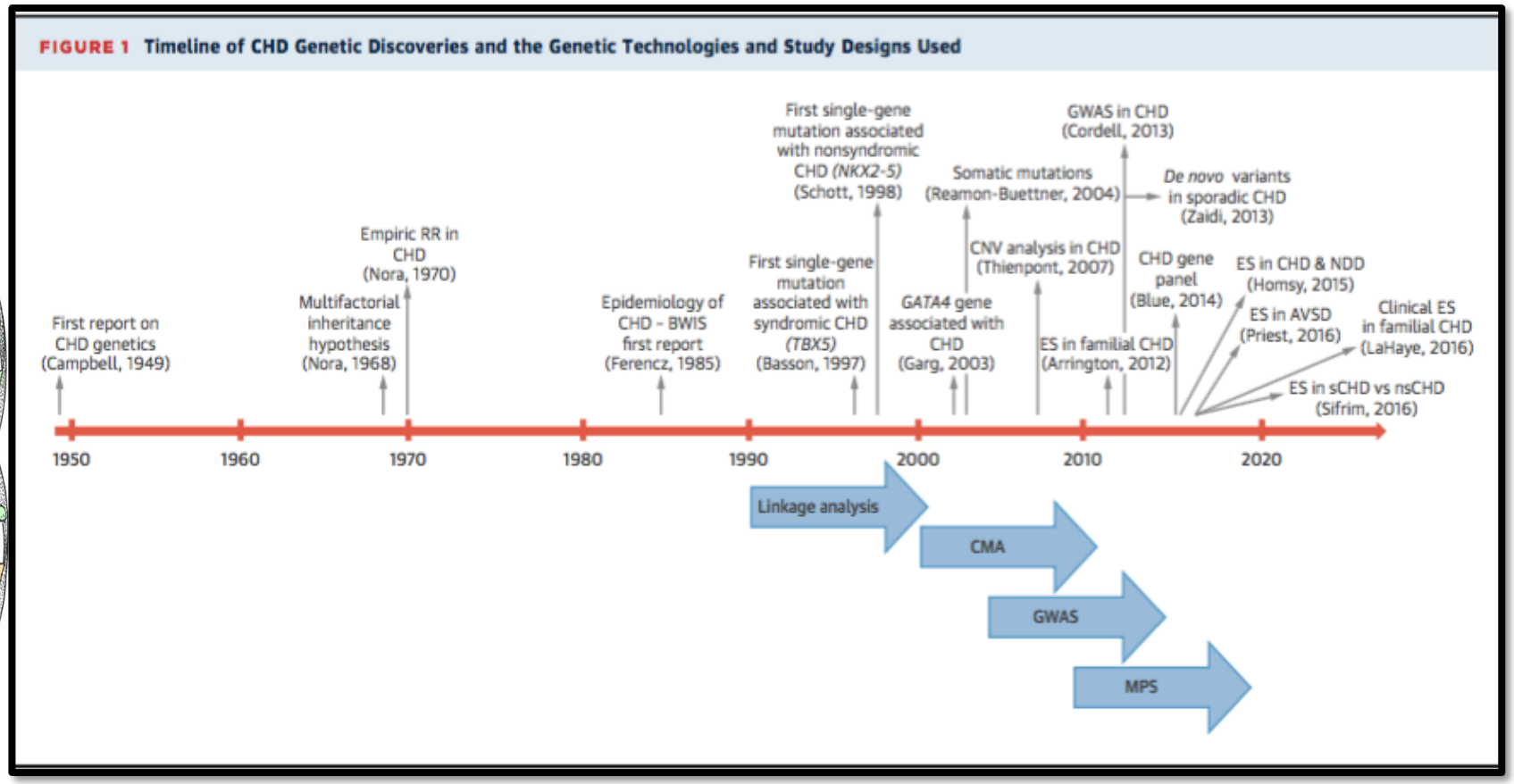
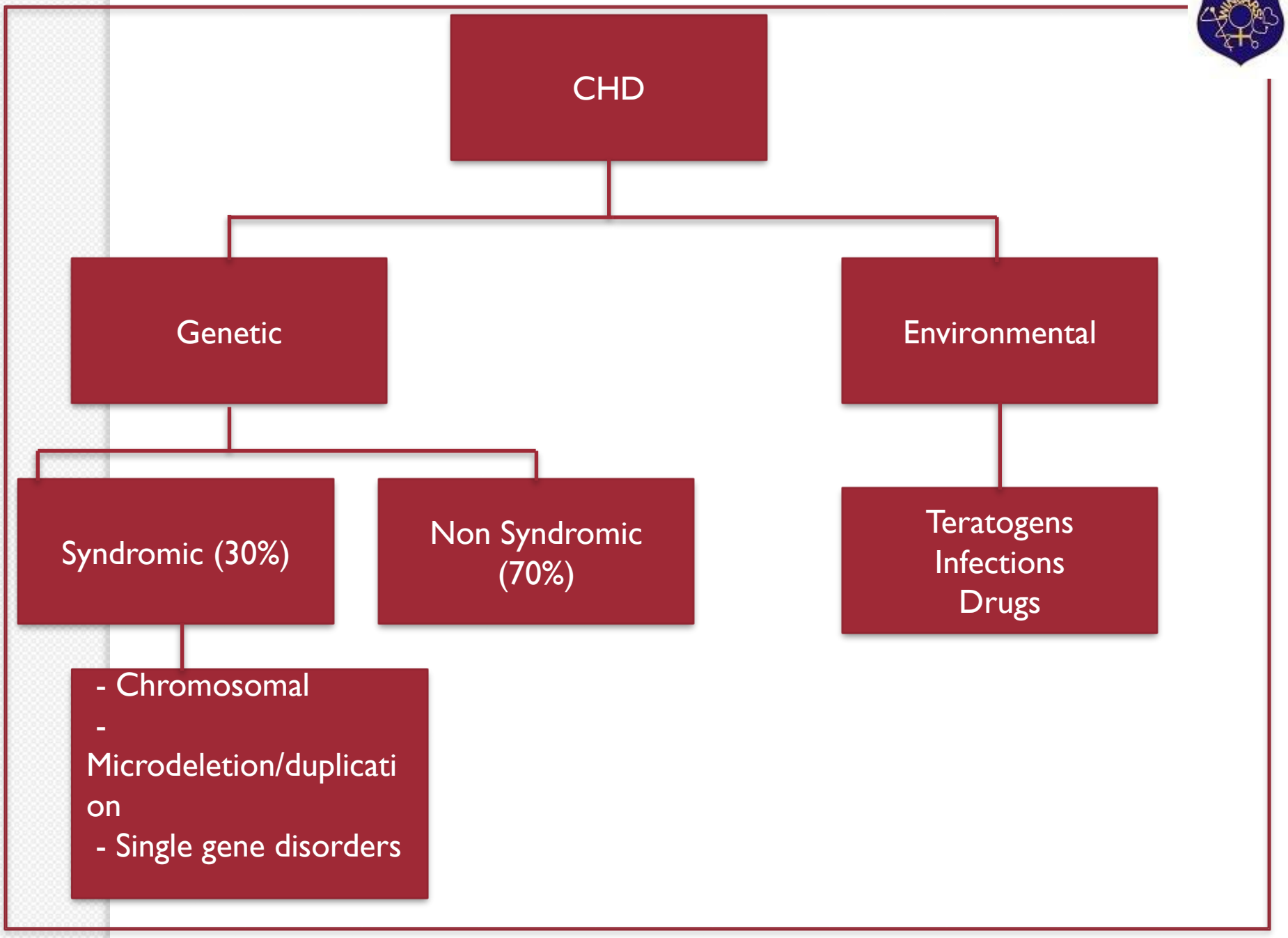


FIGURE 1 Timeline of CHD Genetic Discoveries and the Genetic Technologies and Study Designs Used

(JACC VOL. 69, NO. 7, 2017 FEBRUARY 21, 2017:859–70)


CHD
Genetic
Environmental
Syndromic (30%)
Non Syndromic (70%)
Teratogens
Infections
Drugs
- Chromosomal
- Microdeletion/duplication
- Single gene disorders

Non genetic causes

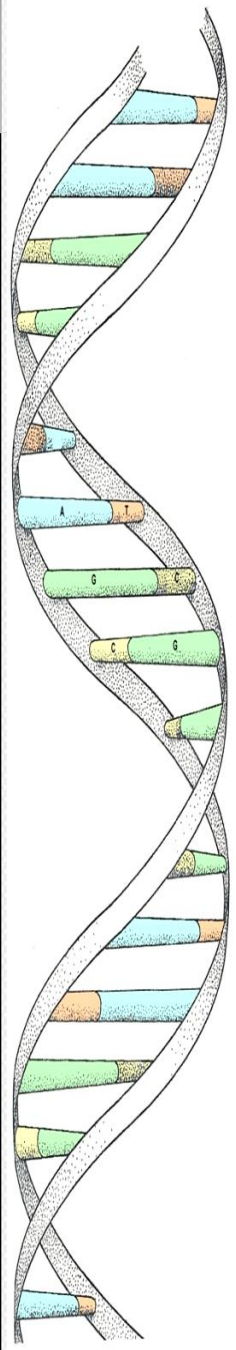
- Critical period of cardiac development: 2-7 weeks
- Infectious agents: Rubella
- Maternal diabetes
- Maternal exposure to alcohol, isotretinoin, thalidomide, AED
- Environmental teratogens (dioxins, pesticides)

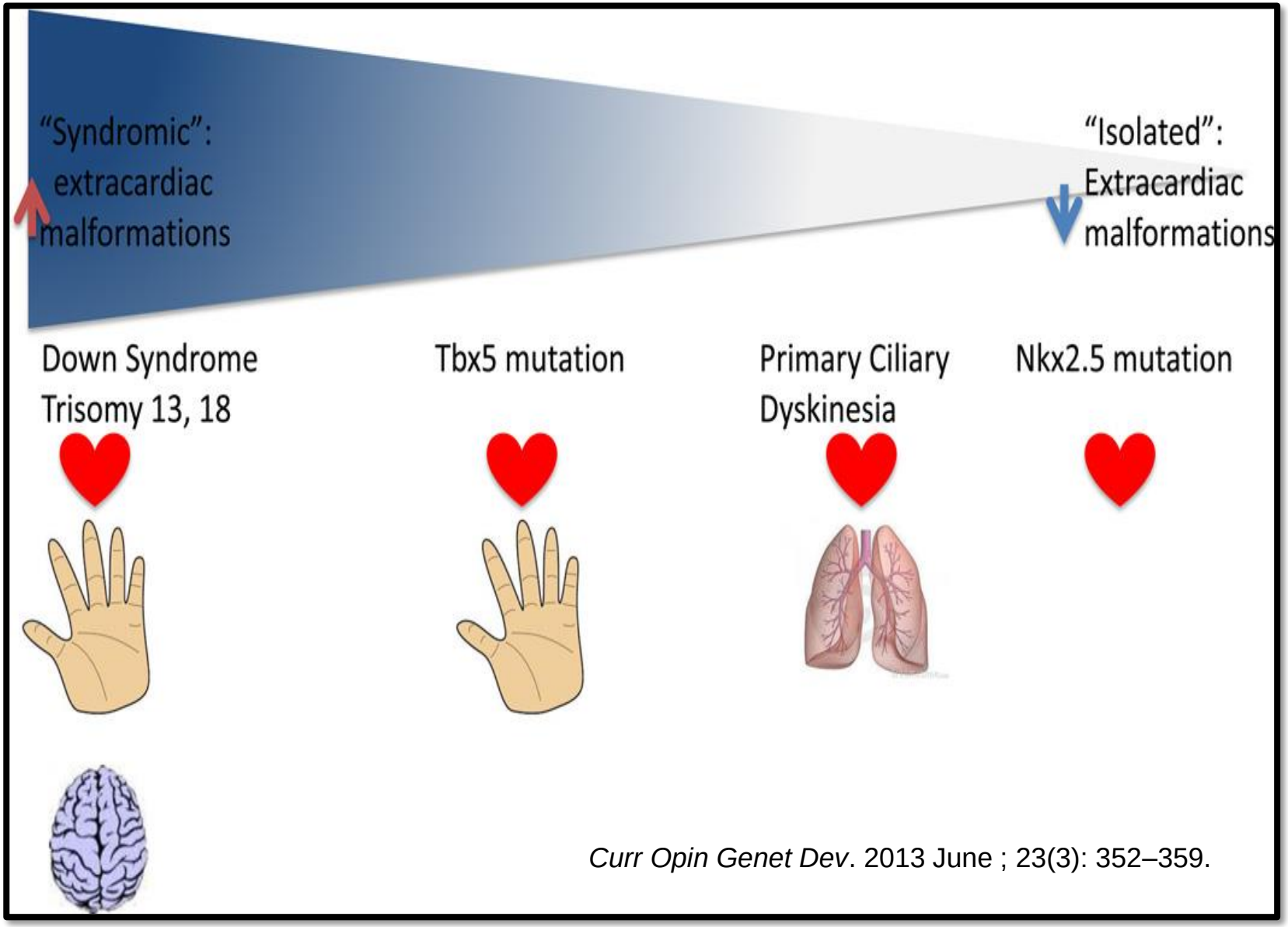
TABLE 46-3 Some Common Teratogens

Teratogenic Influence	Risk of Heart Defect (%)	Most Common Type
Maternal rubella	35	PDA, peripheral pulmonary artery stenosis, septal defects
Maternal diabetes	3–5	VSD, coarctation, TGA
Maternal phenylketonuria	25–50	Tetralogy of Fallot
Systemic lupus erythematosus	20–40	Complete heart block
Maternal alcohol abuse	25–30	Septal defects
Hydantoin	2–3	Pulmonary and aortic stenosis, coarctation of aorta, PDA
Trimethadione	15–30	Tetralogy of Fallot, TGA, hypoplastic left heart
Thalidomide	<5	Tetralogy of Fallot, septal defects, truncus arteriosus
Lithium		Ebstein anomaly, tricuspid atresia, ASD
Retinoic acid	10–20	Conotruncal heart defects
Cocaine	5	Excess situs disturbance

Emery and Rimoin's, 5th edition

Continuous spectrum

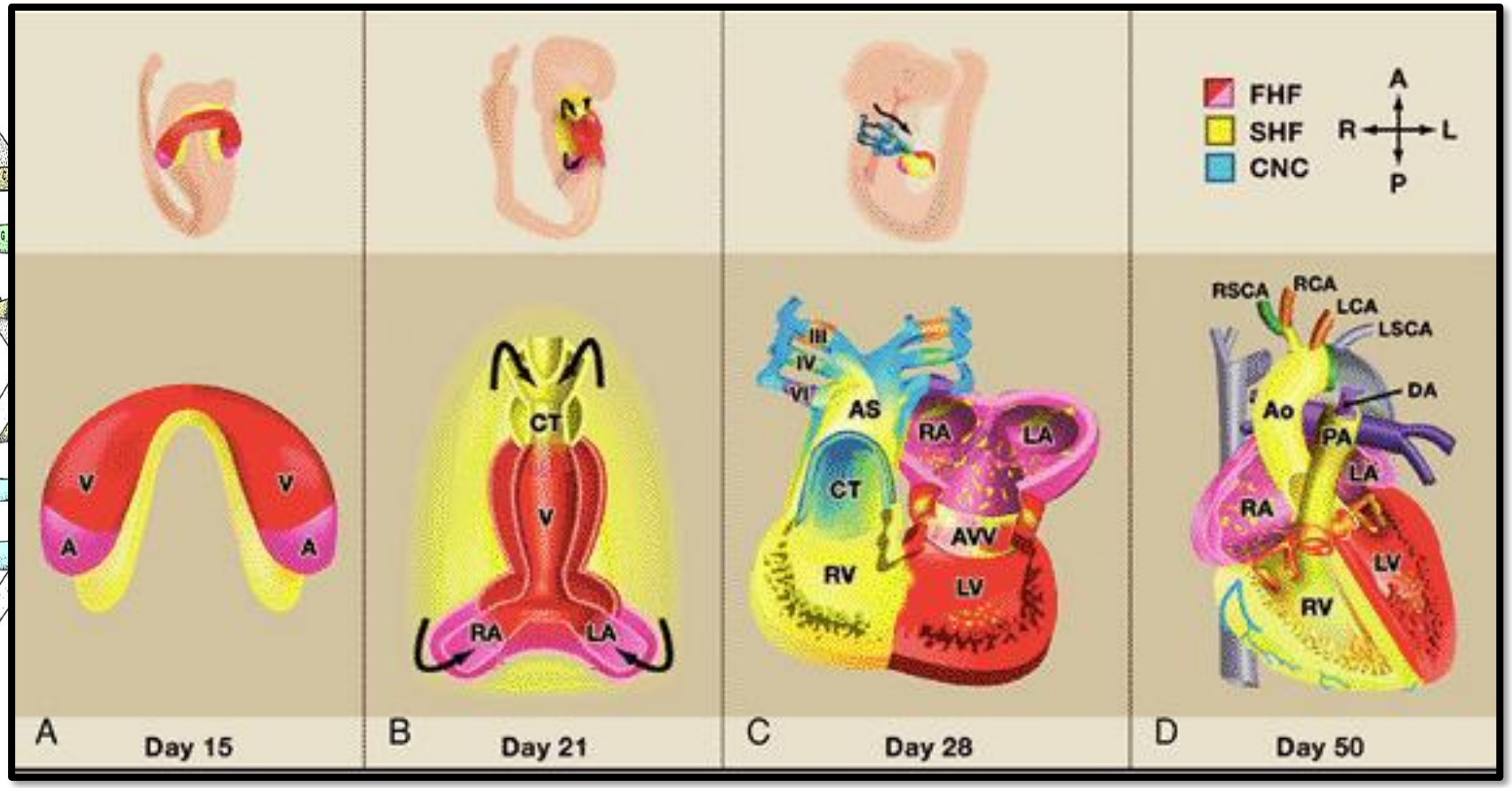




Curr Opin Genet Dev. 2013 June ; 23(3): 352–359.

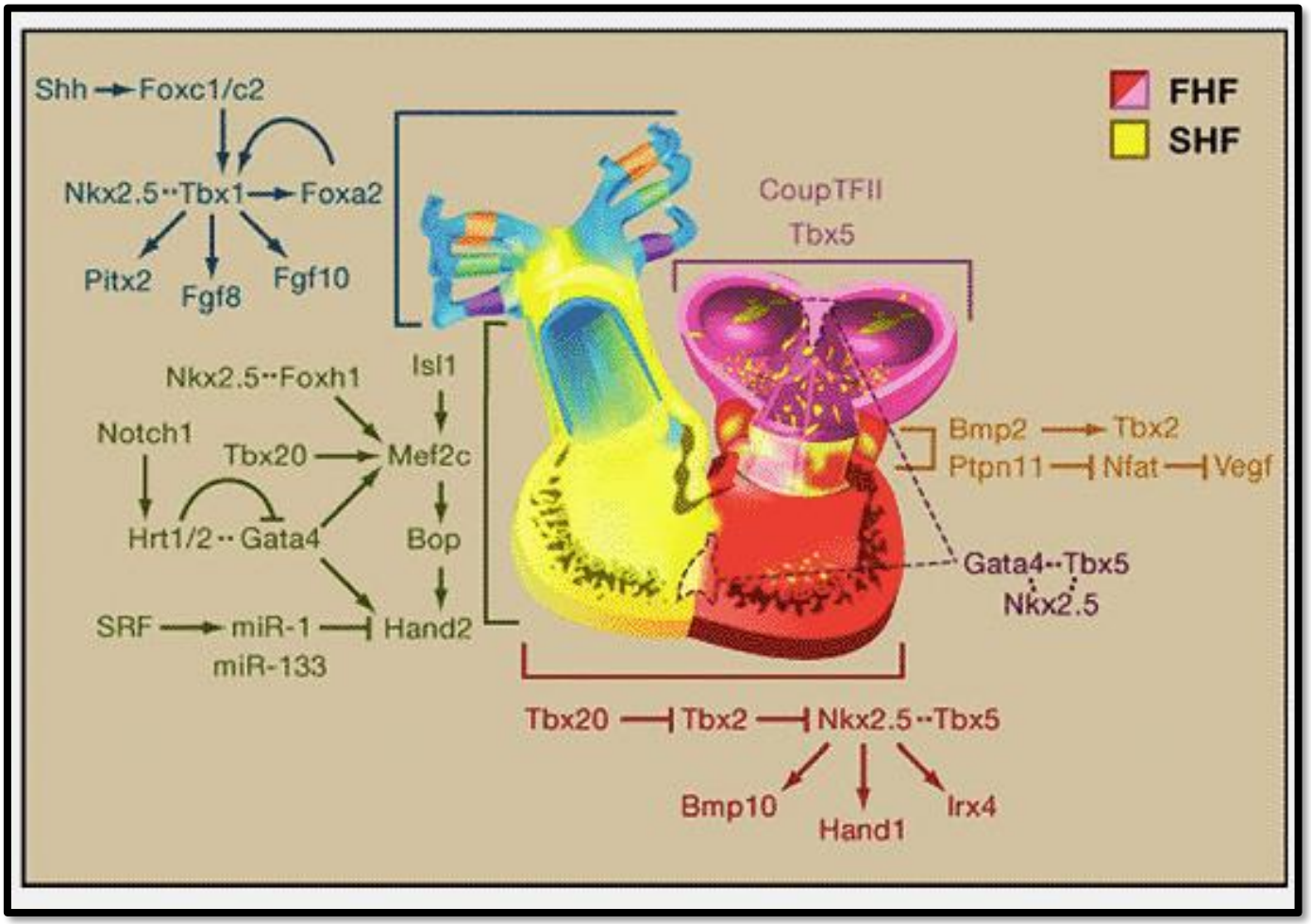
Embryology

Field theory of cardiac development



Moss and Adams, 7th edition

Transcriptional factors



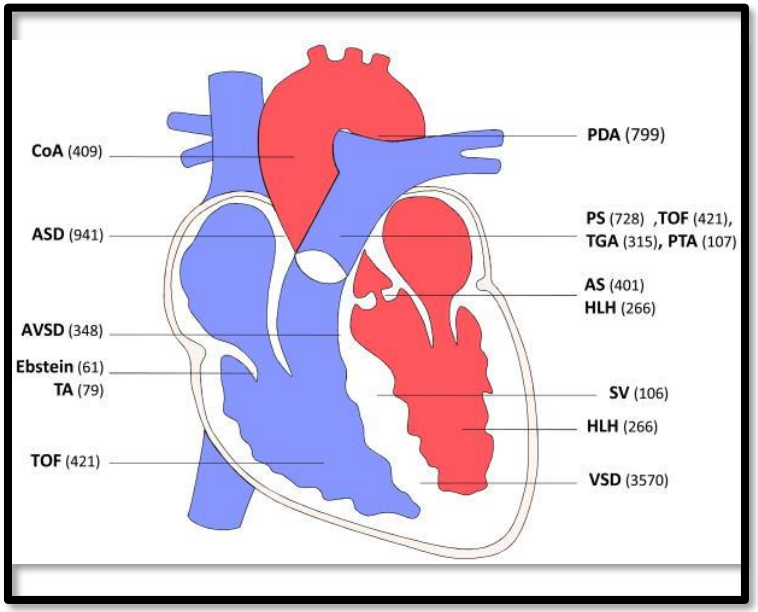
Moss and Adams, 7th edition

Factors influencing development of heart

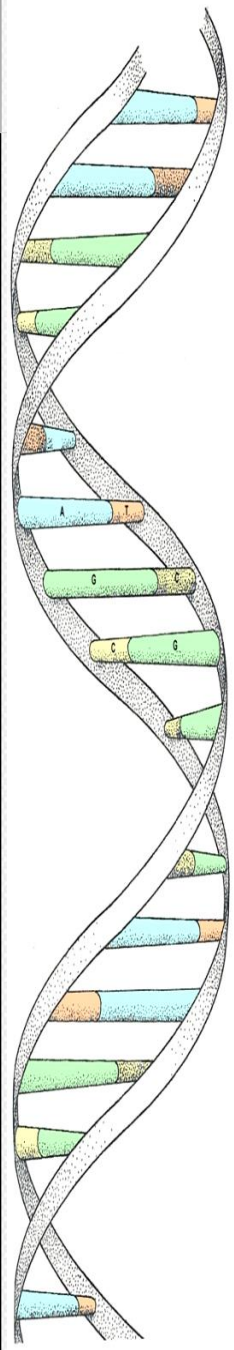
Factor	Examples	Diseases associated
Transcriptional regulators	TBX5, NKX2-5 GATA4 TBX1 SALL4	Holt Oram Inherited ASD,VSD 22q deletion syndrome, Duane radial ray defects
Signalling pathway	Wnt RAS MAPK NOTCH, TGF beta Bmp, FGF	Rasopathies Robinow syndrome
Micro RNA	miR- 1 1 and miR-I-2	Conduction defect,VSD
Epigenetic regulators	Smyd I	Regulates cardiac chamber growth and differentiation
Hemodynamic factors	Primary outflow tract disorders can cause secondary structural defect	

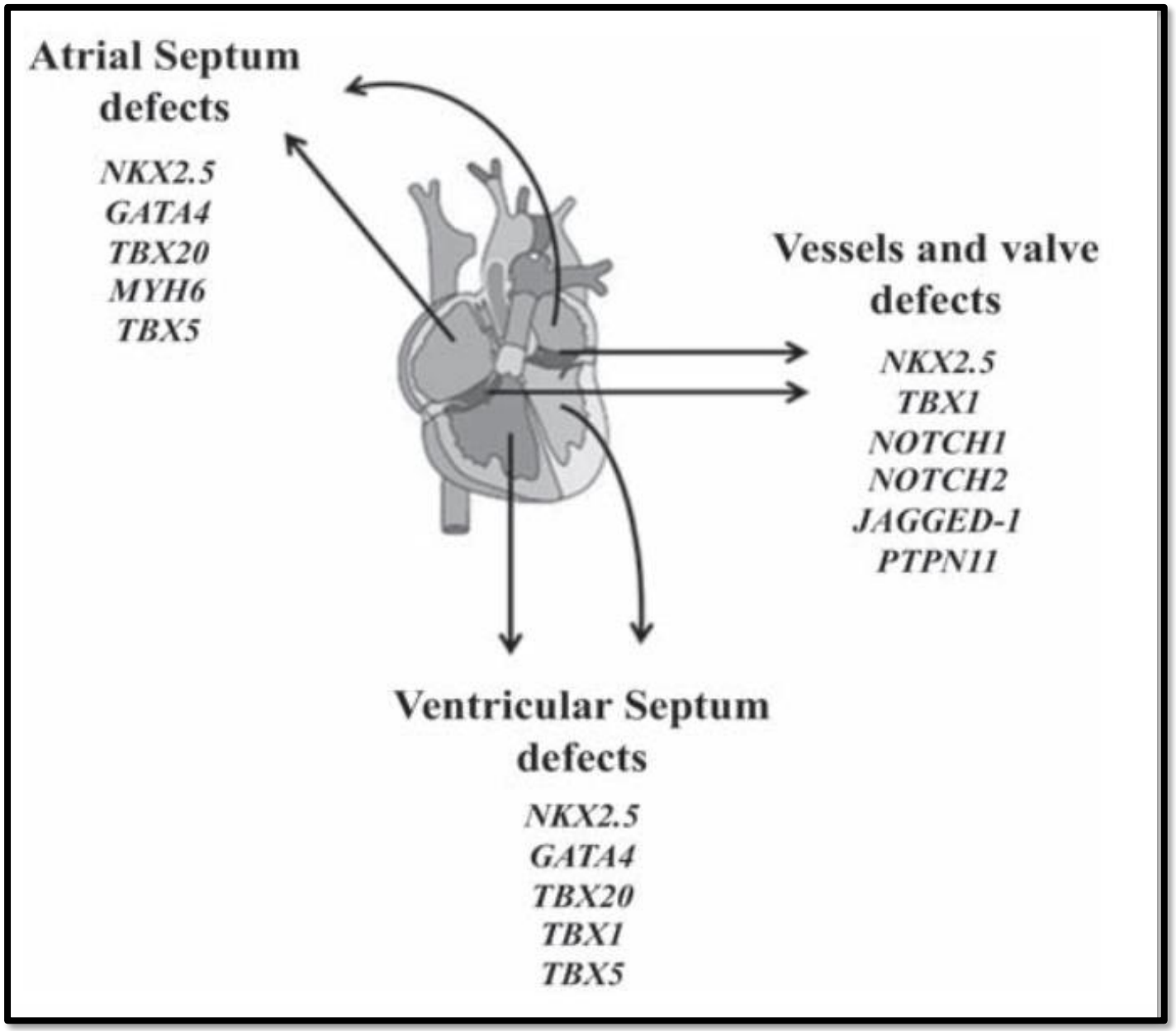
Isolated CHD

- Genetically heterogeneous
- More than 50 genes are implicated
- Bulk falls in some genes involved in development(*NKX2-5*, *GATA4*, *NOTCH1*)



Circ Res. 2013 February 15; 112(4)





Current Genomics, 2014, *15*, 390-399

Gene	Protein	Phenotypes*	OMIM
Transcription Factors and Co-factors			
ANKRD1	Ankyrin Repeat Domain	TAPVR	609599
CITED2	c-AMP Responsive Element- Binding Protein	ASD; VSD	602937
FOG2/ZFPM2	Friend of GATA	TOF, DORV	603693
GATA4	GATA4 Transcription Factor	ASD, PS, VSD, TOF, AVSD, PAPVR	600576
GATA6	GATA6 Transcription Factor	ASD, TOF, PS, AVSD, PDA, OFT defects, VSD	601656
HAND2	Helix-Loop-Helix Transcription Factor	TOF	602407
IRX4	Iroquois Homeobox 4	VSD	606199
MED13L	Mediator Complex Subunit 13- like	TGA	608771
NKX2-5/NKX2.5	Homeobox Containing Transcription Factor	ASD, VSD, TOF, HLH, CoA, TGA, DORV, IAA, OFT defects	600584
NKX2-6	Homeobox Containing Transcription Factor	PTA	
TBX1	T-Box 1 Transcription Factor	TOF, (22q11 deletion syndromes)	602054
TBX5	T-Box 5 Transcription Factor	AVSD, ASD, VSD, (Holt Oram syndrome)	601620
TBX20	T-Box 20 Transcription Factor	ASD, MS, VSD	606061
TFAP2B	Transcription Factor AP-2 Beta	PDA, (Char syndrome)	601601
ZIC3	Zinc Finger Transcription Factor	TGA, PS, DORV, TAPVR, ASD, HLH, VSD, Dextrocardia, L-R axis defects	300265

Circ Res. 2013 February 15; 112(4)

Receptors, Ligands, and Signaling			
ACVR1/ALK2	BMP Receptor	AVSD	102576
ACVR2B	Activin Receptor	PS, DORV, TGA, Dextrocardia,	602730
ALDH1A2	Retinaldehyde Dehydrogenase	TOF	603687
CFC1/CRYPTIC	Cryptic Protein	TOF; TGA; AVSD; ASD; VSD; IAA; DORV	605194
CRELD1	Epidermal Growth Factor- Related Proteins	ASD; AVSD	607170
FOXH1	Forkhead Activin Signal Transducer	TOF, TGA	603621
GDF1	Growth Differentiation Factor-1	Heterotaxy, TOF, TGA, DORV	602880
GJA1	Connexin 43	ASD, HLH, TAPVR, (Oculodentodigital dysplasia)	121014
JAG1	Jagged-1 Ligand	PAS, TOF, (Alagille syndrome)	601920
LEFTY2	Left-Right Determination Factor	TGA, AVSD, IAA, CoA, L-R axis defects, IVC defects	
NODAL	Nodal homolog (TGF-beta superfamily)	TGA, PA, TOF, DORV, Dextrocardia, IVC defect, TAPVR, AVSD	601265
NOTCH1	NOTCH1 (Ligand of JAG1)	BAV, AS, CoA, HLH	190198
PDGFRA	Platelet-Derived Growth Factor Receptor Alpha	TAPVR	173490
SMAD6	MAD-related protein	BAV, CoA, AS	602931
TAB2	TGF-beta Activated Kinase	OFT defects	605101
TDGF1	Teratocarcinoma-Derived Growth Factor 1	TOF, VSD	187395
VEGF	Vascular Endothelial Growth Factor	CoA, OFT defects	192240
Structural Proteins			
ACTC	Alpha Cardiac Actin	ASD	102540
ELN	Elastin	SVAS, PAS, PS, AS, (Williams-Beuren syndrome)	130160
MYH11	Myosin Heavy Chain 11	PDA, Aortic Aneurysm	160745
MYH6	Alpha Myosin Heavy Chain	ASD, TA, AS, PFO, TGA	160710
MYH7	Beta Myosin Heavy Chain	Ebstein Anomaly, ASD, NVM	160760

Circ Res. 2013 February 15; 112(4)

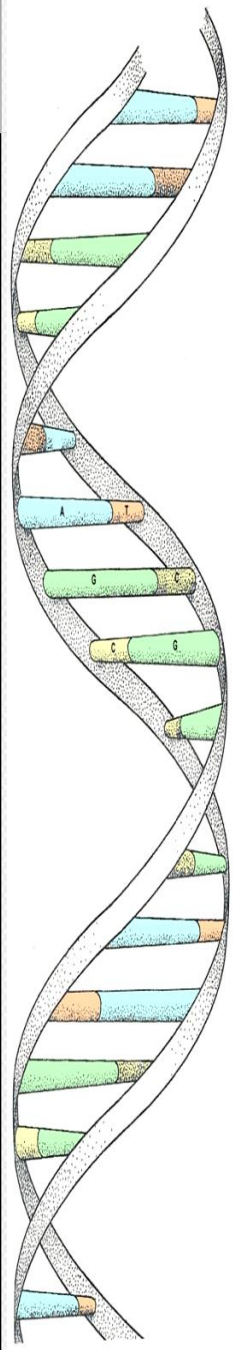
Recurrence risk

Table 2 Recurrence risks for non-syndromic congenital heart disease in first-degree relatives

Type of non-syndromic CHD	Recurrence risk of same CHD in first-degree relatives (%)	Recurrence risk of discordant CHD in first-degree relatives (%)	Recurrence risk of any CHD in first-degree relatives (%)
ASVD	1.10	2.2	3.30
ASD	0.88	2.4	3.28
VSD	0.67	1.9	2.57
ASD and VSD	0.24	2.2	2.44
Conotruncal defect[1]	1.30	2.4	3.70
Right ventricular outflow tract obstruction[2]	1.70	3.0	4.70
Left sided obstructions[3]	0.79	2.4	3.19

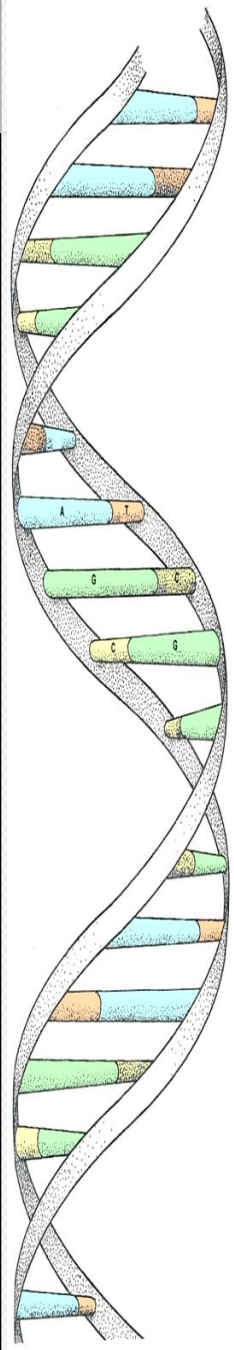
- RR for siblings 1-6%
- If two siblings affected: 10%
- RR higher for offspring
- Higher if proband is mother
- Higher for left sided lesions(8-10%)

World J Cardiol 2016 February 26; 8(2): 180-191



When to consider genetic testing

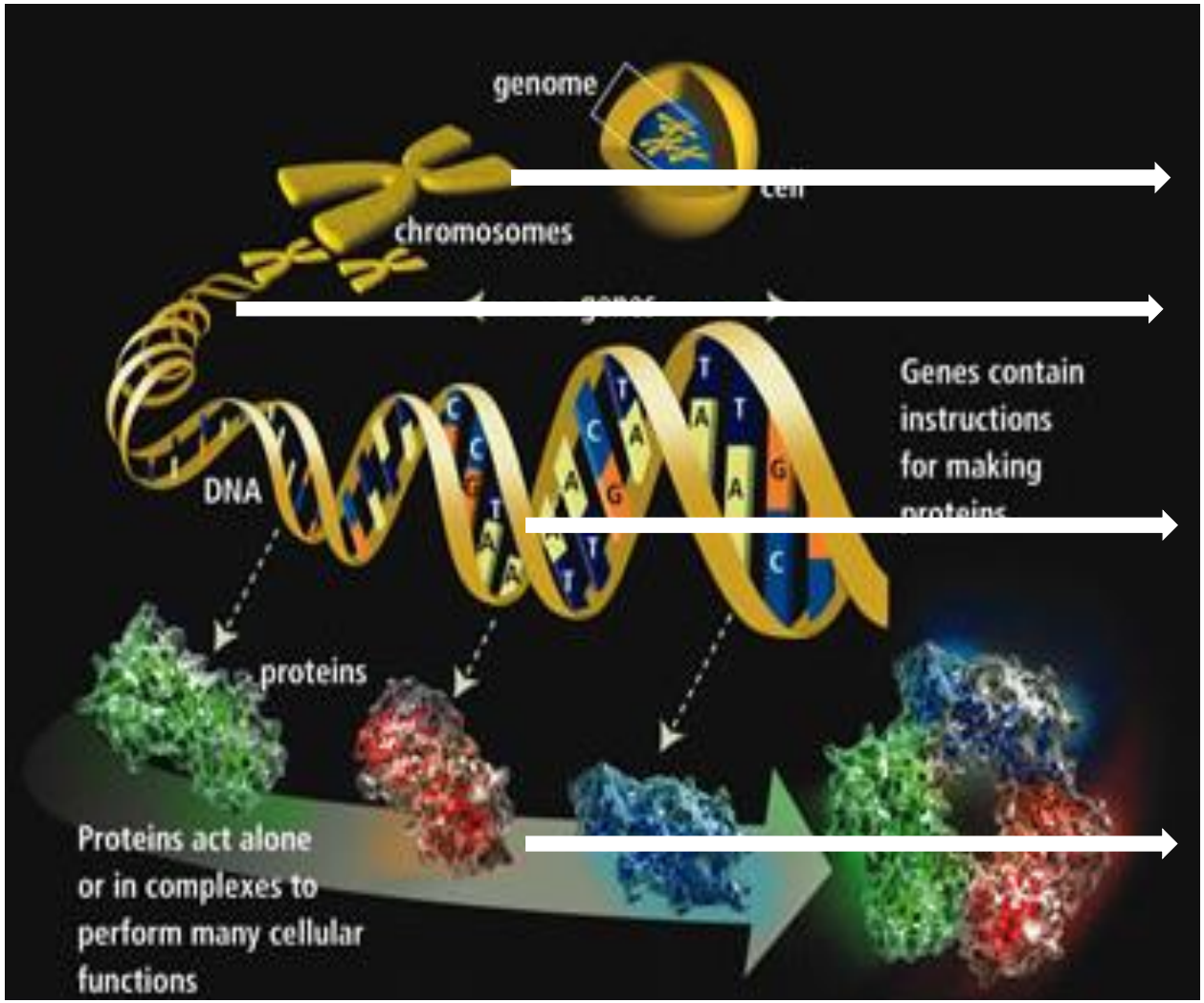
- Facial dysmorphism
- Limb defects
- Growth delay
- Mental subnormality
- Abnormalities pertaining to other systems
- Family history of other affected members



Genetic syndromes with cardiac diseases

- Chromosomal disorders
- Microdeletion disorders
- Monogenic disorders

Types of genetic testing

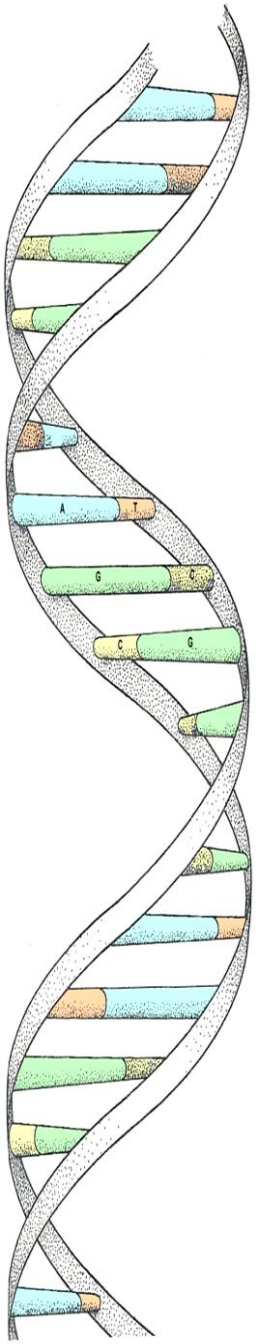


Cytogenetics

Molecular Cytogenetics

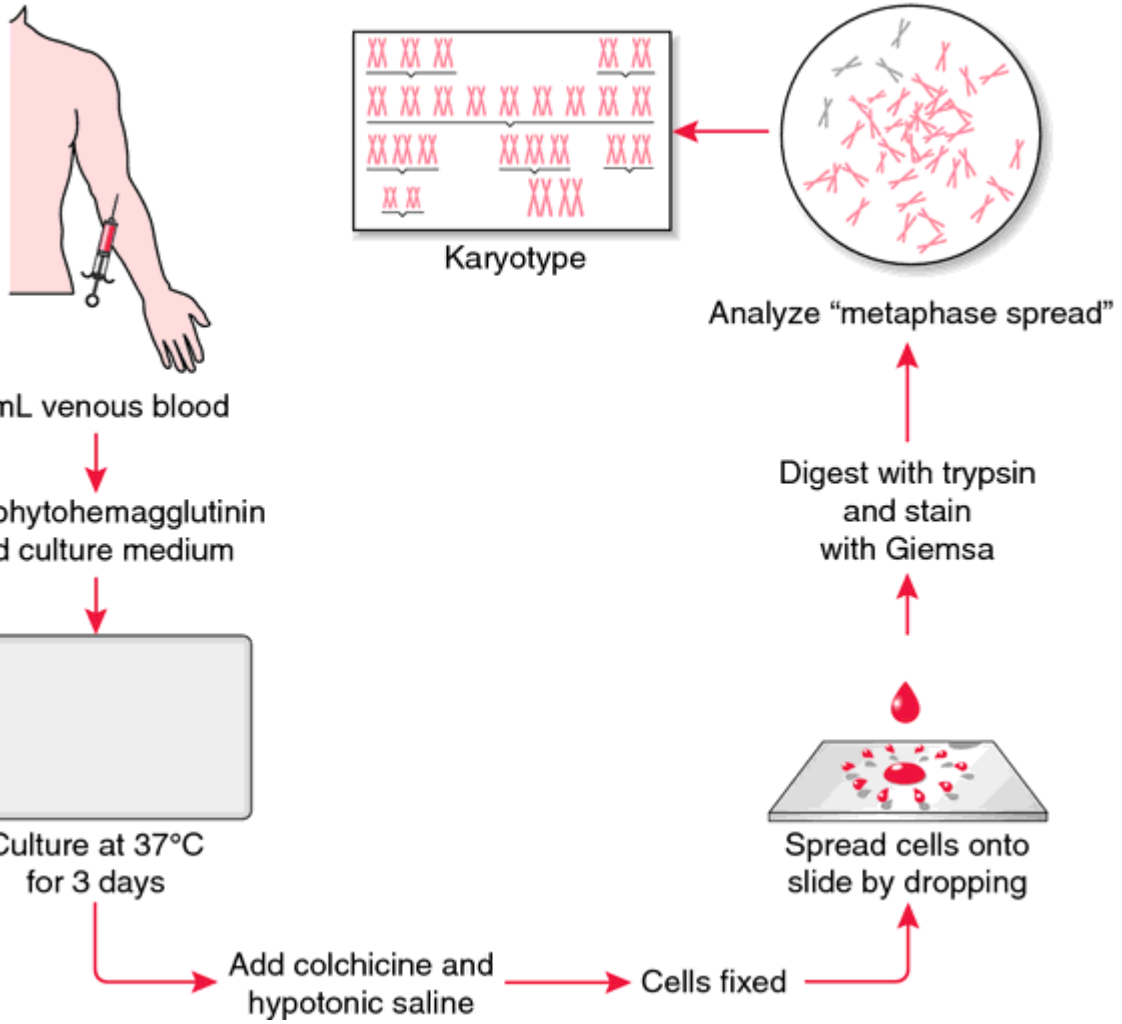
Molecular genetics

Biochemical genetics



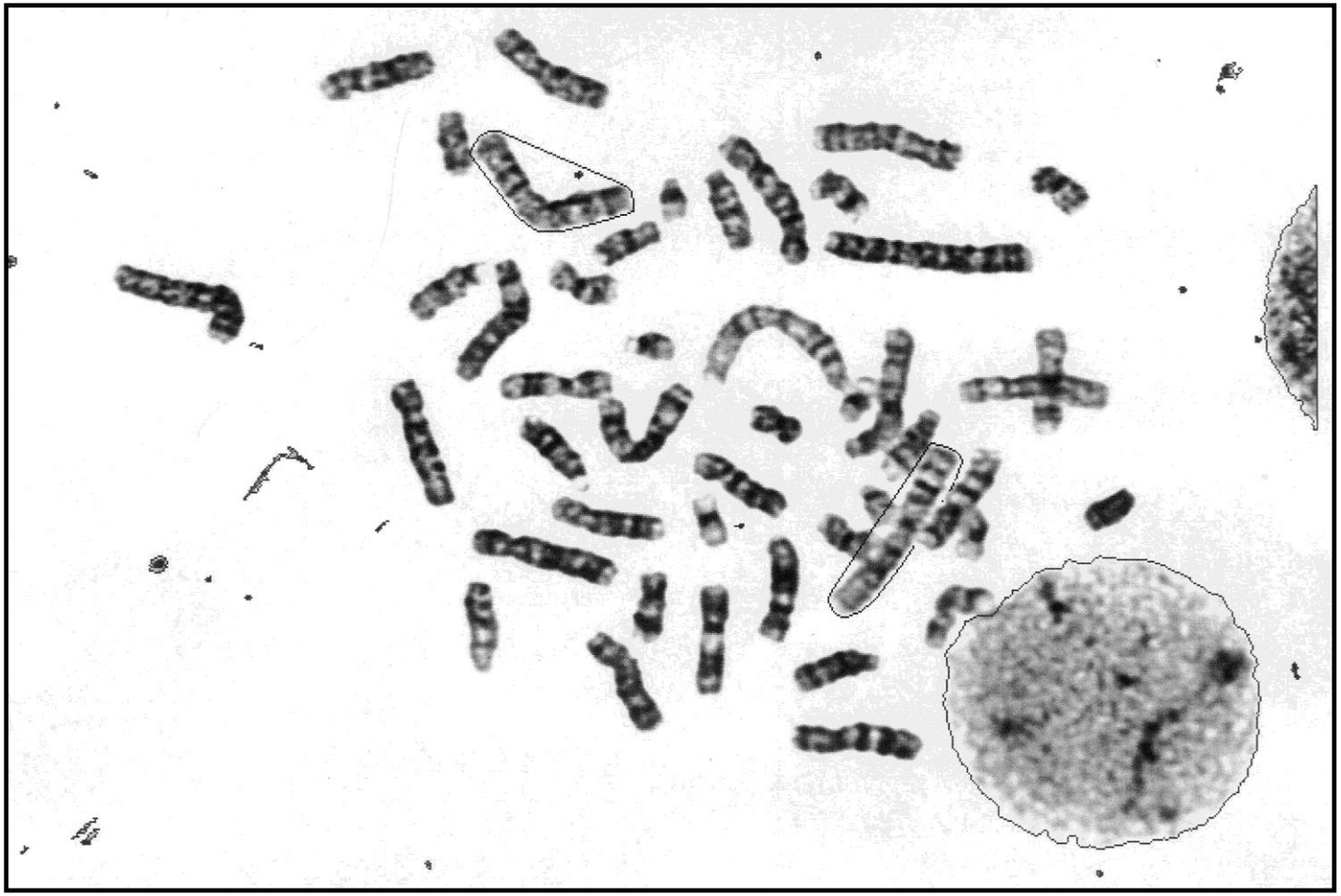
Cytogenetic testing

Karyotyping



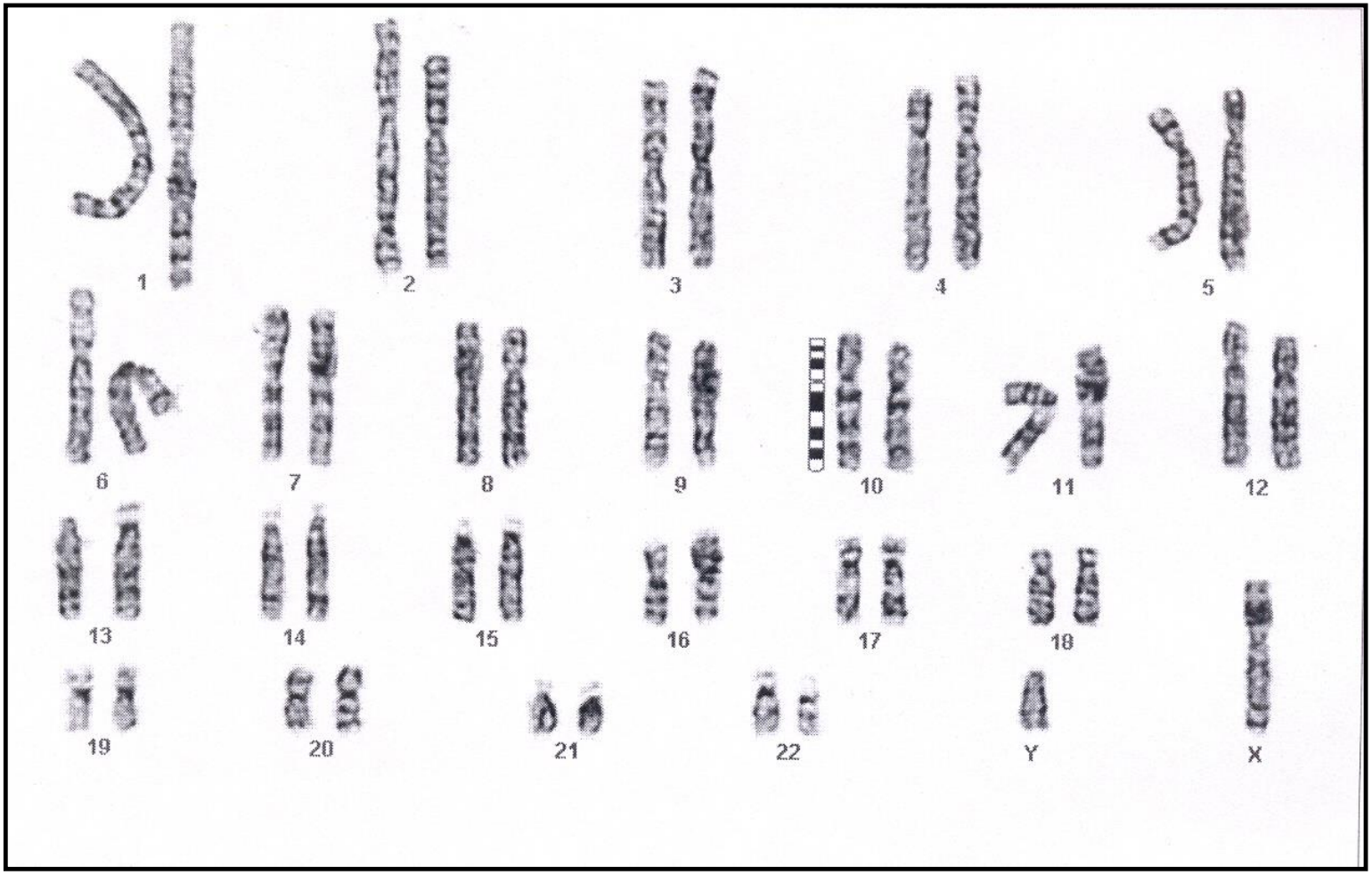
(http://medical-dictionary.thefreedictionary.com/karyotype)

Karyotyping



Metaphase spread
(100X magnification under microscope)

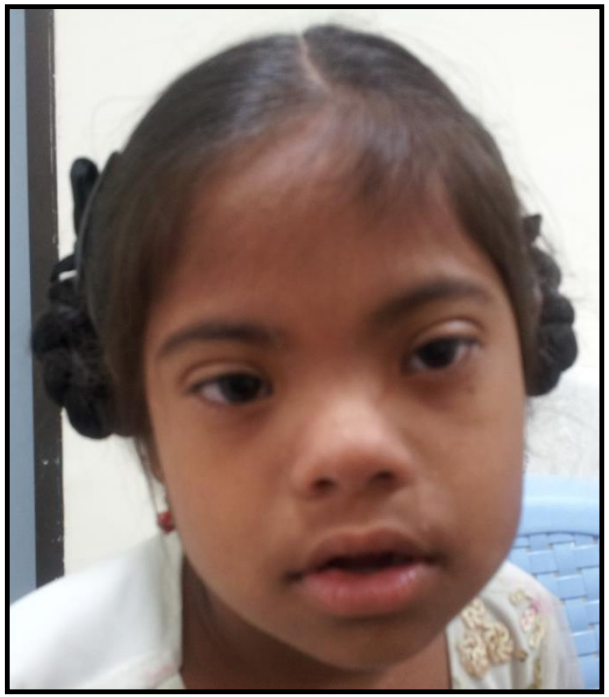
Karyotyping

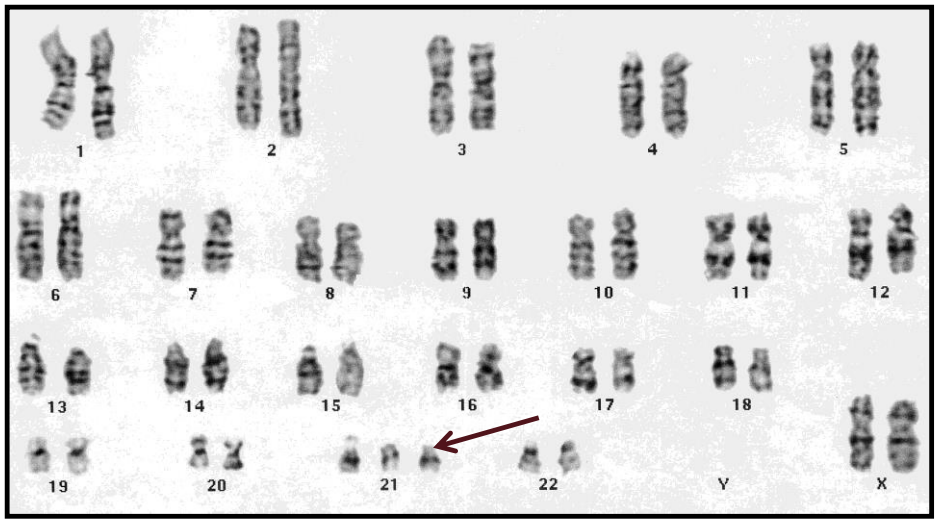


46, XY. Normal male karyotype

When to do karyotyping?

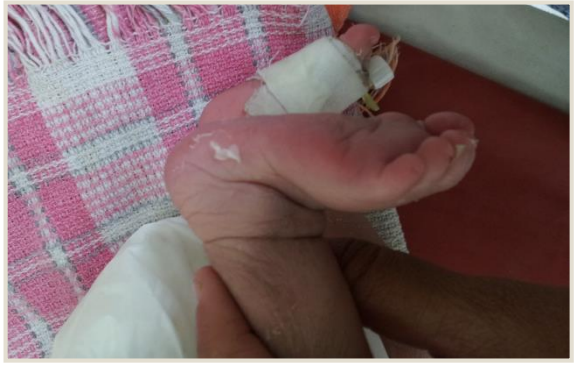
- Clinical suspicion of a chromosomal disorder



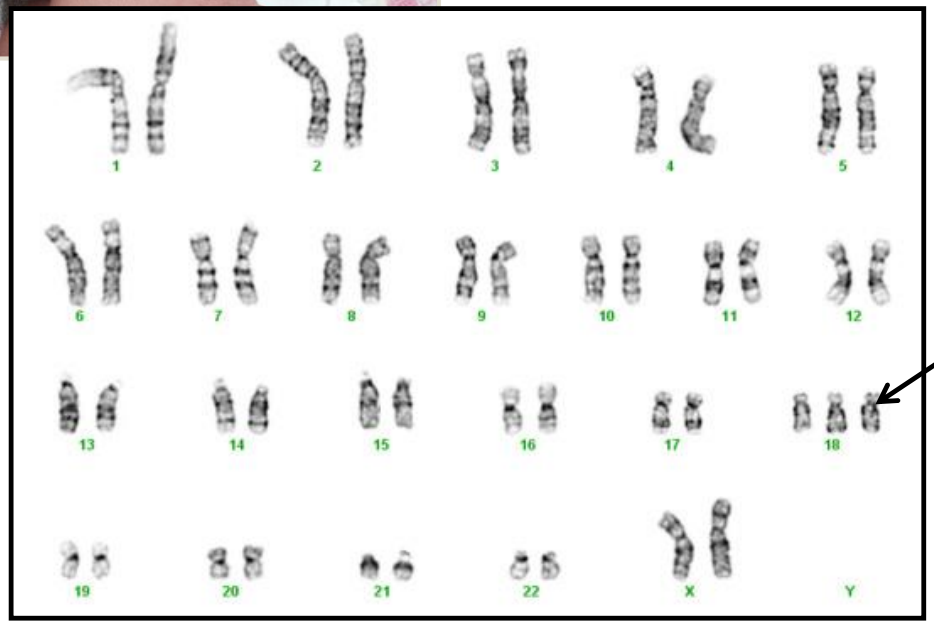


Down syndrome: Trisomy 21

When to do karyotyping?

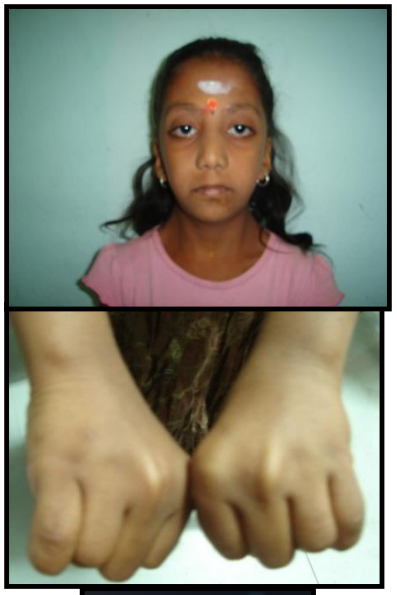


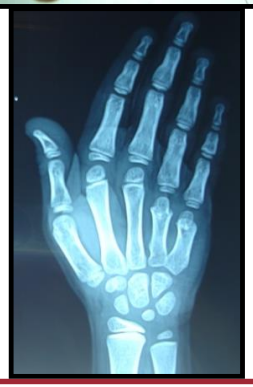
Edwards syndrome:
Trisomy 18

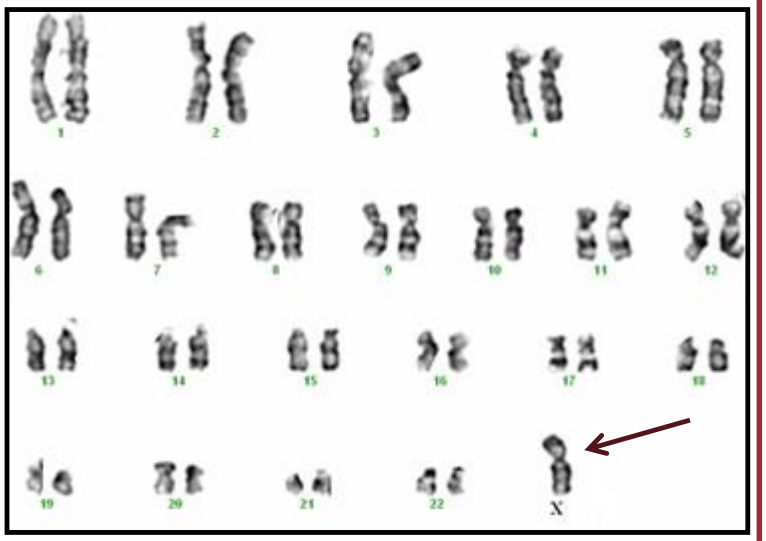


When to do karyotyping?

- Clinical suspicion of a chromosomal disorder



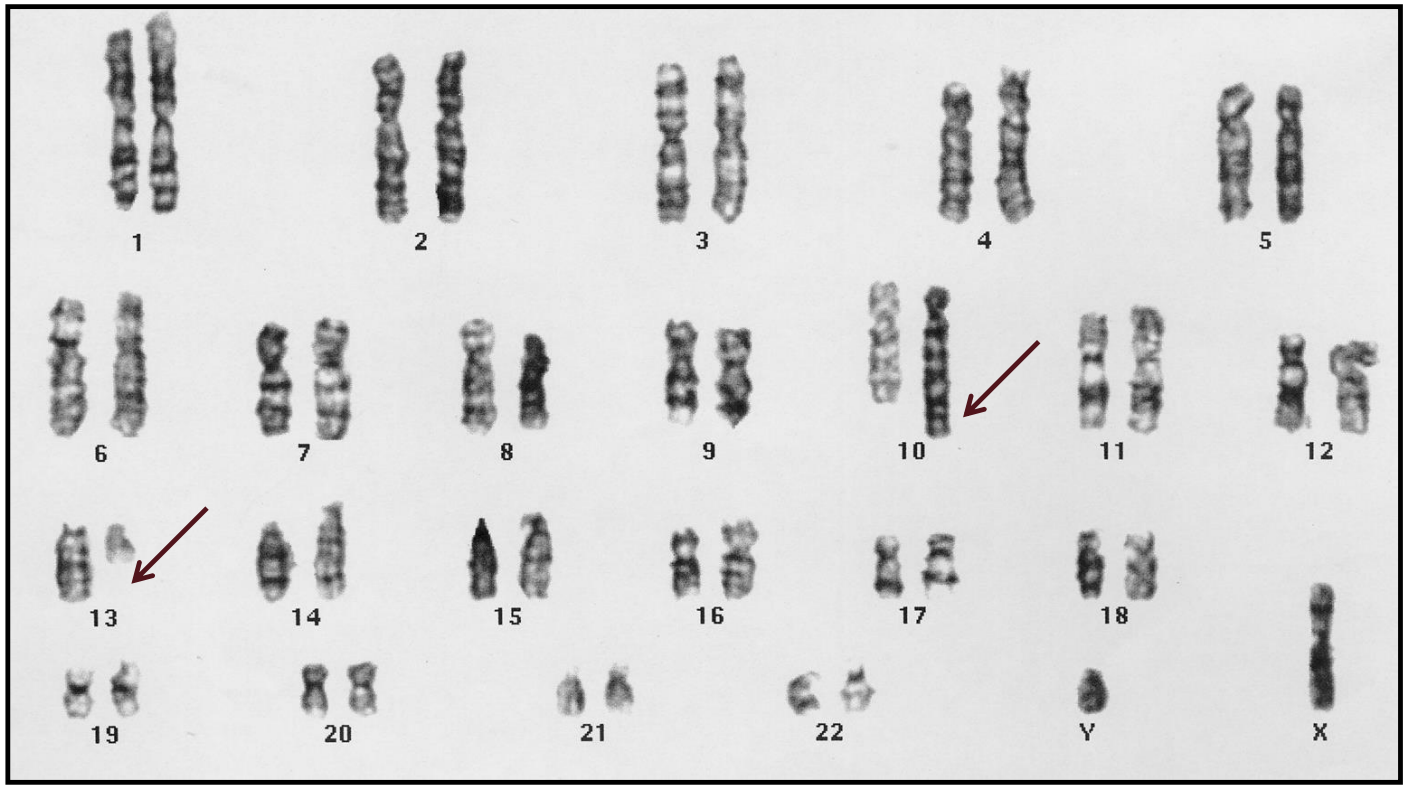


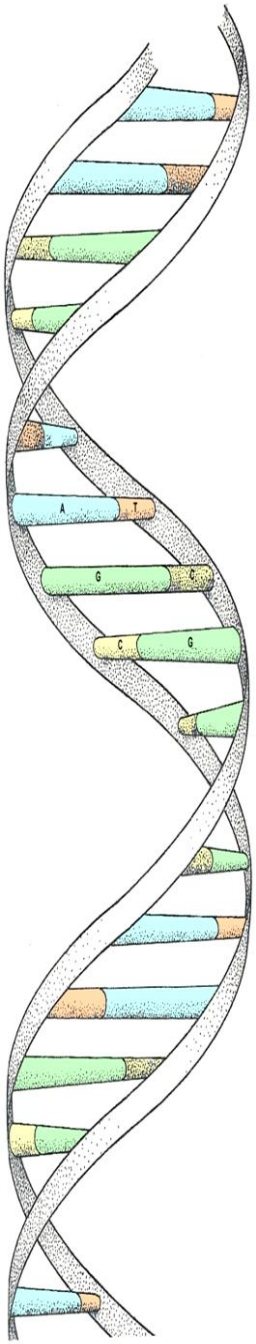


Turner syndrome: 45,X

When to do karyotyping?

Any case of multiple malformation syndrome with/ without idiopathic intellectual disability/ global developmental delay: 3-5% yield





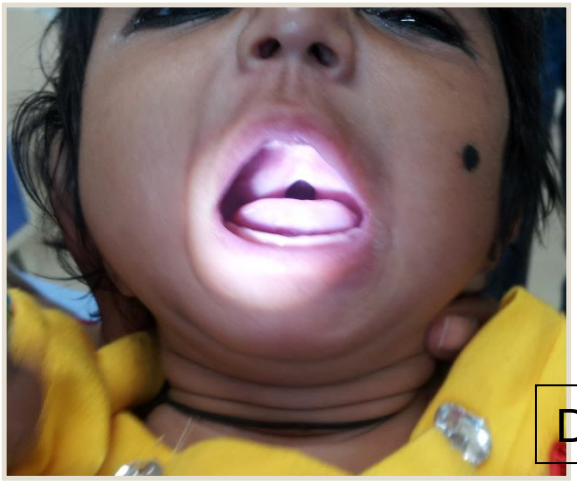
Molecular cytogenetic testing

Molecular cytogenetic studies

- Karyotyping not useful for sub- microscopic chromosomal abnormalities: microdeletion/ microduplication

- Phenotype suggestive of a specific microdeletion syndrome

Molecular cytogenetic testing

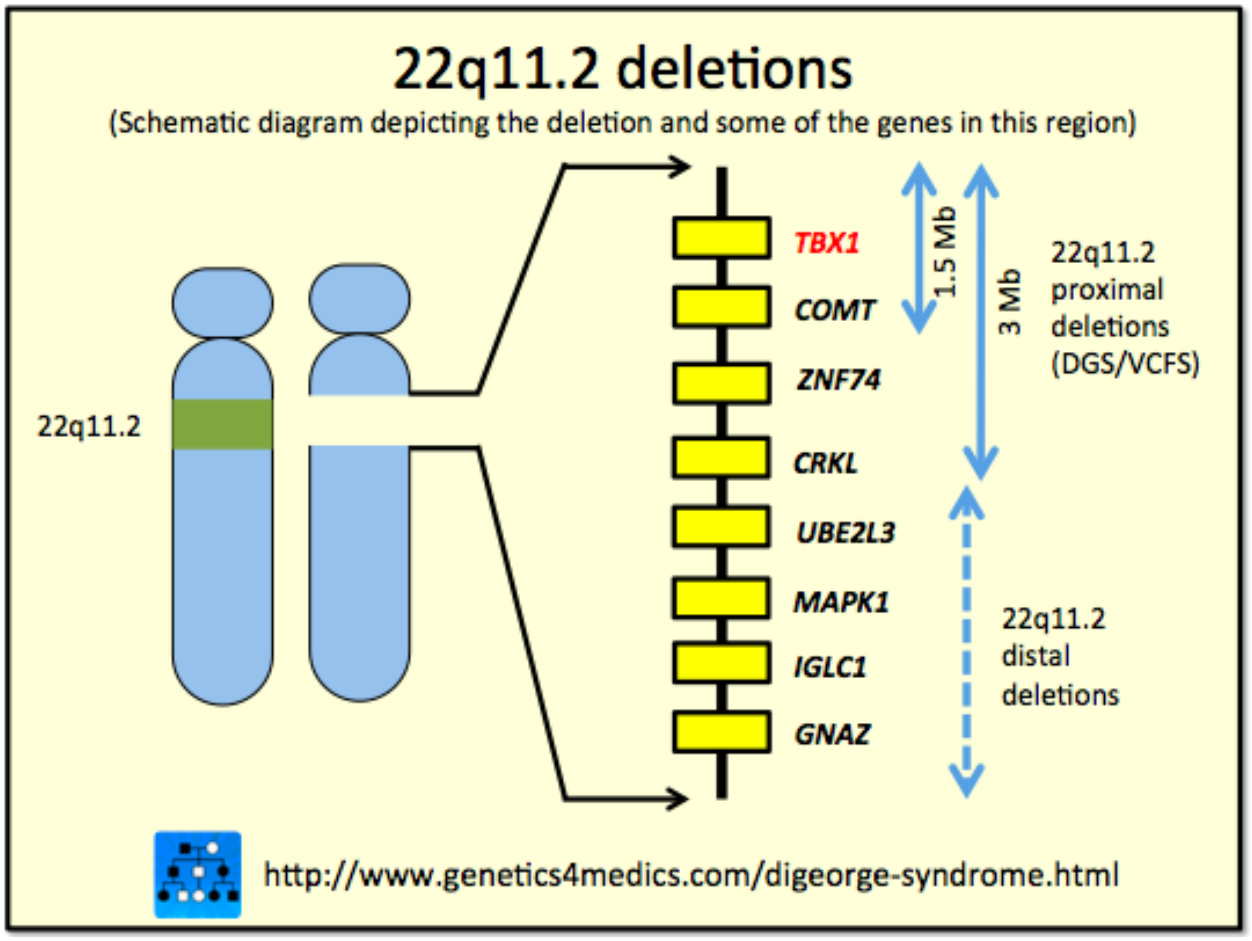


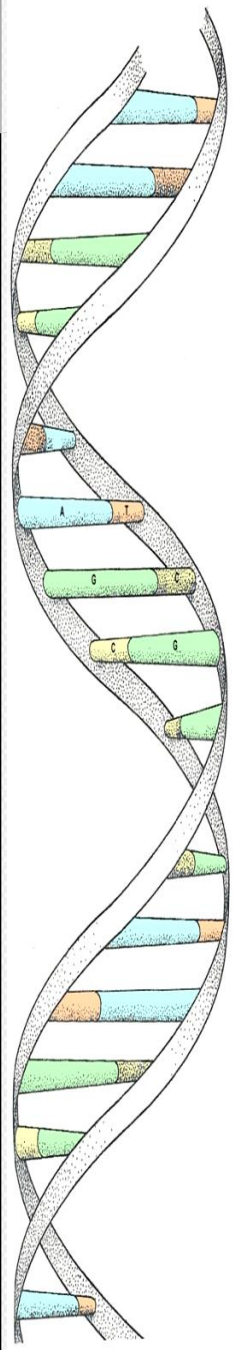
2D Echo – Tetralogy of Fallot

DiGeorge syndrome

22q Microdeletion

- 22q microdeletion: due to sub-microscopic deletion on long arm of chromosome 22





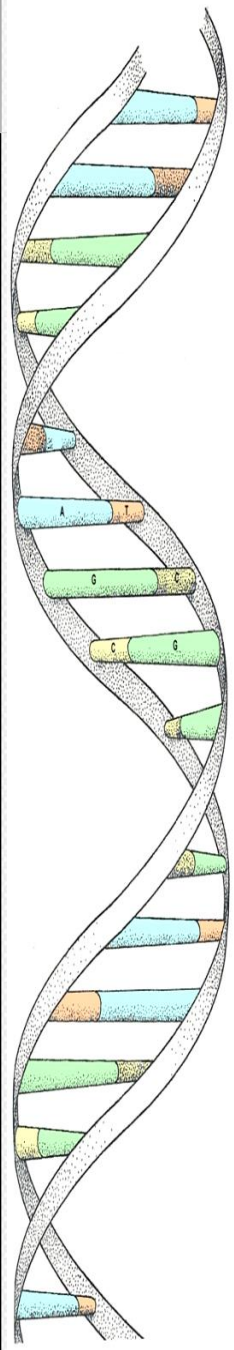
22q microdeletion

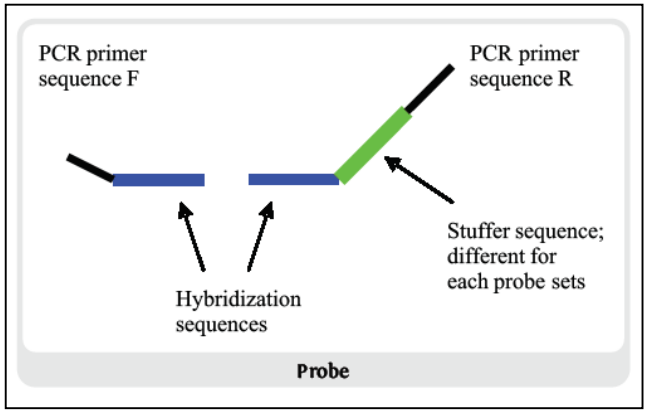
Deleted region too small to be detected in karyotype

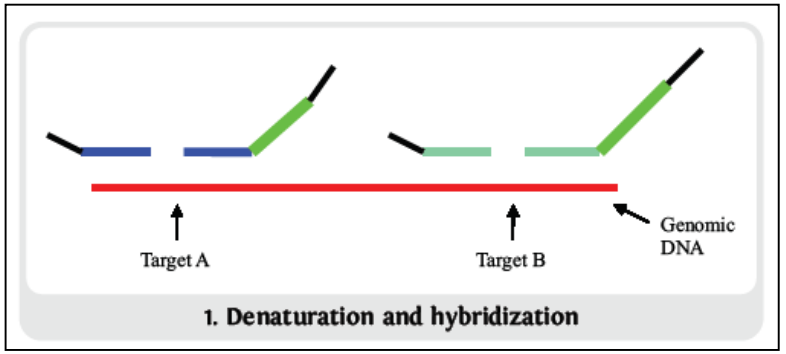
Requires molecular cytogenetic tests:

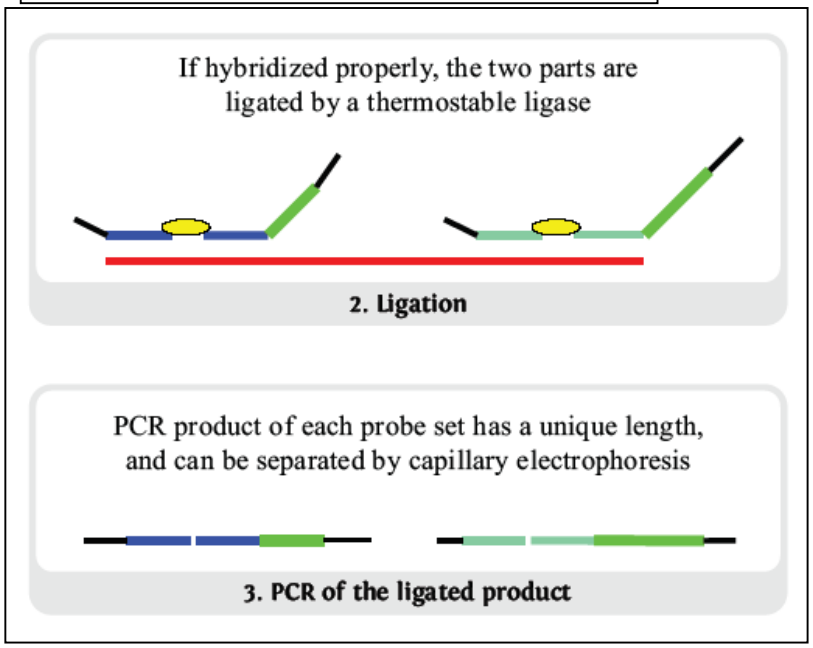
- Fluorescent in-situ hybridization(FISH)
- Multiplex ligation-dependent probe amplification (MLPA)
- Cytogenetic microarray (CMA)

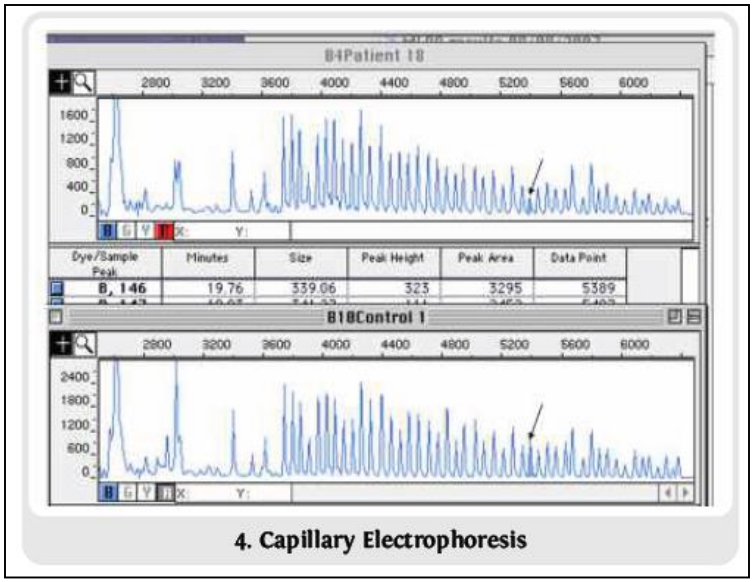
Multiplex ligation dependent probe amplification (MLPA)





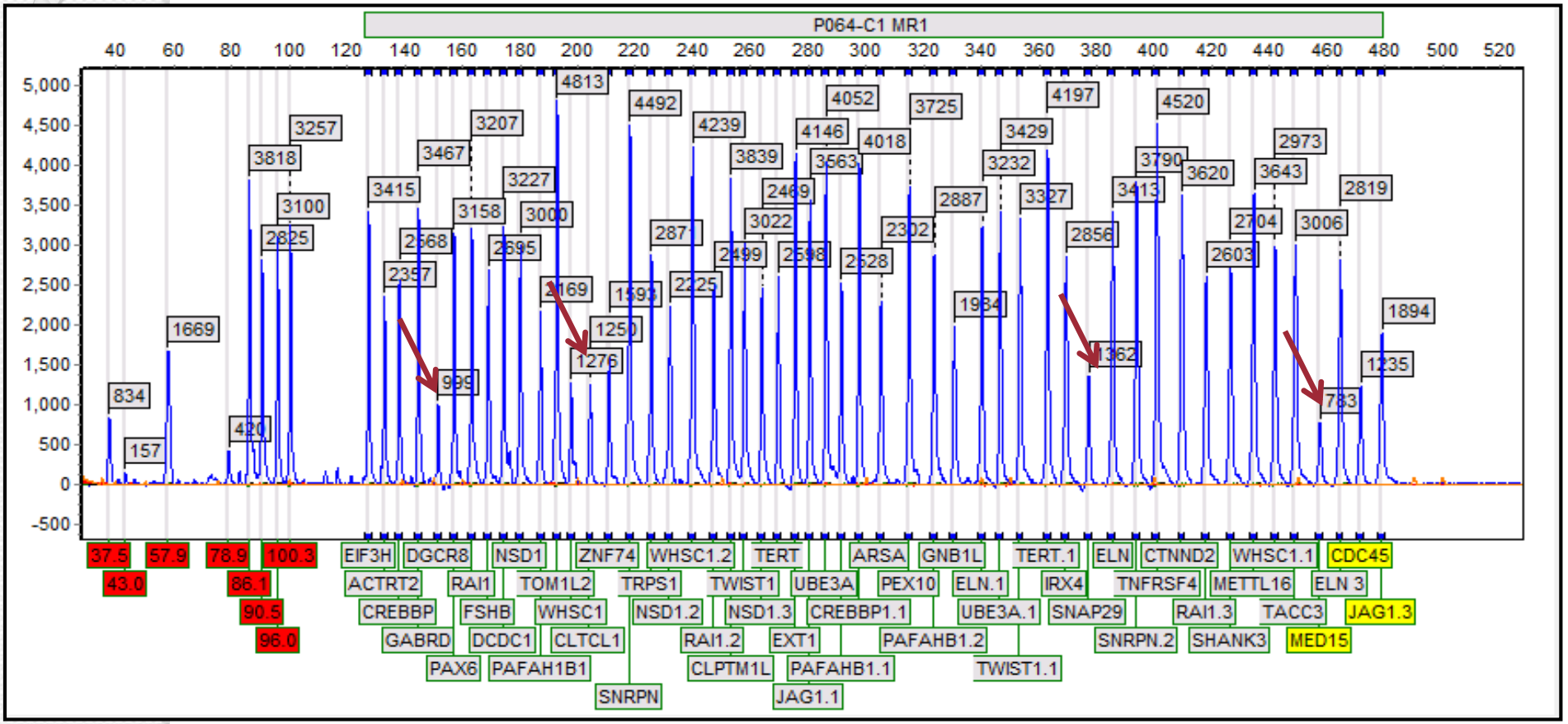




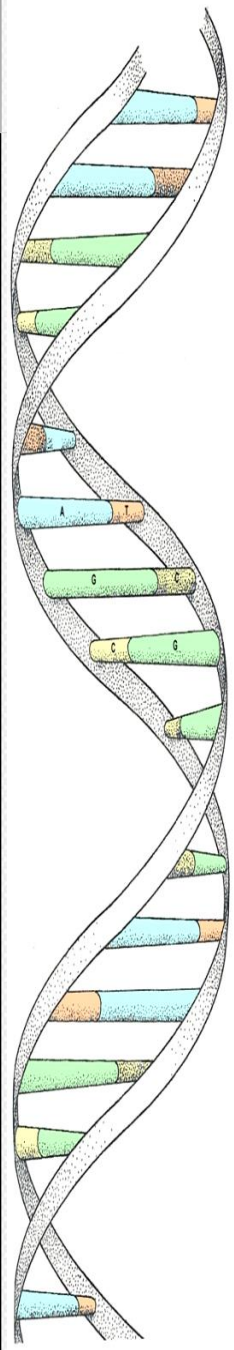


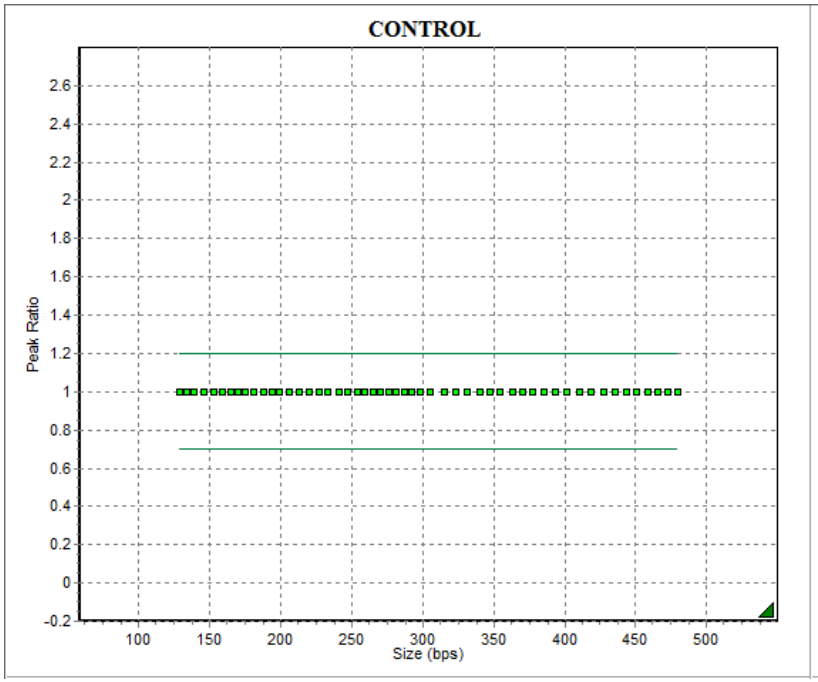
3 ml of EDTA blood

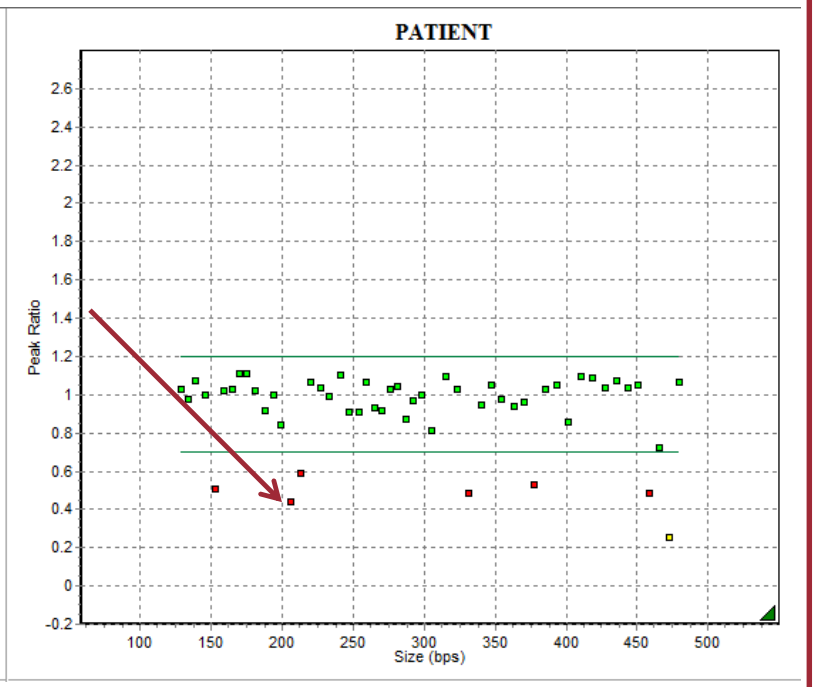
Patient's MLPA result



Patient's MLPA result

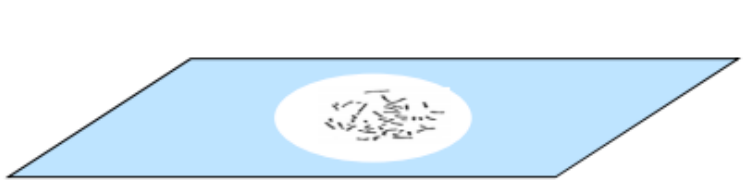






Diagnosis: 22q microdeletion syndrome

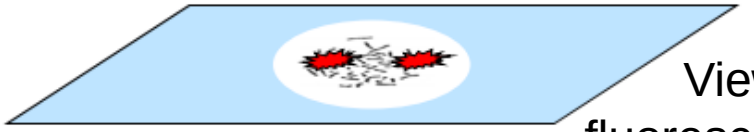
Fluorescence in situ hybridization (FISH)



Denatured

Denatured

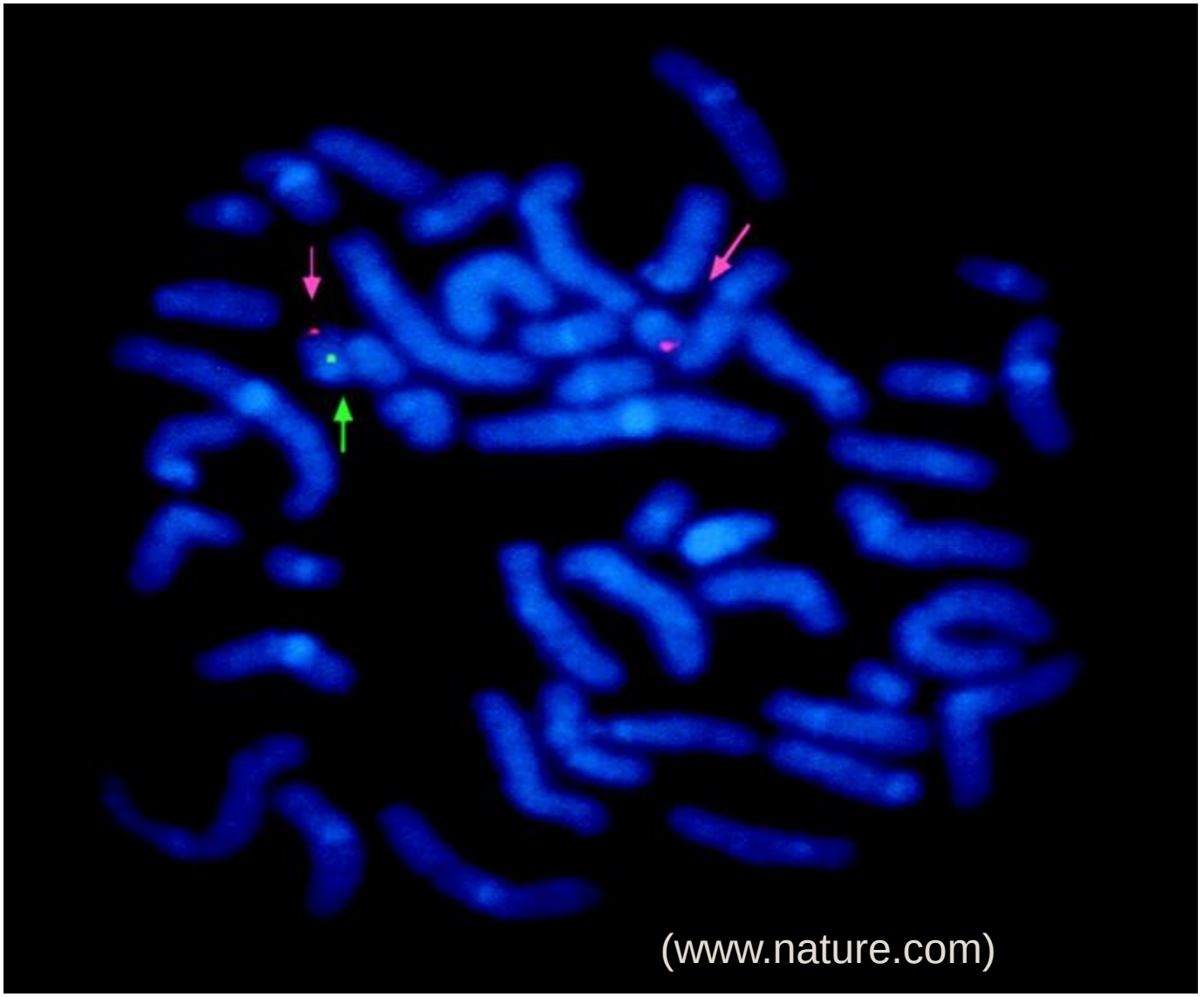
Hybridized



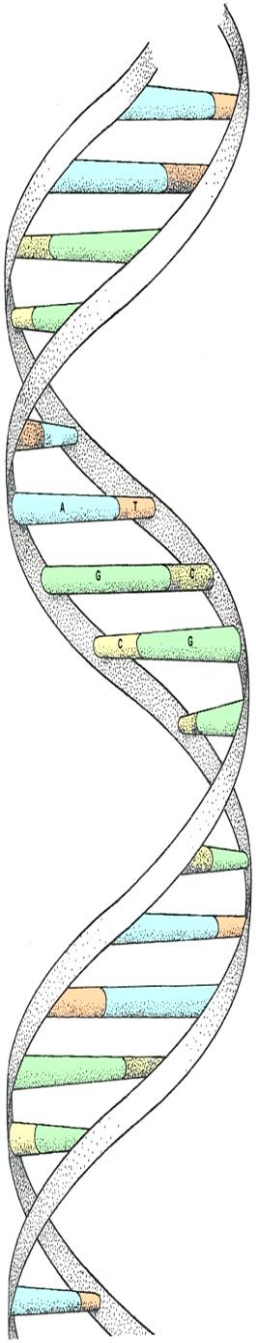
Viewed under a fluorescence microscope

3 ml of heparinized blood (green-top tube)

Fluorescence in situ hybridization

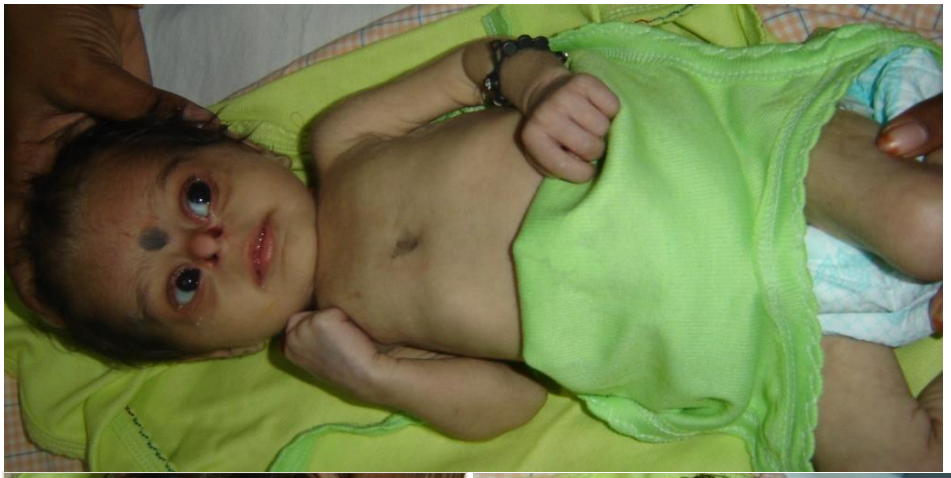


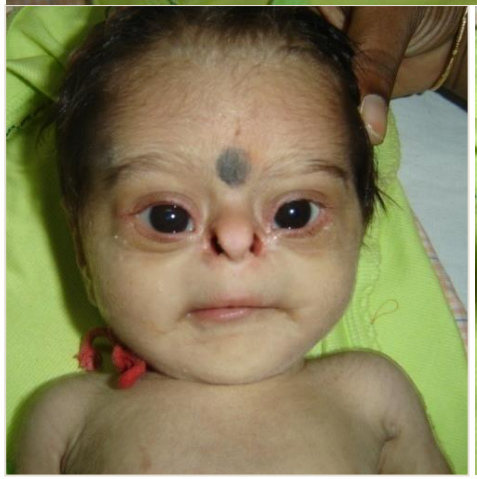
(www.nature.com)

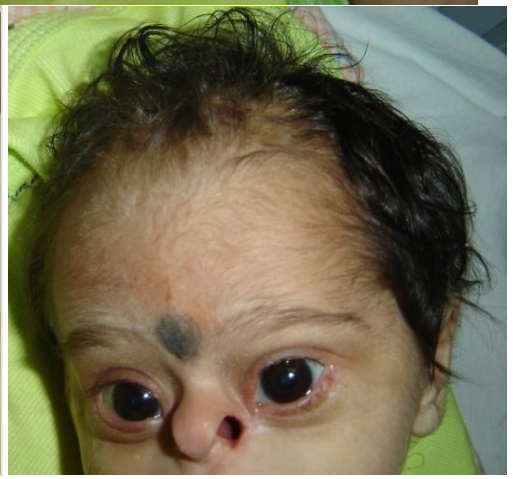


Molecular genetic testing

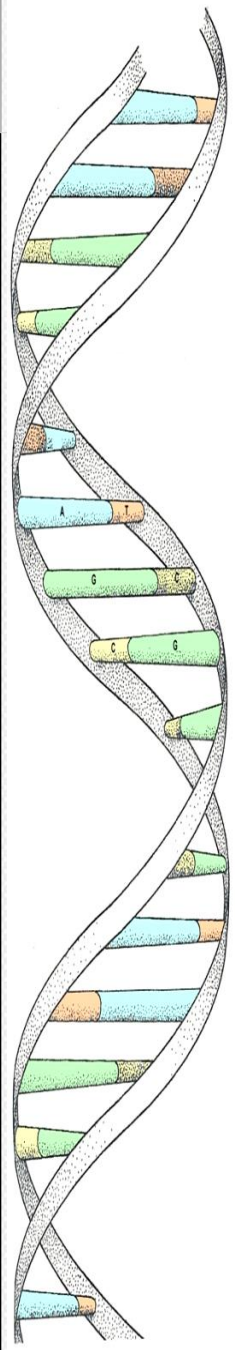
Single gene disorders with CHD







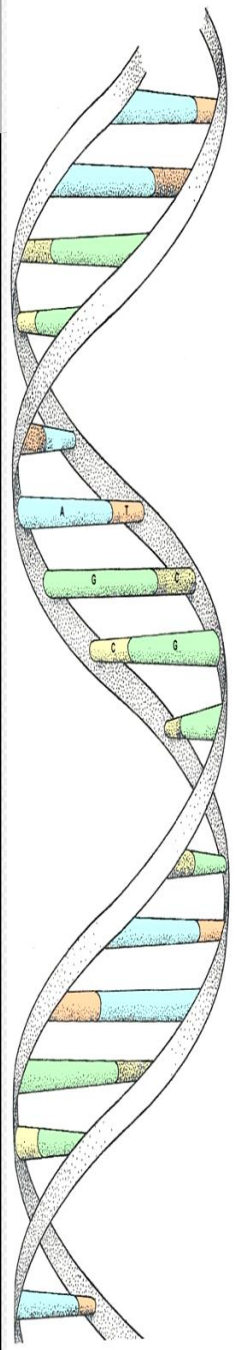
Johanson Blizzard syndrome:
UBR1 gene mutation analysis

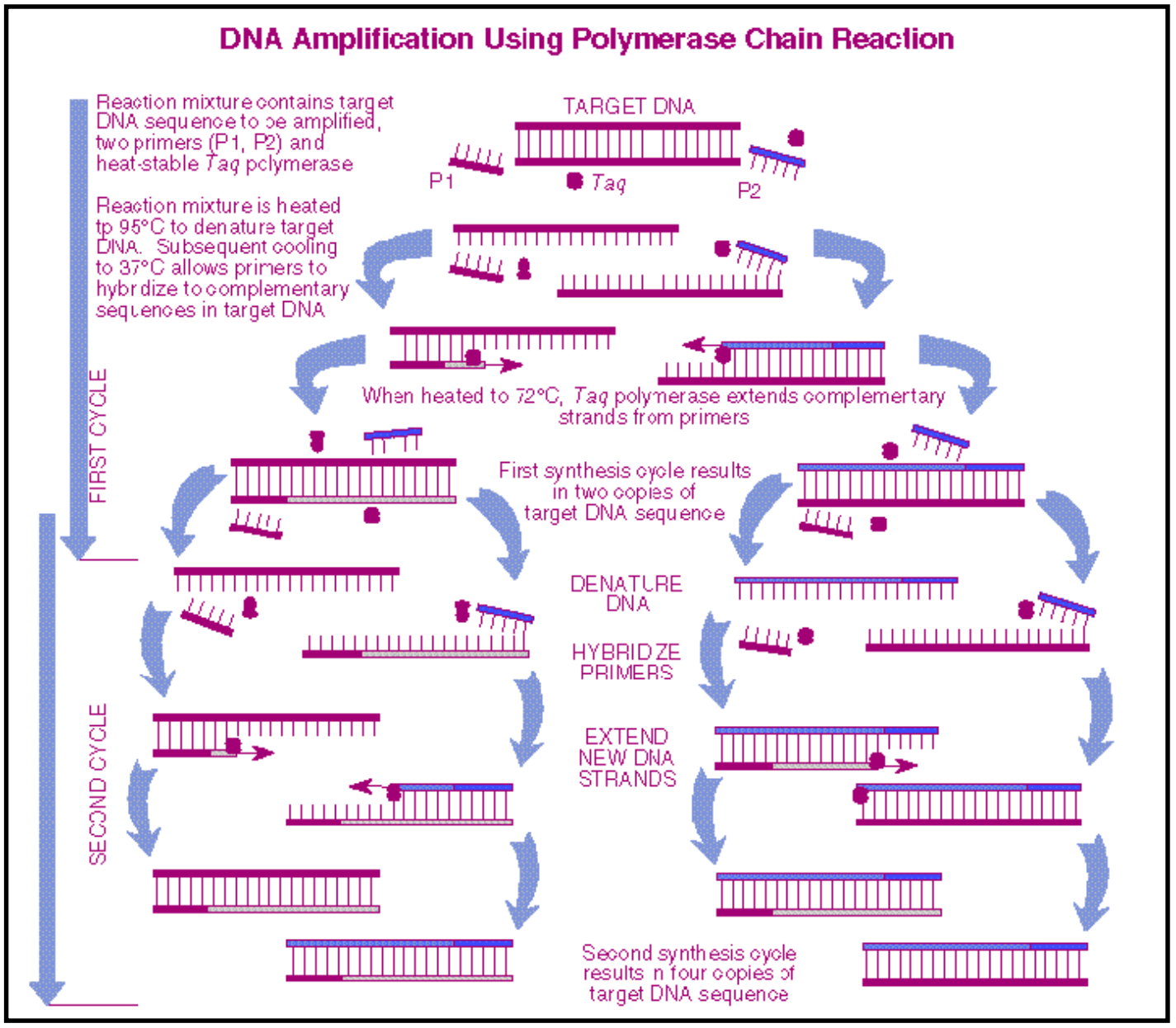


Molecular genetic studies

- **Single gene disorders:** Karyotyping / FISH/ MLPA not useful
- ***DNA-based gene sequence analysis*** - when a specific monogenic disorder is suspected

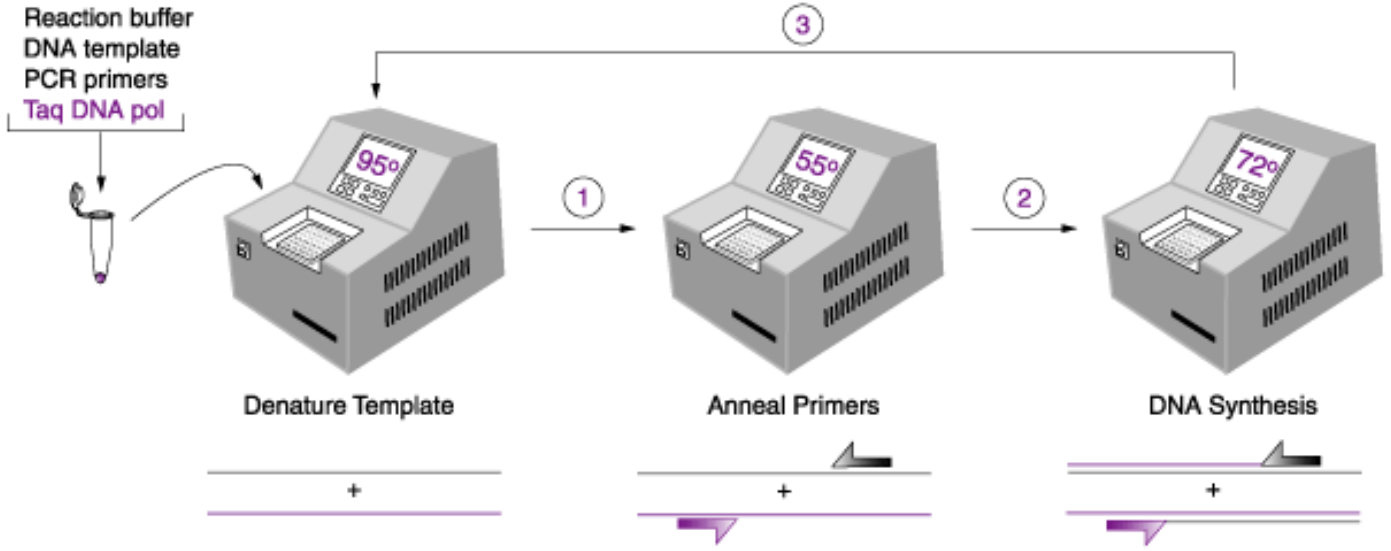
Polymerase chain reaction (PCR)



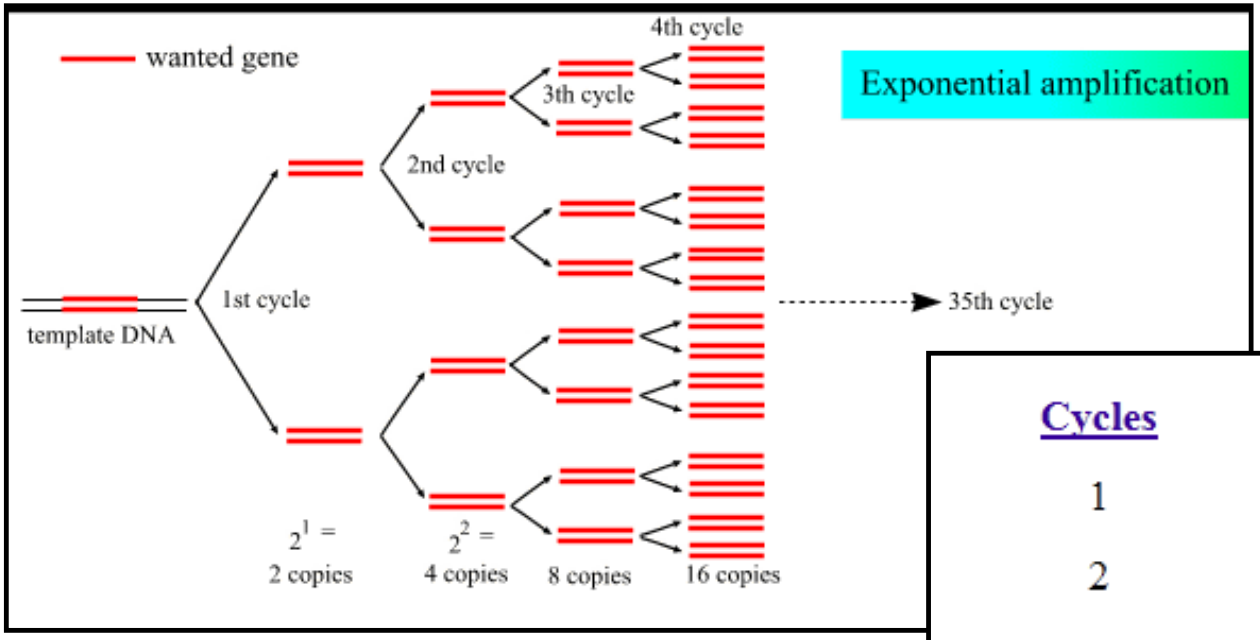


Polymerase chain reaction

- Carried out in a **thermocycler**



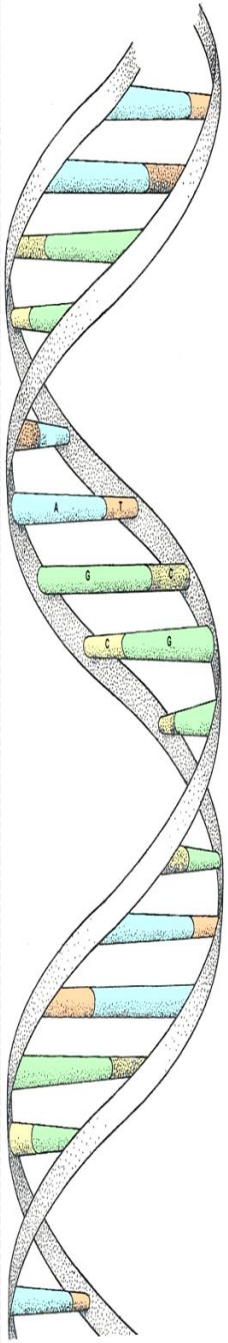
Polymerase chain reaction

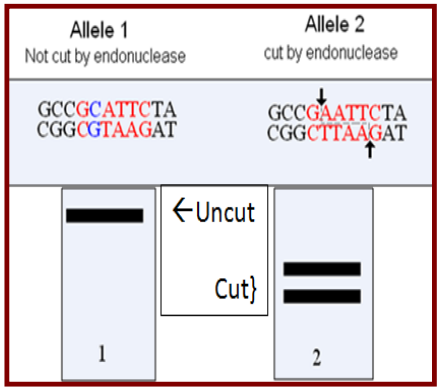


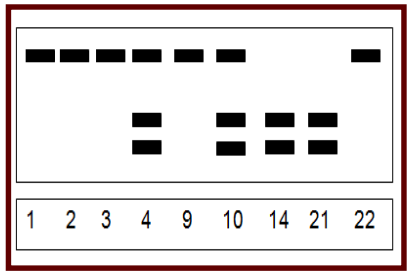
Exponential amplification

Cycles	Copies
1	2
2	4
4	16
10	1,024
15	32,768
20	1,048,576
25	33,554,432
30	**1,073,741,824**

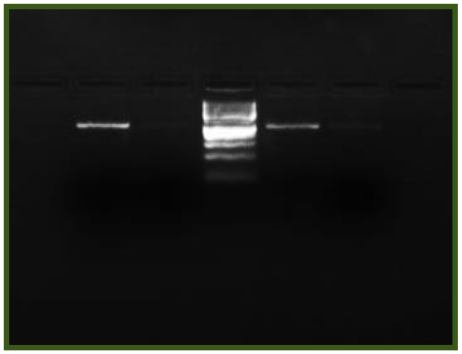
Molecular genetic tests



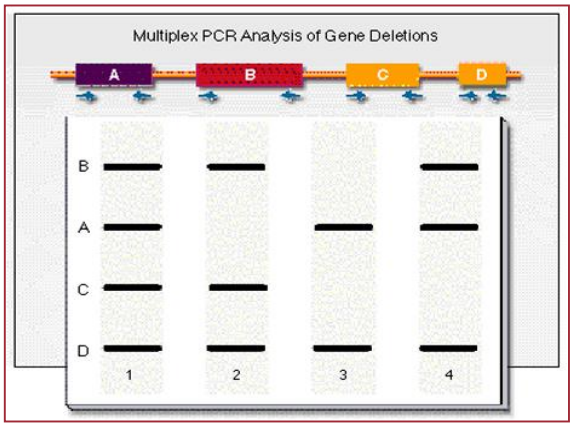




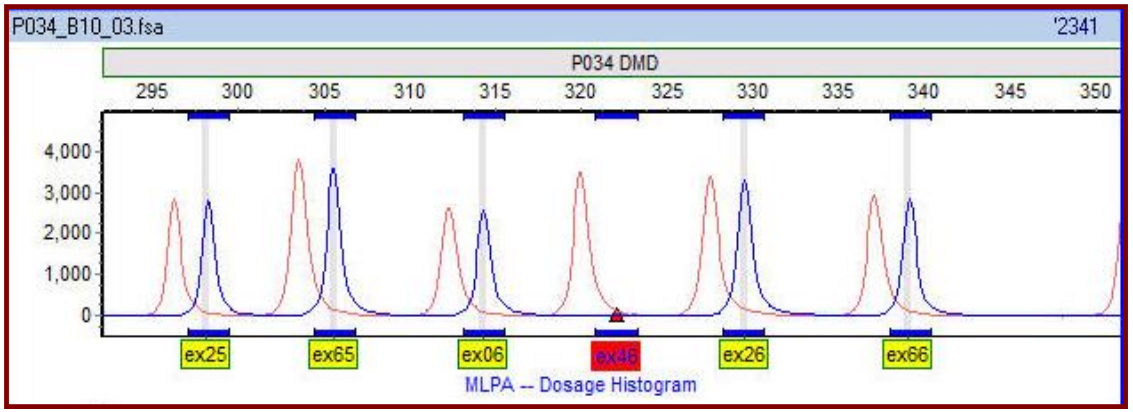
PCR - RFLP



ARMS - PCR



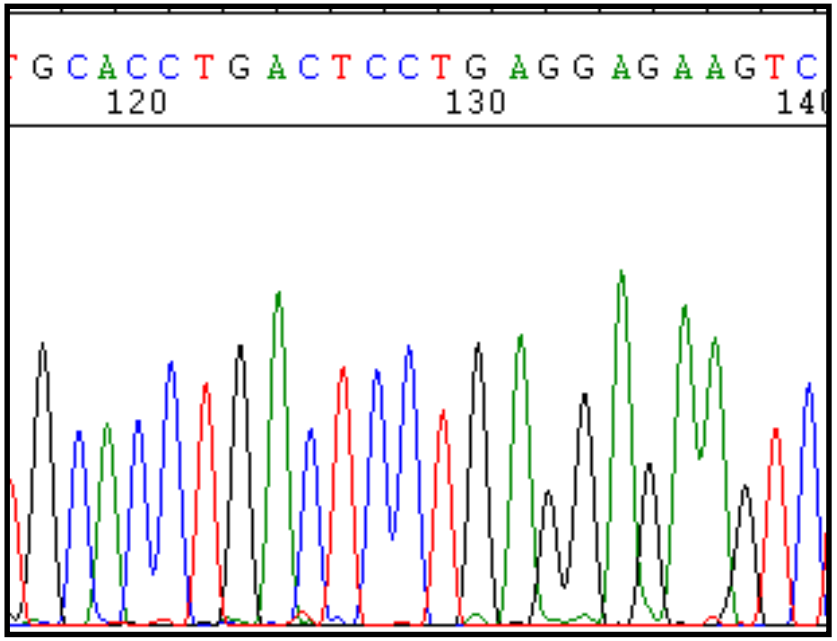
Multiplex - PCR



MLPA

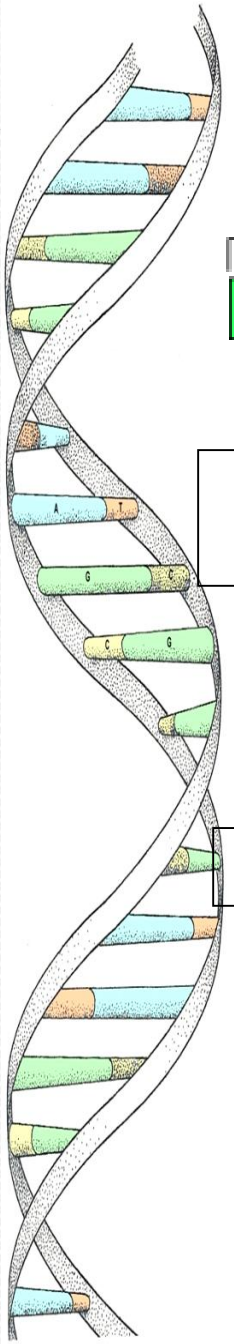
DNA sequence analysis

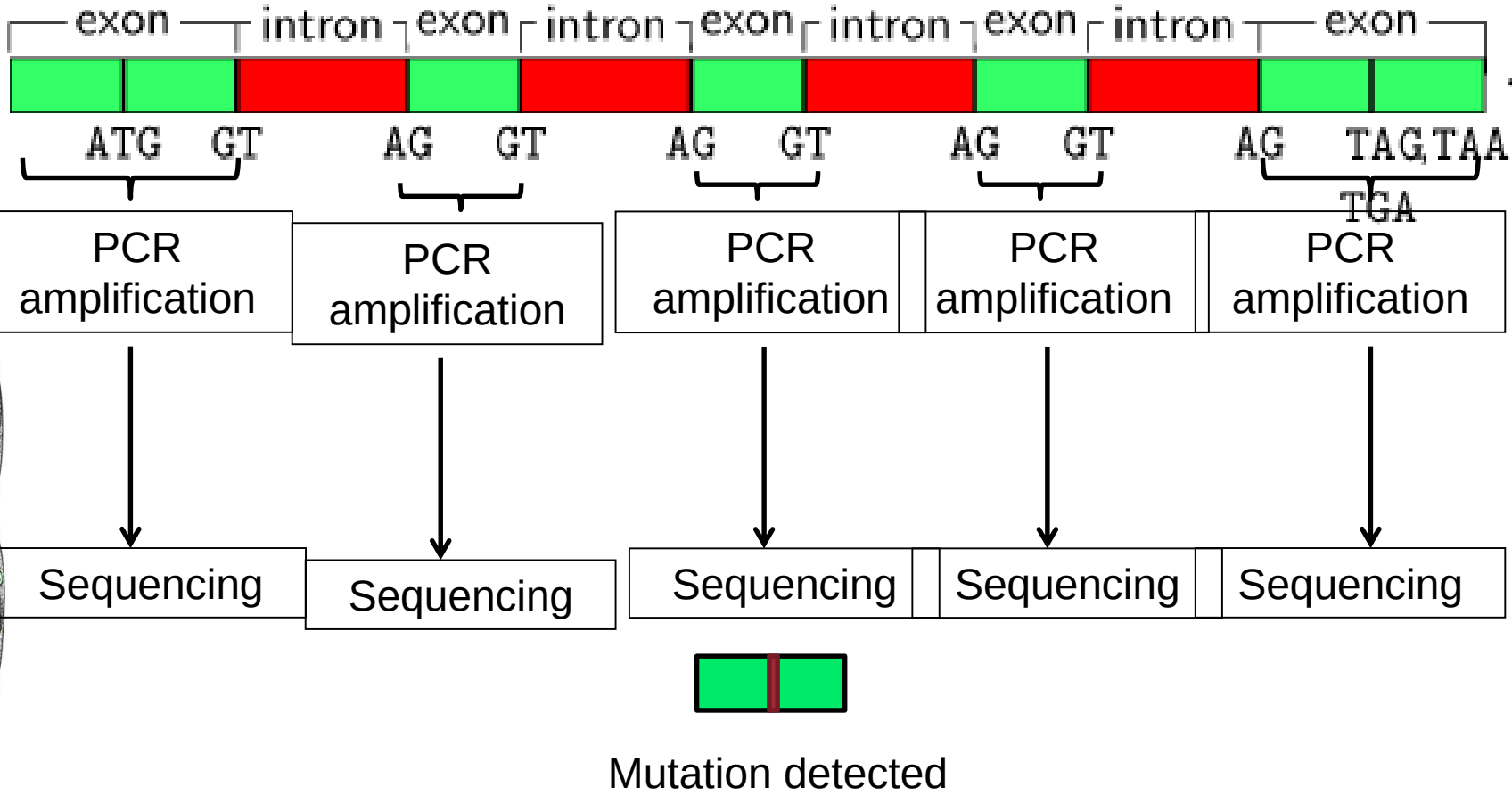
DNA Sequencer



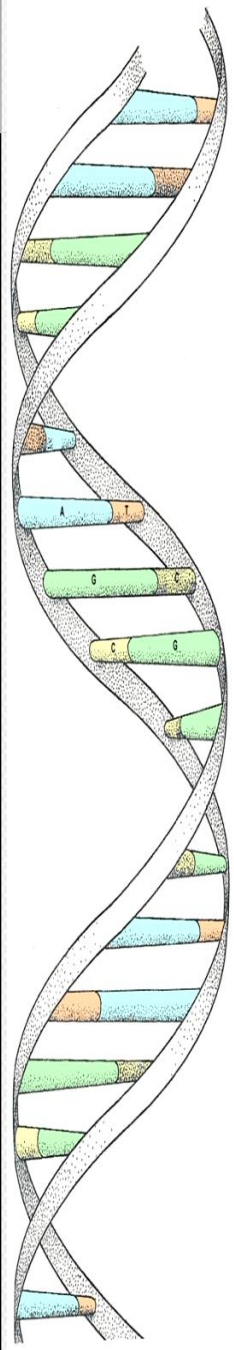
Sequence chromatogram

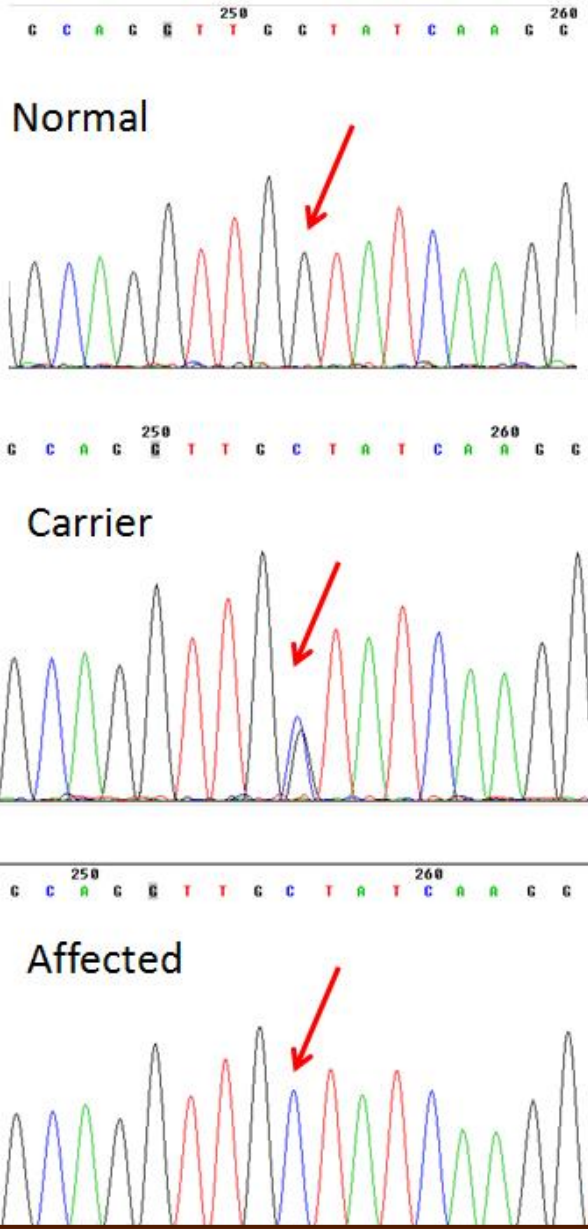
DNA sequence analysis





DNA sequence analysis



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# Similarity:   701/779 (90.0%)
# Gaps:          64/779 ( 8.2%)
# Score: 3368.5
#
#
#=======================================

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EMBOSS_001         1 TCCTAAGCCAGTGCCAG----AAGAGCCAAGGACAGGTACGGCTGTCATC      46

EMBOSS_001        31 ---------------------------------TCGGCC-ATCTACTC      44
                                                      |.|||| ||||||||
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EMBOSS_001        45 CCAGGAGCAGGGAGGGCAGGAGCCAGGGCTGGGCATAAAAGTCAGGGCAG      94
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EMBOSS_001        97 CCAGGAGCAGGGAGGGCAGGAGCCAGGGCTGGGCATAAAAGTCAGGGCAG     146

EMBOSS_001        95 AGCCATCTATTGCTTACATTTGCTTCTGACACAACTGTGTTCACTAGCAA     144
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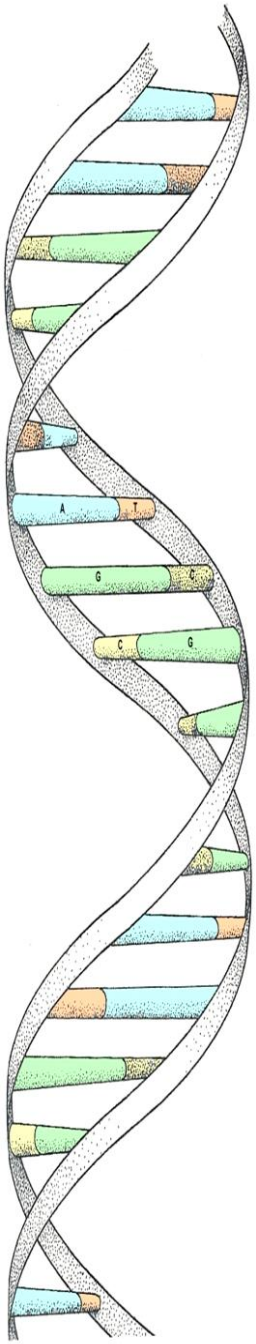
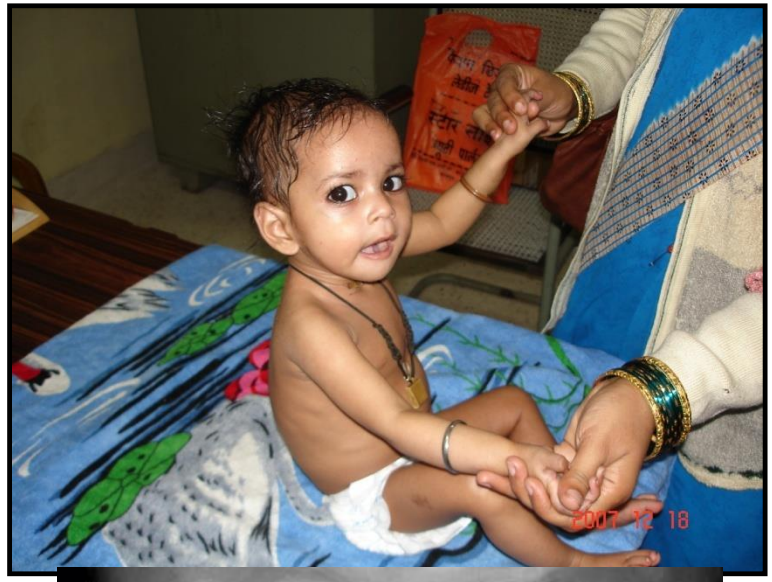


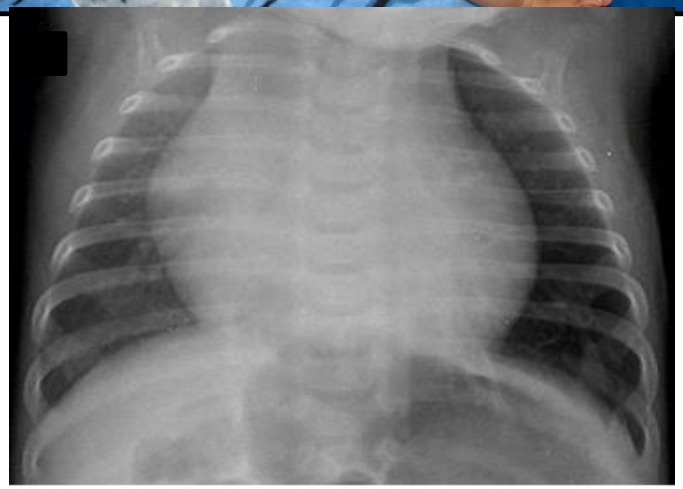
Metabolic genetic testing

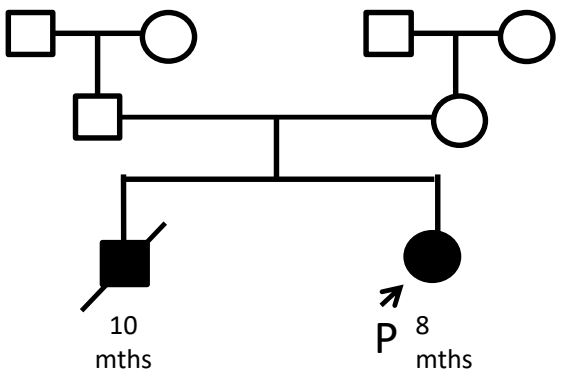
Inborn Errors of Metabolism

Salient features:

- Motor developmental delay
- Floppiness & arreflexia
- Hepatomegaly
- Growth retardation
- Cardiomegaly
- Hypertrophic cardiomyopathy
- Similarly affected sibling





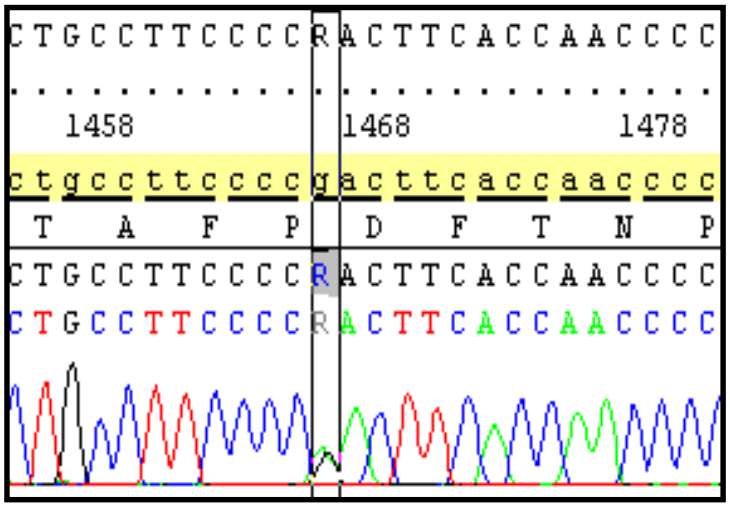


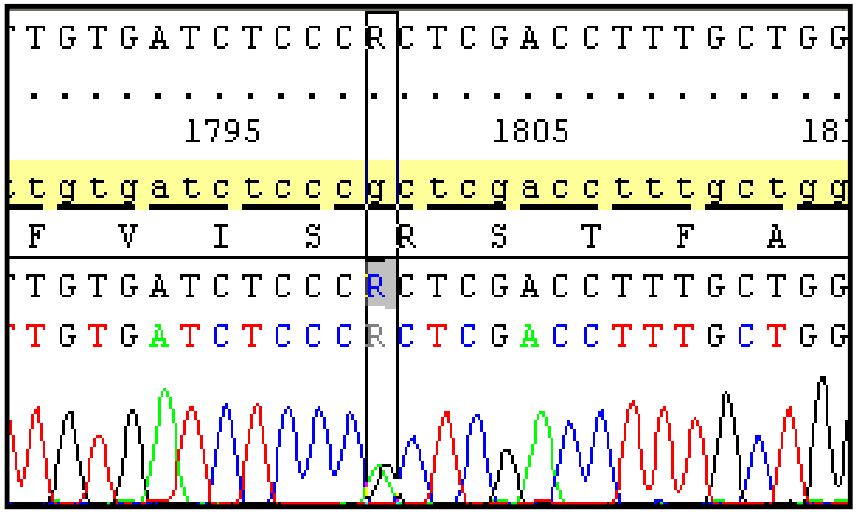
Pompe Disease

Case Scenario

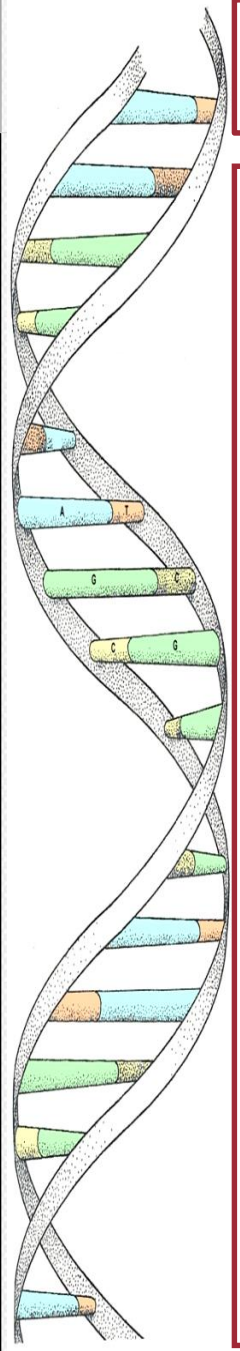
- Alpha glucosidase enzyme assay (acarbose inhibition): 3 nmol/ hr/ mg (ref: 60-120 nmol/ hr/ mg)

- *GAA* gene mutation analysis: c.1465 G>A/ c.1799 G>A





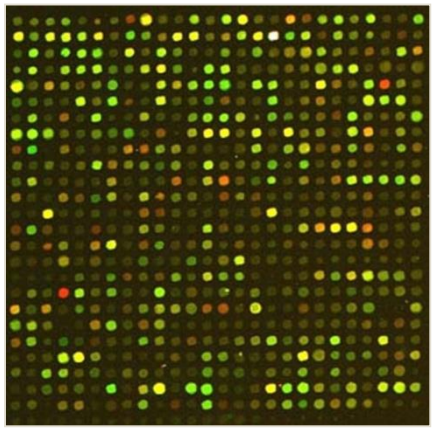
Molecular genetic studies

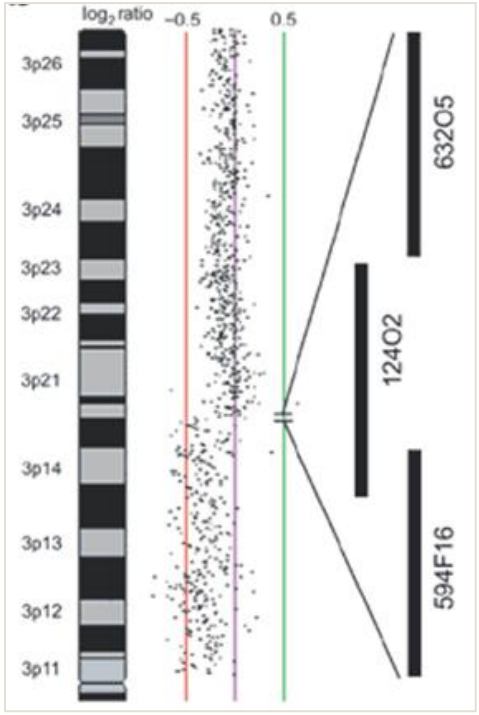


What if the features do not fit into a clinically identifiable syndrome?

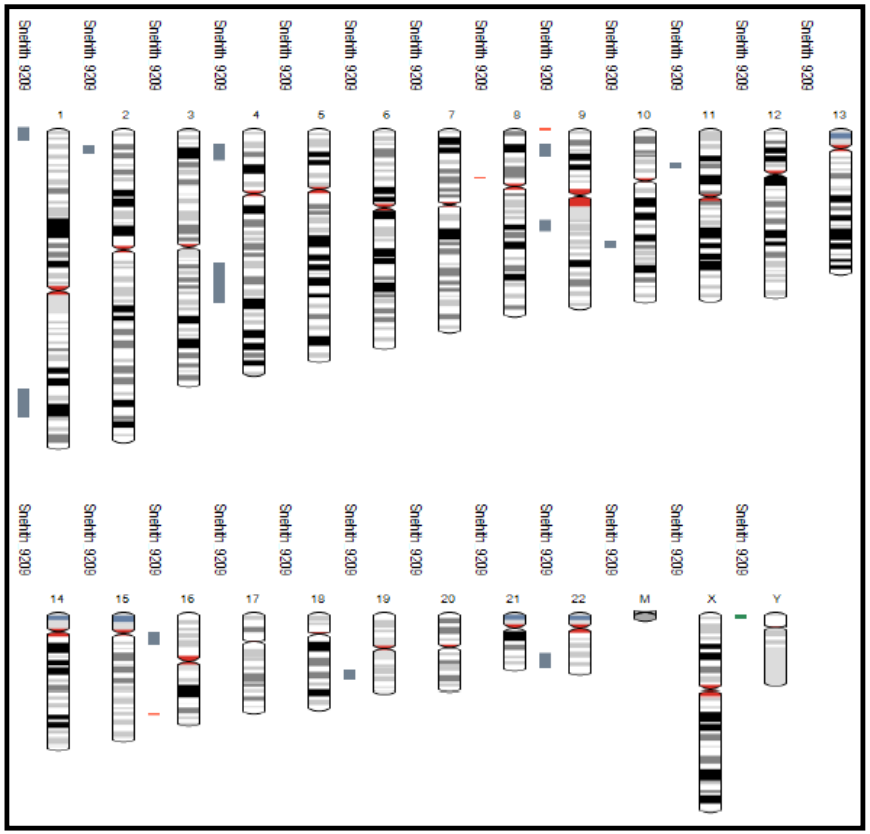
Molecular genetic studies

- **Chromosomal Microarray :**
  - Scans entire genome for microdeletions/ microduplications
  - For multiple malformation conditions without an identifiable syndromic association/ etiology



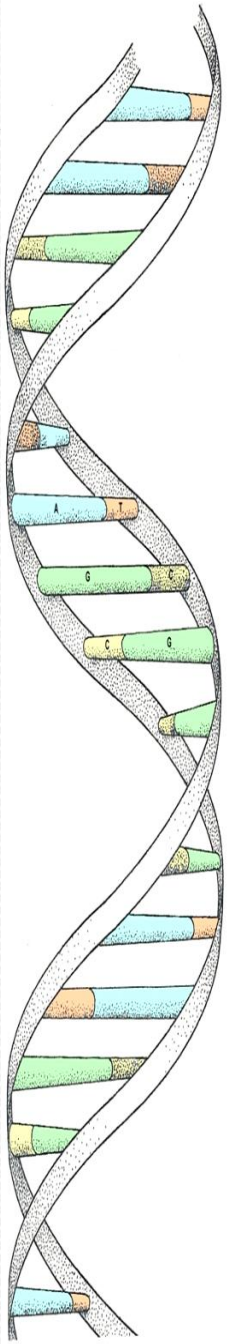


Chromosomal microarray



Aberration Details:

Chr	Aberration Length	CNV Conf	Variation Type	Gene	DGV/CHOP similarity	Statistical Significance
8	135252	119.3264	Hemizygous Deletion	Present	Low	Significant
9	170967	104.9423	Hemizygous Deletion	Absent	No Data	No Significance
16	368061	39.30399	Hemizygous Deletion	Absent	No Data	No Significance
Y	730130	137.6444	Duplication	Present	No Data	No Significance
Y	200284	172.5503	Triplication	Absent	No Data	No Significance
Y	2674135	196.6163	Duplication	Absent	No Data	No Significance
1	11487135	674.5375	Copy Neutral LOH	Present	No Data	No Significance
1	22980276	1067.465	Copy Neutral LOH	Present	Moderate	To be evaluated at Gene Level
2	7266816	374.5963	Copy Neutral LOH	Present	Moderate	
4	13735431	532.6191	Copy Neutral LOH	Present	Moderate	
4	32041545	993.1531	Copy Neutral LOH	Present	Moderate	
9	11223873	469.8707	Copy Neutral LOH	Present	Moderate	
9	11600526	369.8175	Copy Neutral LOH	Present	Moderate	
9	9241584	499.7567	Copy Neutral LOH	Present	Moderate	
10	5586723	264.8291	Copy Neutral LOH	Present	Moderate	
11	4288644	108.2642	Copy Neutral LOH	Present	Moderate	
16	11198854	480.2805	Copy Neutral LOH	Present	Moderate	
19	8337912	262.0085	Copy Neutral LOH	Present	Moderate	
22	11981097	547.3286	Copy Neutral LOH	Present	Moderate	



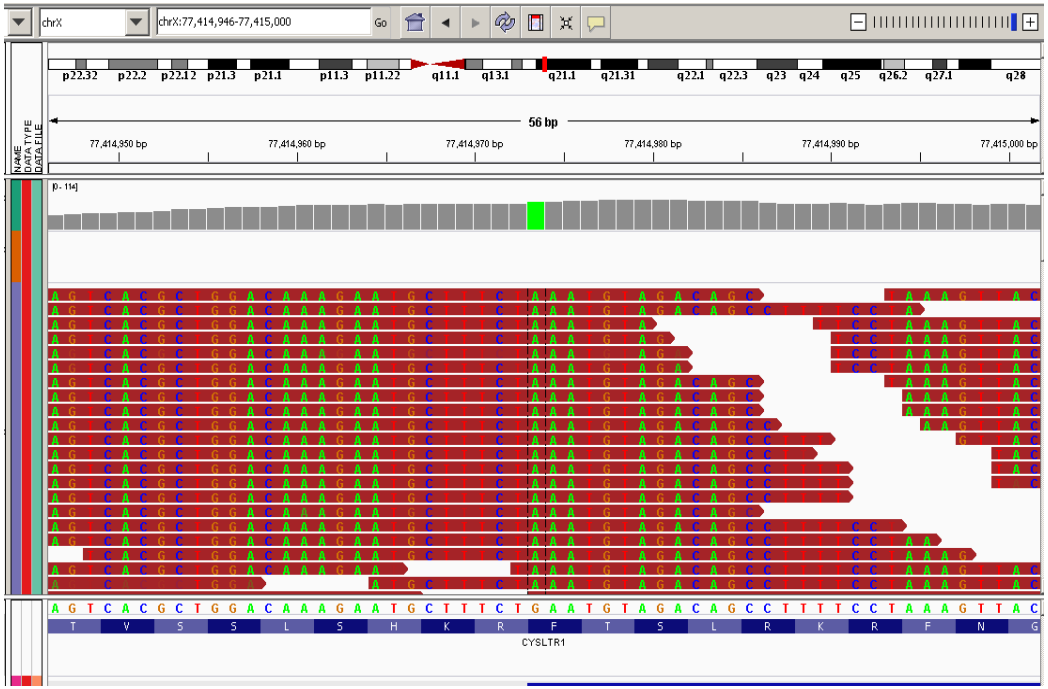
Molecular genetic studies

Exome sequencing:

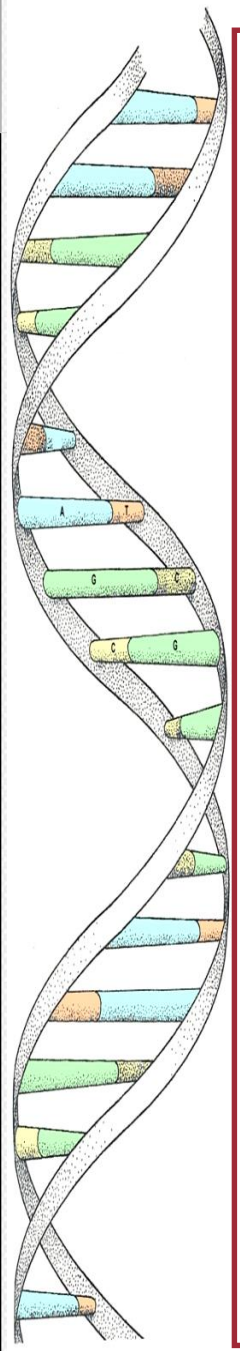
- Scans all coding portions of all genes (exome) for sequence variants
- For multiple malformation conditions without an identifiable syndromic association/ etiology
- For multiple malformation conditions with overlapping phenotypes/ genetically heterogeneous

Whole exome/genome sequencing

- Next generation sequencing: massively parallel sequencing strategy that can be used to sequence entire genome/ entire coding portion of genome

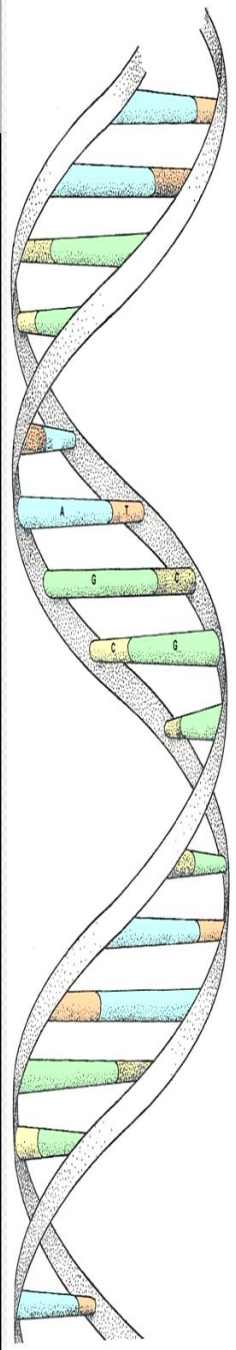


- Being used as a final resort testing for all undiagnosed conditions with suspected etiology



If the features do not fit into a clinically identifiable syndrome?

Chromosomal microarray → if inconclusive
→Exome sequencing

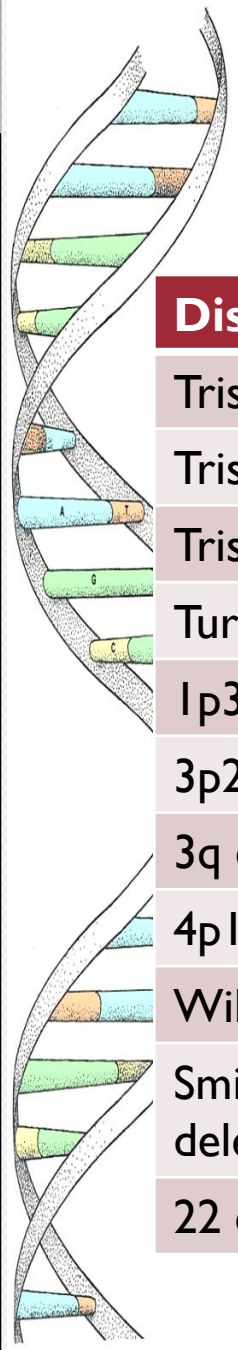


Chromosomal disorders

Table 1 Chromosome abnormality syndromes associated with CHD

Syndrome	% CHD	CHD type
Chromosome aneuploidy		
Trisomy 21	44	AVSD (complete, partial), VSD, ASD, TOF
Trisomy 18	83	VSD, ASD, TOF, DORV, AVSD, CoA
Trisomy 13	51–64	Conotruncal CHD: TOF, DORV; VSD, ASD, AVSD; valvular anomalies
45X (Turner syndrome)	38	Left-sided cardiac structures: bicuspid aortic valve, AS, CoA, mitral valve anomalies, HLHS, aortic dilation, dissection
Chromosome deletion		
22q11.2 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome)	75–80	"Conotruncal anomalies": interrupted aortic arch type B, truncus arteriosus, TOF, TGA, perimembranous VSD, isolated aortic arch anomalies
7p11.23 microdeletion (Williams–Beuren syndrome)	82	Supravalvular aortic and pulmonary stenosis, peripheral pulmonary stenosis
1p36 deletion syndrome	35	VSD, ASD, TOF, CoA, PDA
11q23 deletion syndrome (Jacobson syndrome)	56	VSD, left heart anomalies

Biochem Genet (2017) 55:105–123



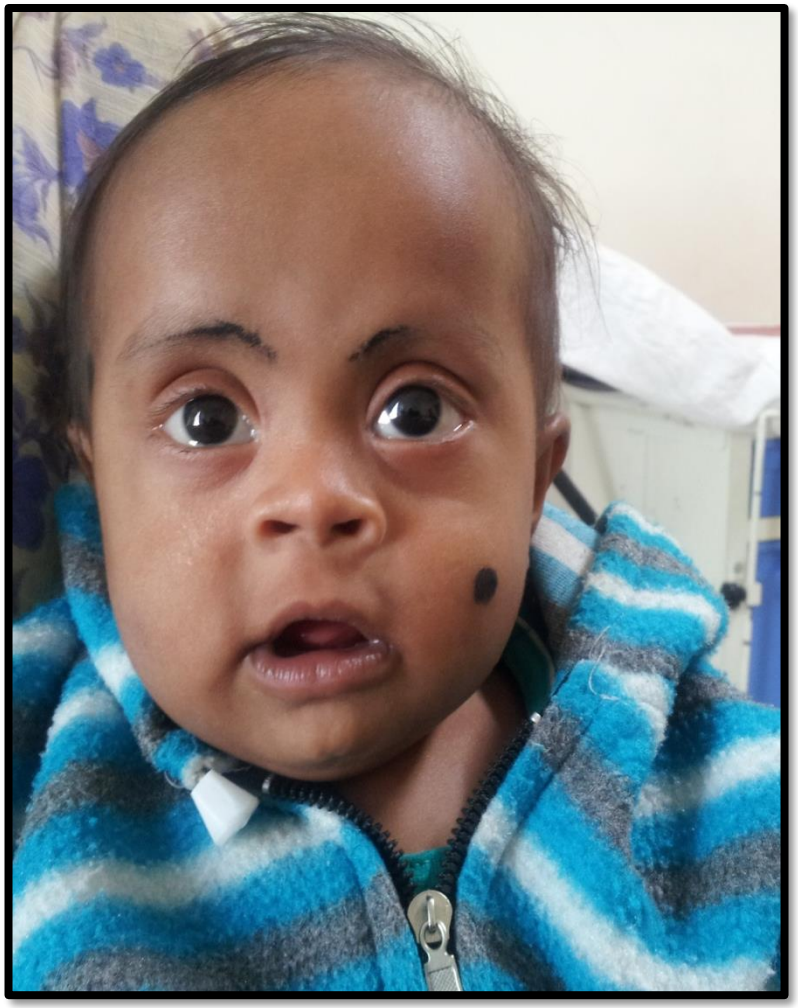
Frequency of CHD in various chromosomal disorders

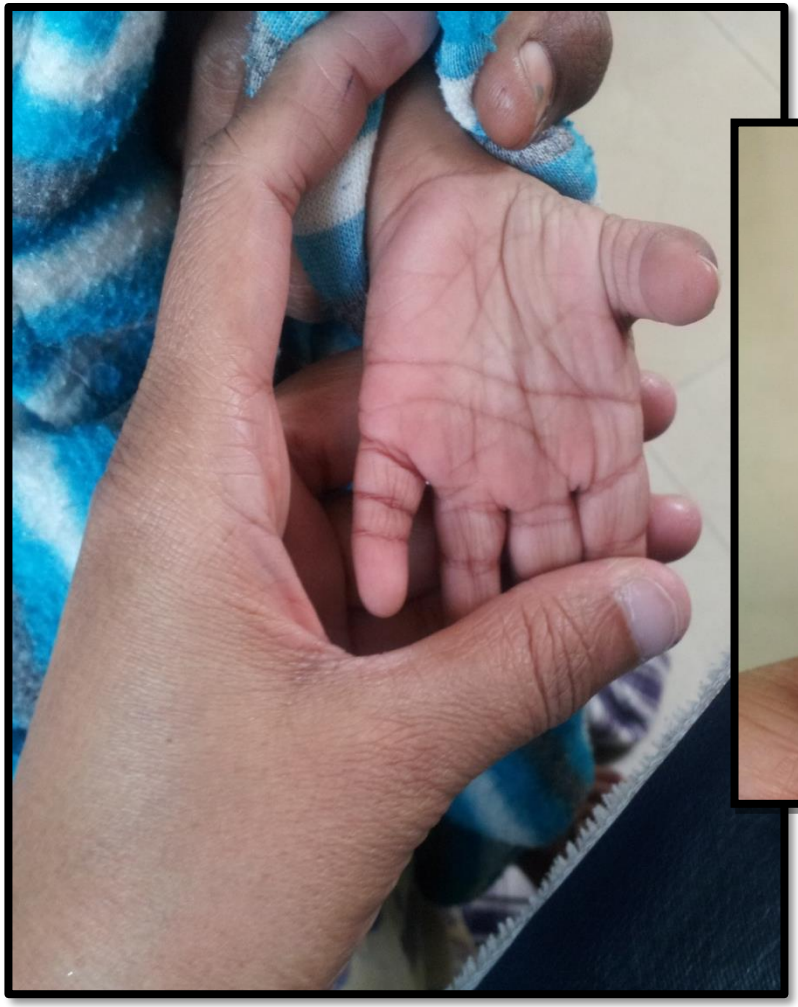
Disease	Frequency of CHD
Trisomy 13	50%
Trisomy 18	95%
Trisomy 21	40%
Turner	25%
1p36 deletion	35%
3p25 deletion	25%
3q duplication	75%
4p16 deletion	30-50%
William syndrome(7p13 deletion)	75%
Smith Magenis syndrome(17p11.2 deletion)	10%
22 q deletion	75-85%

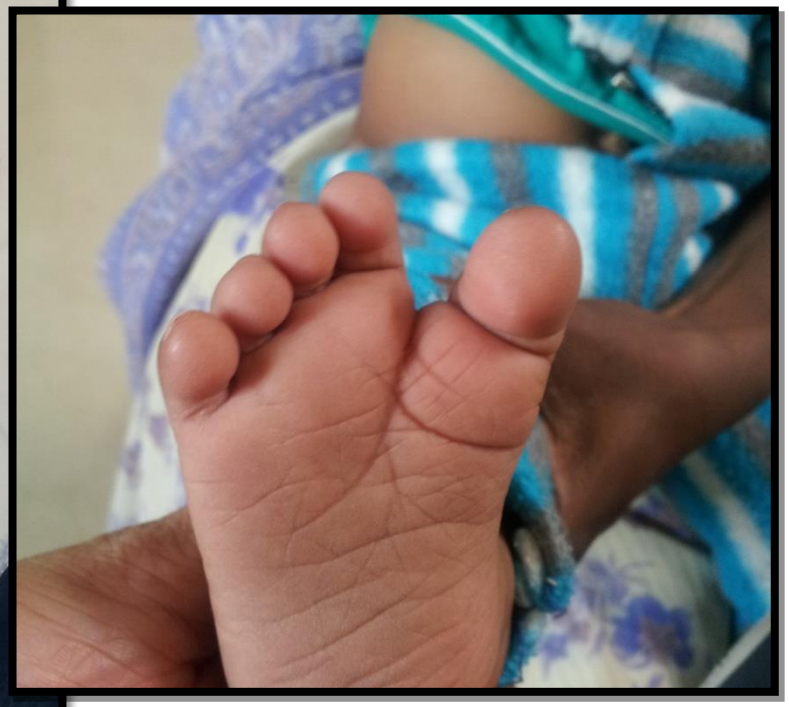
Moss and Adams, 7th edition

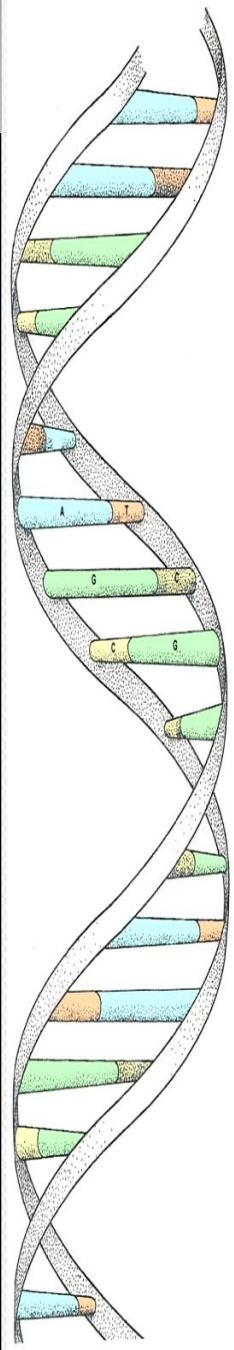
Down syndrome

- 44% have CHD(Freeman et al)
- AVSD: most common
- Flat facial profile
- Thyroid abnormalities
- Developmental delay
- 95%: Non disjunction
- 4%: Translocation
- 1%: Mosaicism





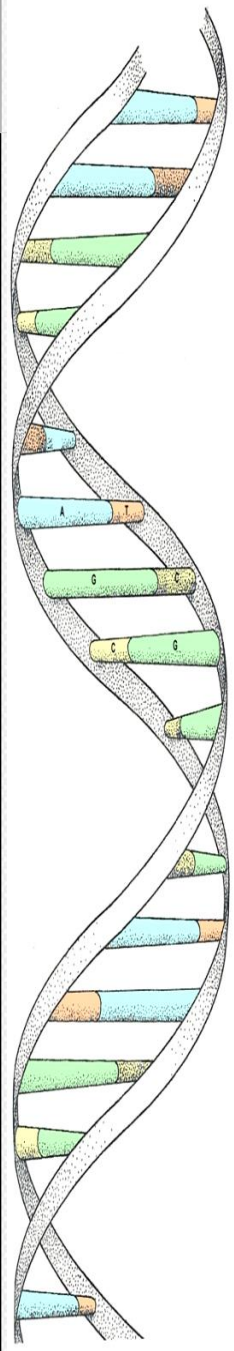




CHD in Down syndrome

- AVCD: 45%
- Isolated VSD: 35%
- ASD: 8%
- PDA 7%
- TOF: 5%
- In older patients: MVP, MR, AR
- Pulmonary hypertension is common

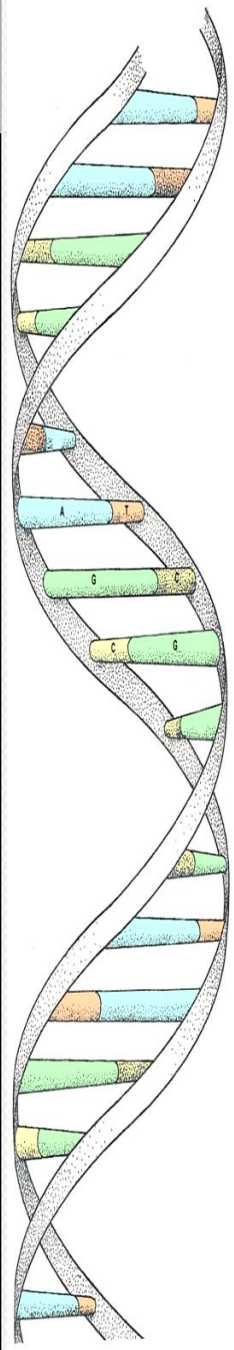
Trisomy 13



Trisomy 13

- Maternal history of severe preeclampsia
- Post axial polydactyly of hands and feet
- Microcephaly
- Anophthalmia/microophthalmia
- Scalp defects:50%
- Renal abnormality
- Heart defect: 50% ; VSD, PDA
- Holoprosencephaly: 66%

Trisomy 18

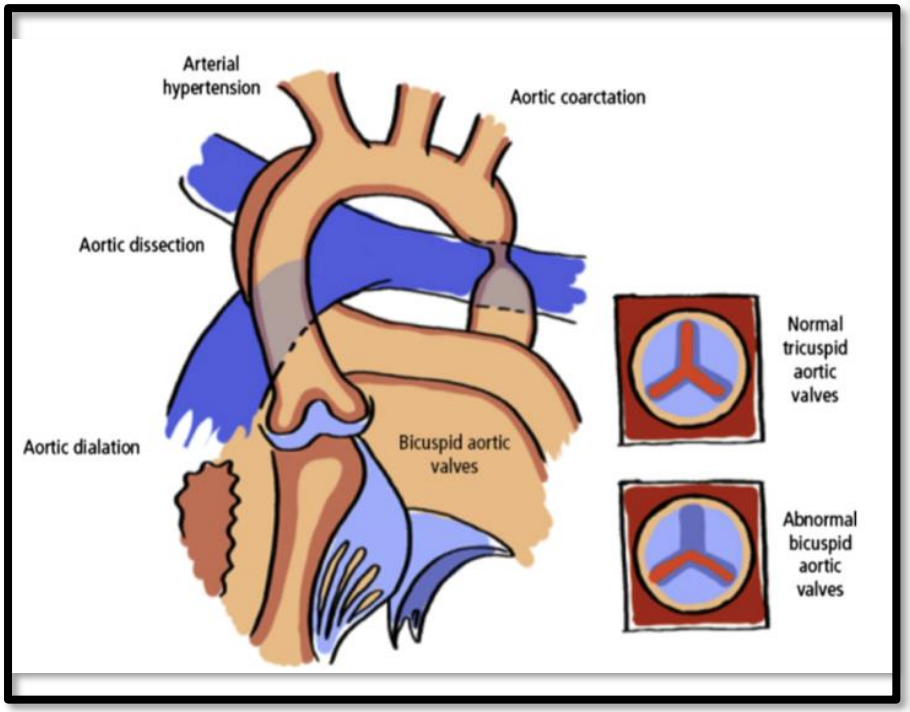


Trisomy 18

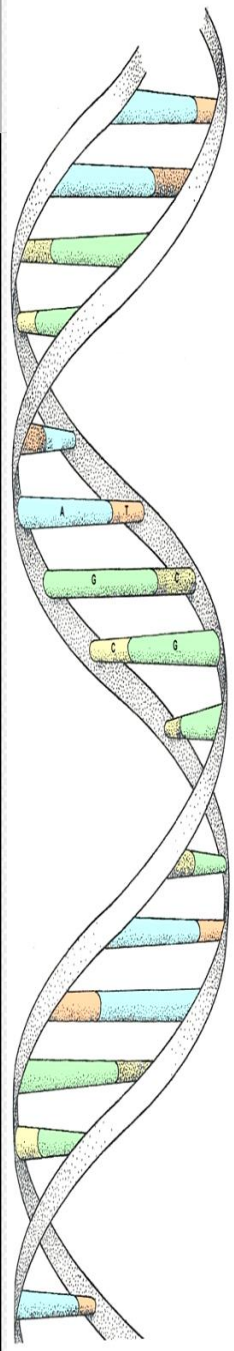
- Polyhydramnios
- Hypertonia
- Large septal defects, PDA, TOF
- Median survival is 1-2 weeks
- 90% die by 6 months of age

Turner syndrome

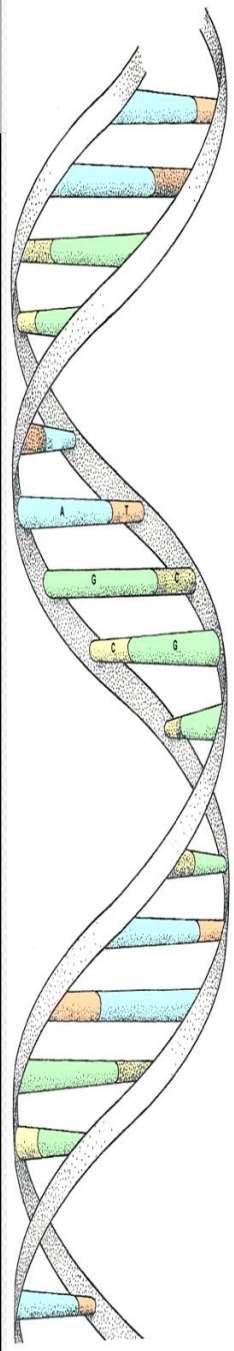
- Most common: Bicuspid aortic valve, followed by coarctation of aorta
- Others: PAPVR, ASD, VSD
- 10% have clinically detected heart disease
- 10% have ECHO abnormalities



Emery and Rimoin's, 5th edition

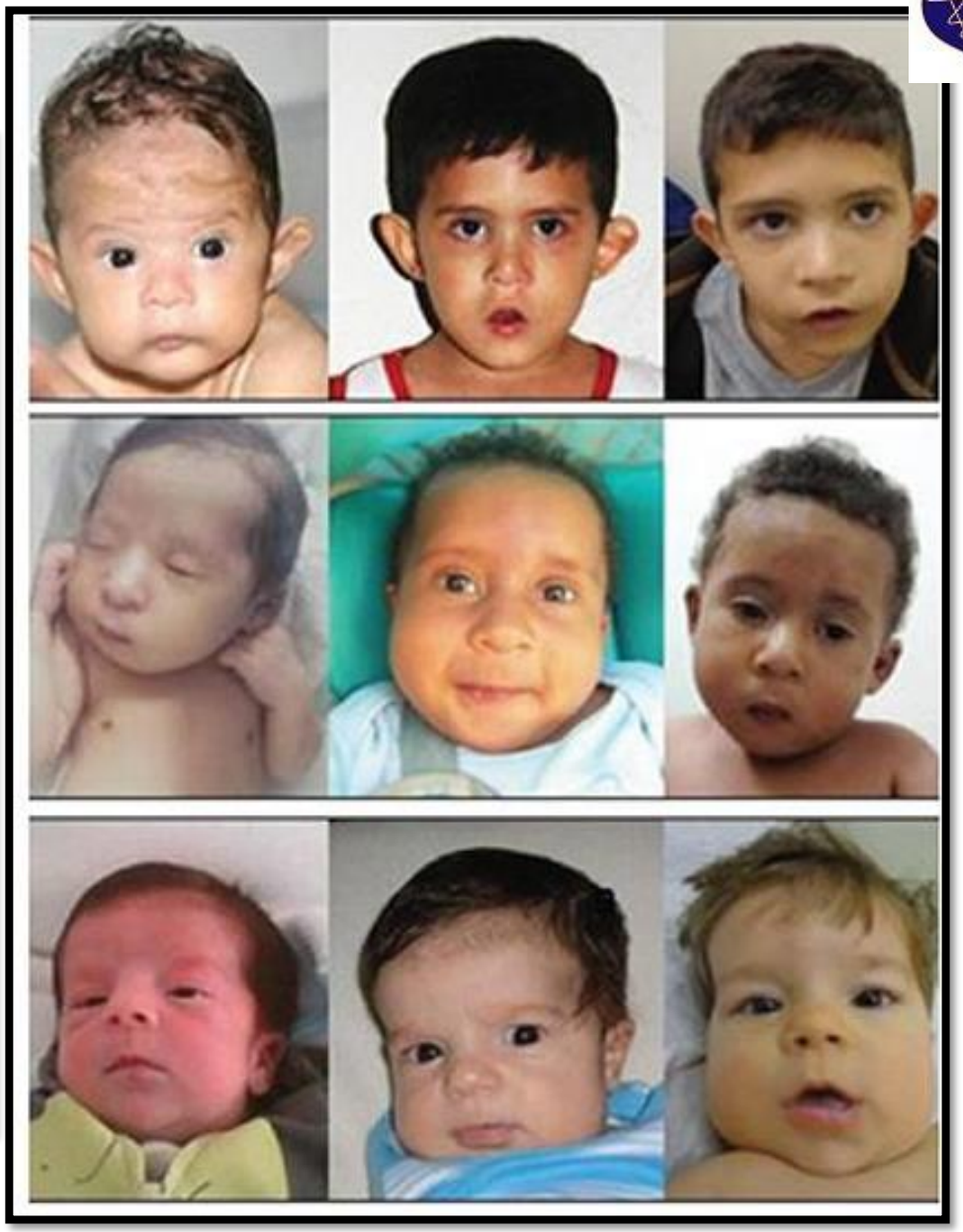


- More than 30% are hypertensive
- Aortic dissection at around 35 years of age
- Increased risk of CV event
- Need regular follow up from Cardiologist

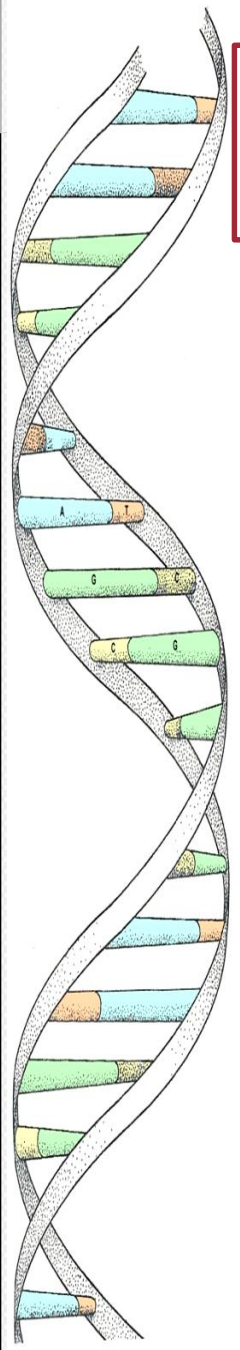


22 q deletion syndrome

- Most common microdeletion syndrome
- Learning impairment
- Palate abnormalities
- Thymic hypoplasia
- Hypocalcemia



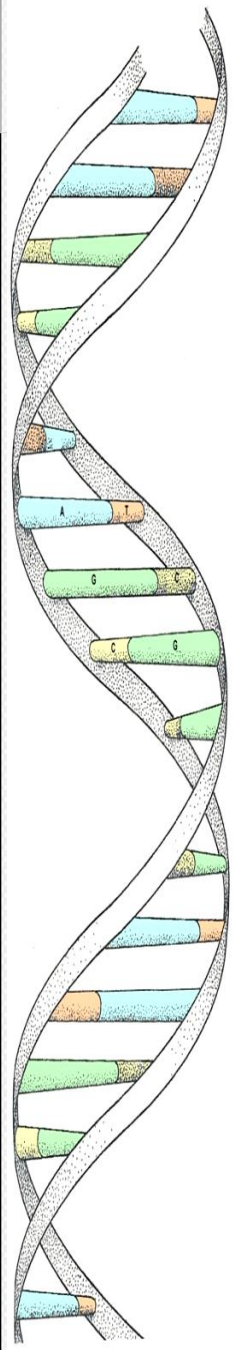
Arq. Bras. Cardiol. [online]. 2014



Cardiac abnormalities

Cardiac Finding	% of Affected Individuals
Tetralogy of Fallot (TOF)	20%
Interrupted aortic arch (IAA)	13%
Ventricular septal defect (VSD)	14%
Truncus arteriosus (TA)	6%
Vascular ring	5.5%
Atrial septal defect	3.5%
VSD; ASD	4%
Other [1]	10%
Normal	24%

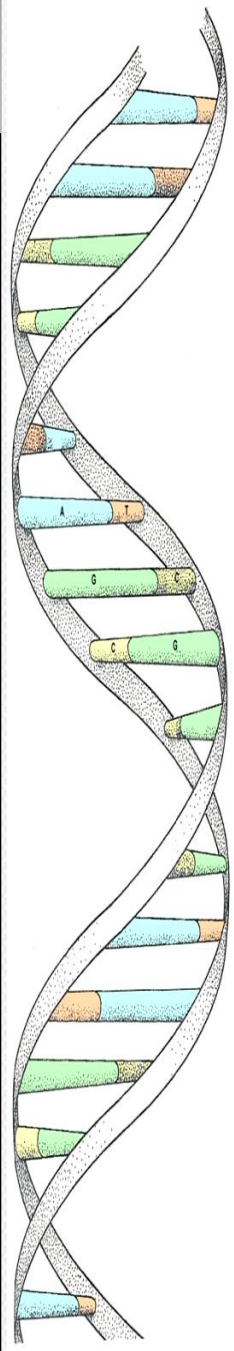
McDonald-McGinn et al [2010b]



William syndrome

- Heterozygous deletion at 7q11.3
- Mild intellectual disability in 75%
- Overfriendliness
- Idiopathic hypercalcemia: 15-50%
- Elastin arteriopathy: 75-80%
- MC is supravalvular AS
- PPS, MR, hypertension

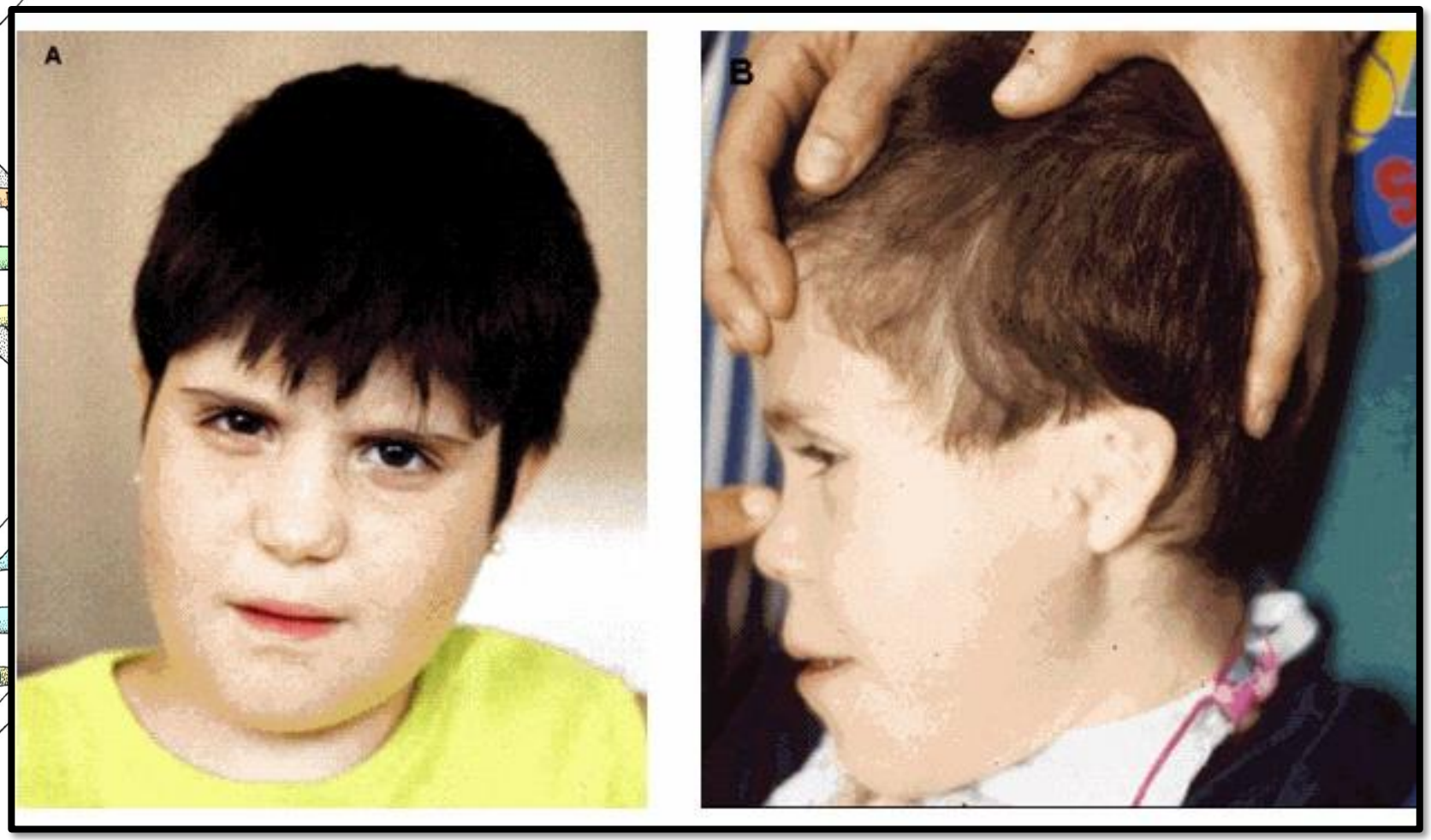
Indian Pediatr 2014;51: 411-412



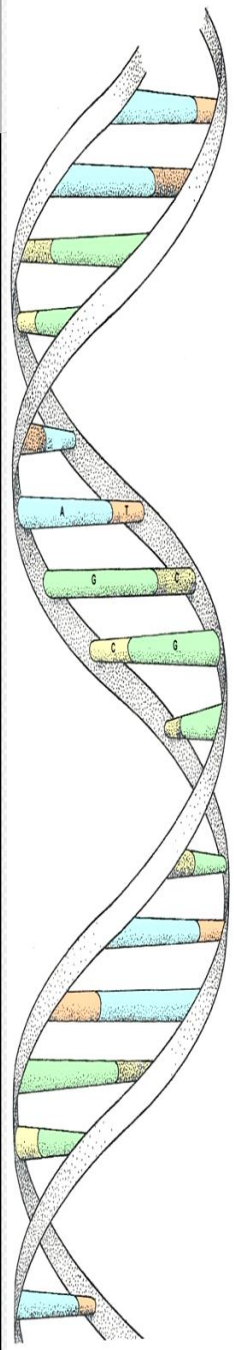
1p36 deletion syndrome

- Developmental delay
- Hypotonia
- Eye/ hearing abnormalities
- Skeletal, renal abnormalities
- Typical facial features

1p36 deletion syndrome



Gene reviews,2013



1p36 deletion syndrome

- Cardiovascular abnormalities in 43-71%
- ASD, VSD, Valvular abnormalities
- PDA, TOF
- Cardiomyopathy in 23%

Less common deletion/duplication syndromes

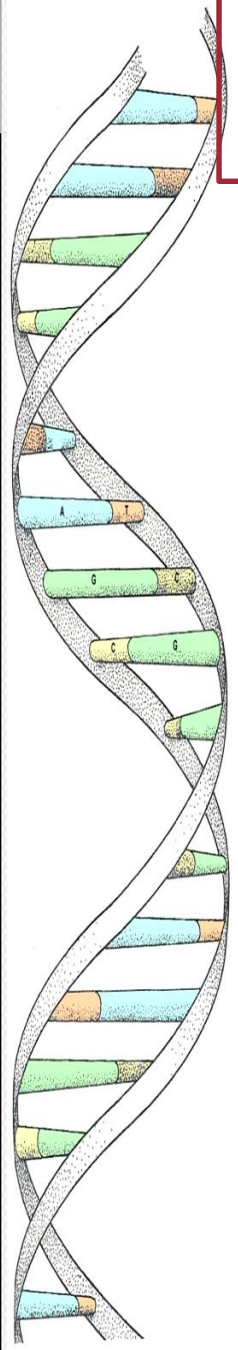
Disorder	Cardiac disease	Distinctive features
3p25 deletion	ASD, Assorted CHD	Ptosis, abnormal ears, postaxial polydactyly
3q duplication	Assorted CHD	Craniosynostosis, cleft palate, clinodactyly
4p16 deletion Wolfe Hisrchhorn	OS ASD, PS, VSD	Greek helmet facies Cleft lip/palate
Deletion 5p15 (Cri du chat syndrome)	Assorted CHD	Cleft lip/palate Abnormal cat cry
17p11.2 deletion Smith Magenis syndrome	Assorted CHD's	Self injurious behaviour Abnormal eyes, ears
Tetrasomy 22p Cat eye sydrome	TAPVC, PAPVC, Assorted CHD's	Coloboma, anorectal anomalies, GU abnormalities

Single gene disorders associated with CHDs

Syndrome	Cardiac Anomalies	Other Clinical Features	Causative Gene(s)
Noonan Syndrome	PS with dysplastic pulmonary valve, AVSD, HCM, CoA	Short stature, webbed neck, shield chest, developmental delay, cryptorchidism, abnormal facies	PTPN11, KRAS, RAF1, SOS1
Costello Syndrome	PS, HCM, cardiac conduction abnormalities	Short stature, developmental delay, coarse facies, nasolabial papillomata, increased risk of solid organ carcinoma	HRAS
LEOPARD Syndrome	PS and cardiac conduction abnormalities	Lentigines, hypertelorism, abnormal genitalia, growth retardation, sensorineural deafness	PTPN11, RAF1
Alagille Syndrome	PS, TOF, ASD, peripheral pulmonary stenosis	Bile duct paucity, cholestasis, typical facies, butterfly vertebrae, ocular anomalies, growth delay, hearing loss, horseshoe kidney	JAG1, NOTCH2
Marfan Syndrome	Aortic root dilatation and dissection, mitral valve prolapse	Tall stature, arachnodactyly, pectus abnormality, scoliosis, ectopia lentis, spontaneous pneumothorax, striae, dural ectasia	FBLN, TGFBR1, TGFBR2
Holt-Oram Syndrome	ASD, VSD, AVSD, progressive AV conduction system disease	Preaxial radial ray malformations (thumb abnormalities, radial dysplasia)	TBX5
Heterotaxy Syndrome	DILV, DORV, d-TGA, AVSD	intestinal malrotation	ZIC3, CFC1
Char Syndrome	PDA	Dysmorphic facies and digit anomalies	TFAP2b
CHARGE Syndrome	ASD, VSD, valve defects	Coloboma, choanal atresia, developmental delay, genital and/or urinary anomalies	CHD7, SEMA3E

(Curr Cardiol Rev. 2010; 6(2): 91–97)

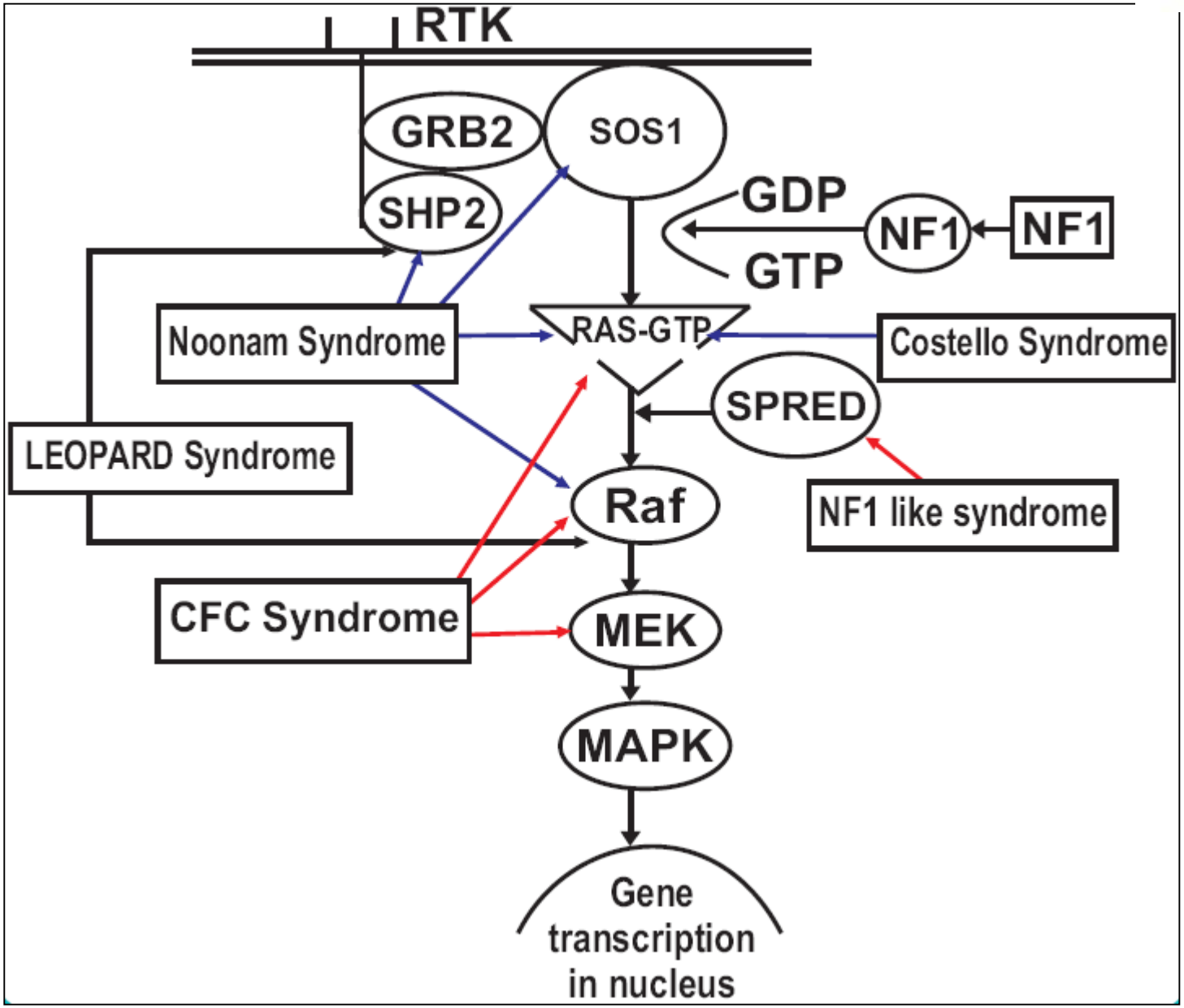
Neuro-Cardio-Facial-Cutaneous syndromes

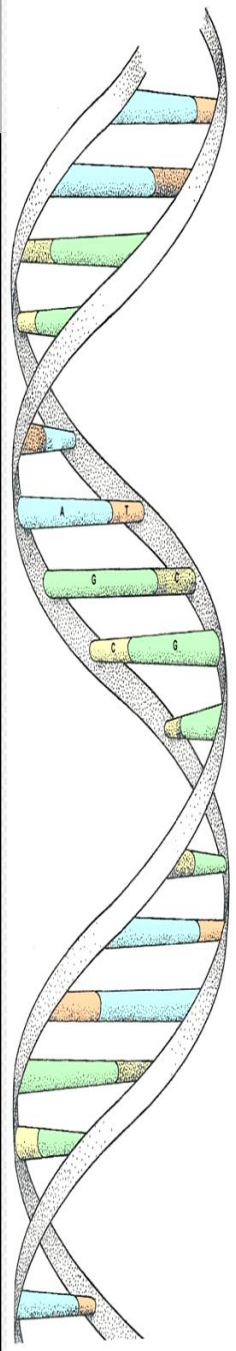


RAS-MAP Kinase Pathway Disorders:

- Noonan syndrome
- Costello syndrome
- Cardio-Facio-Cutaneous syndrome
- LEOPARD syndrome
- Legius syndrome
- Neurofibromatosis I

RAS-MAP Kinase Pathway





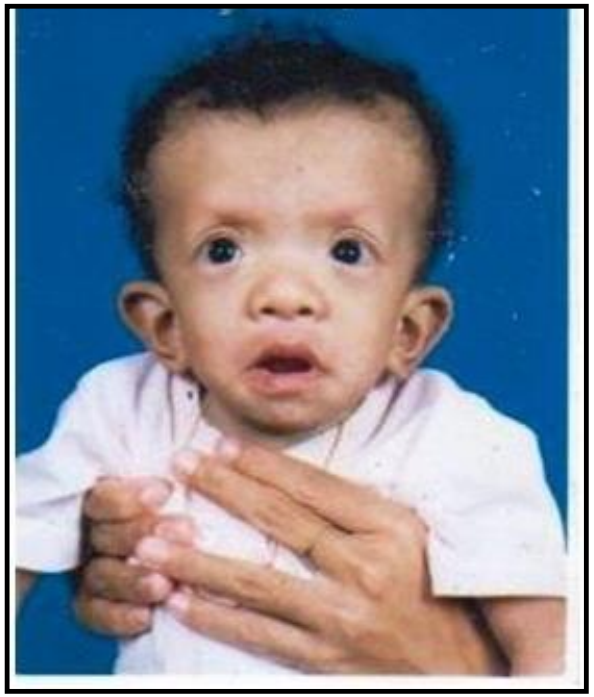
Features common to most Neuro-cardio-facial-cutaneous(NCFC) syndromes are:

- variable degree of mental retardation or learning disabilities
- cardiac defects (particularly pulmonary valve stenosis and hypertrophic cardiomyopathy)
- facial dysmorphism with downslanting eyes
- short stature
- relative macrocephaly
- skin abnormalitie &
- an increased risk for malignancy

Reason for overlap: Genes involved act through a common pathway – the RAS MAPK pathway

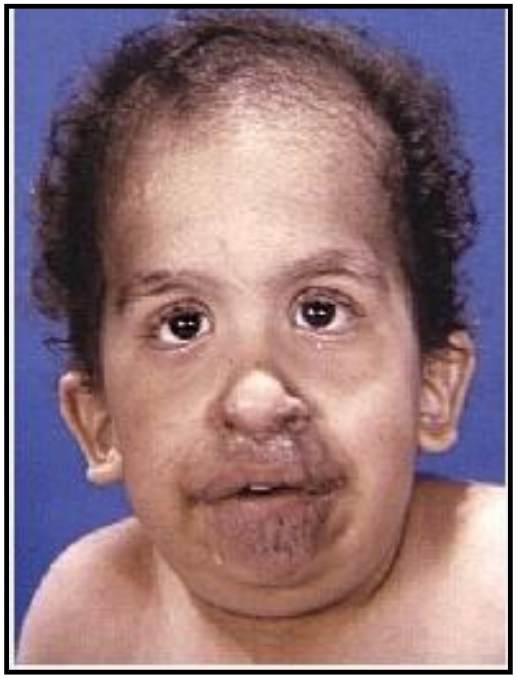
Neuro-Cardio-Facial-Cutaneous Syndromes

Noonan syndrome



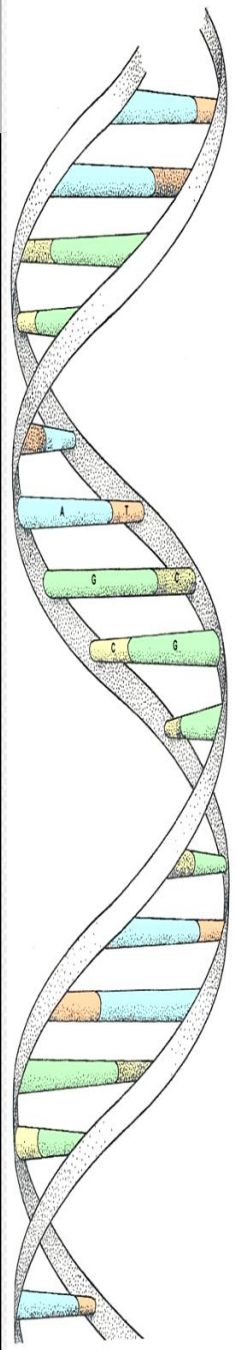
Cardio-Facio-Cutaneous syndrome

(From: Internet Journal of Pediatrics and Neonatology. 2006 Vol 6, No. 2)



Costello syndrome

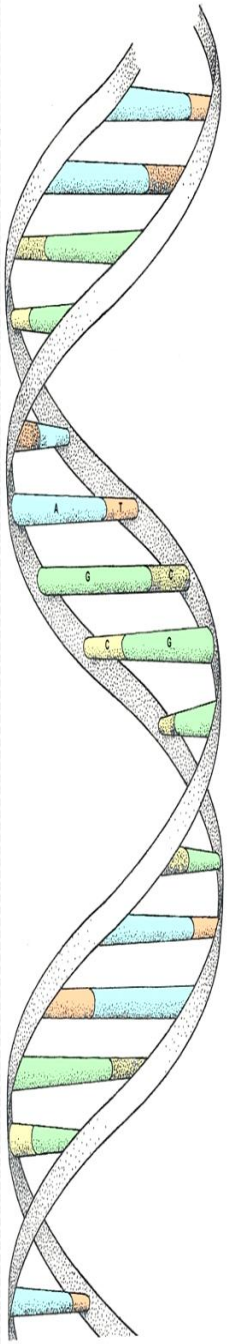
(*From: London Medical Database*)

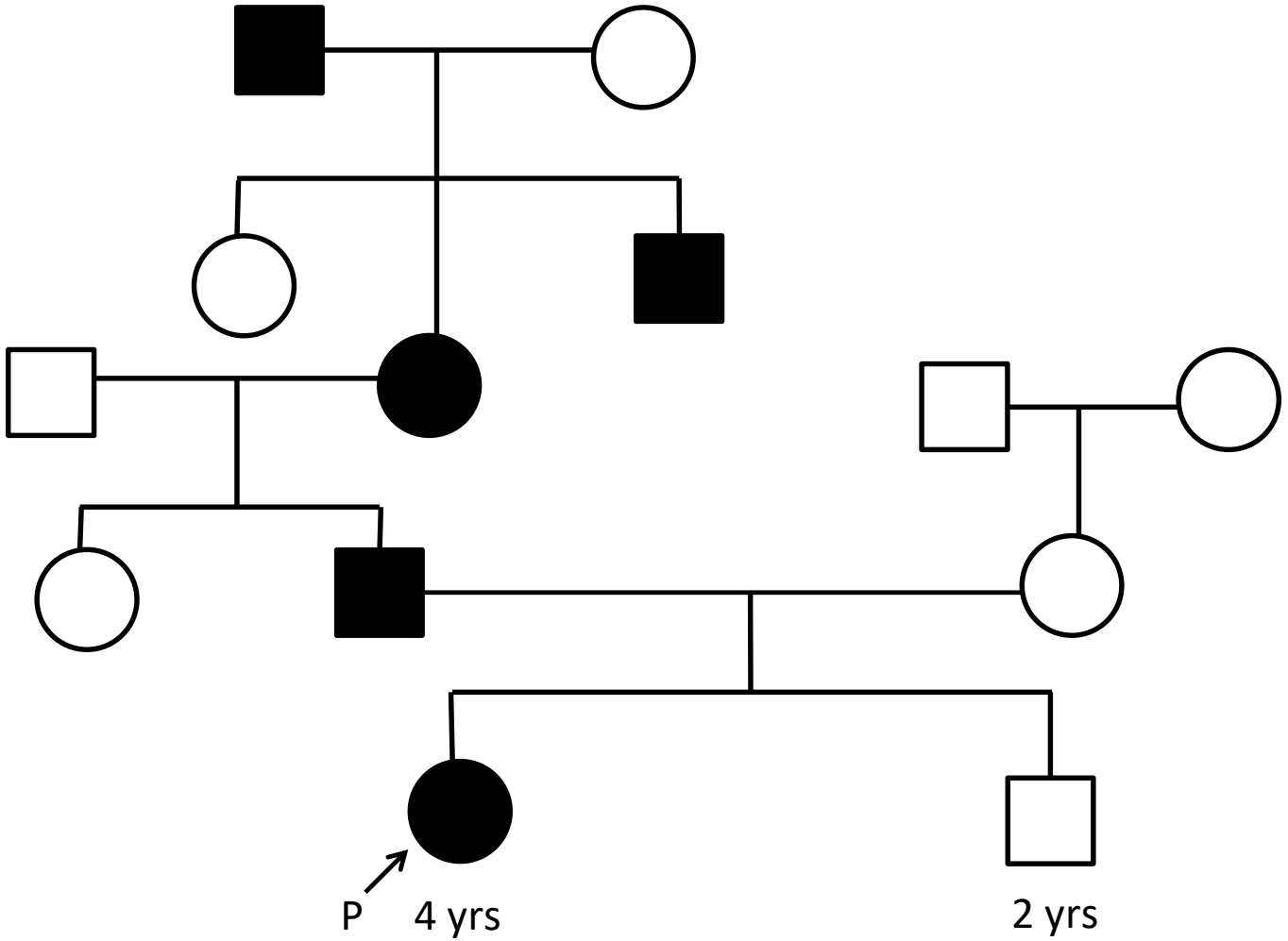


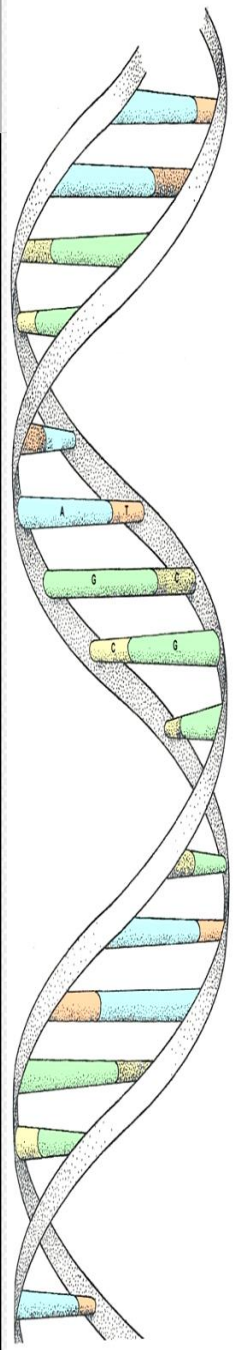
Genetic counseling

- After genetic testing and confirmation of genetic etiology, genetic counseling is provided regarding:
  - Diagnosis, natural history, prognosis and management
  - Recurrence risk for subsequent offspring
  - Prenatal testing options for future pregnancies
- Denovo chromosomal abnormalities/ microdeletions have risk of recurrence of <1%
- Familial chromosomal rearrangements – 5 – 30% risk of recurrence
- In single gene disorders, risk of recurrence will vary according to mode of inheritance: AD/ AR/ XL

Autosomal dominant disorders







Autosomal dominant disorders

- Only 1 copy of abnormal gene required to produce phenotype
- Passed from one generation to the next
- Both males and females equally affected
- May be transmitted to offspring of either sex
- Risk of recurrence in offspring is 50%

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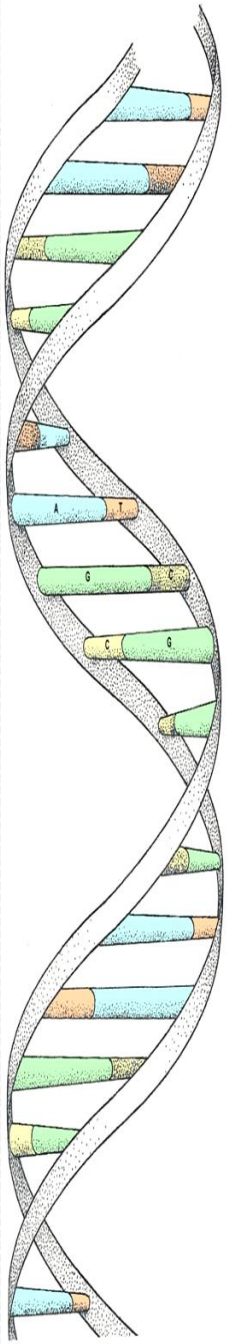
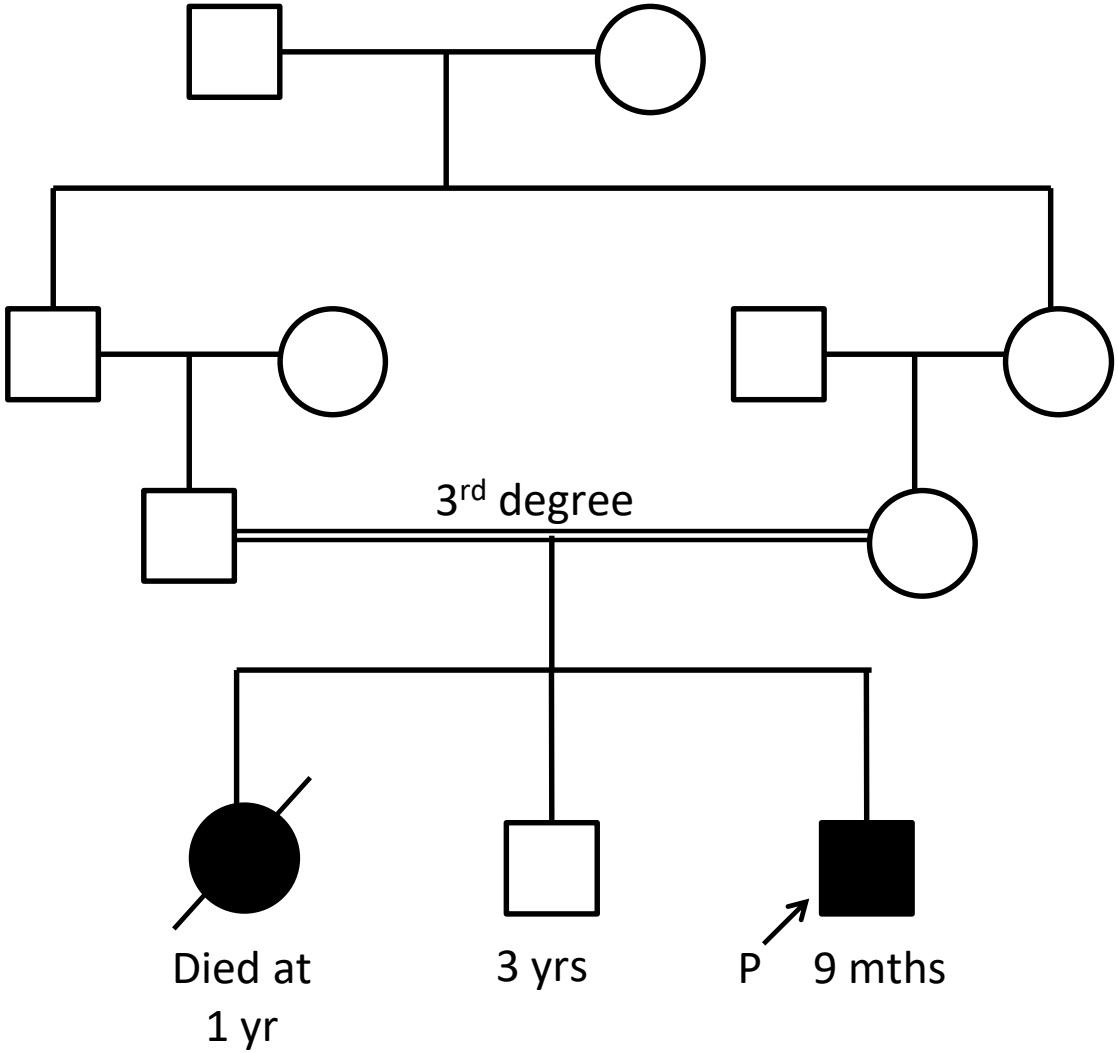
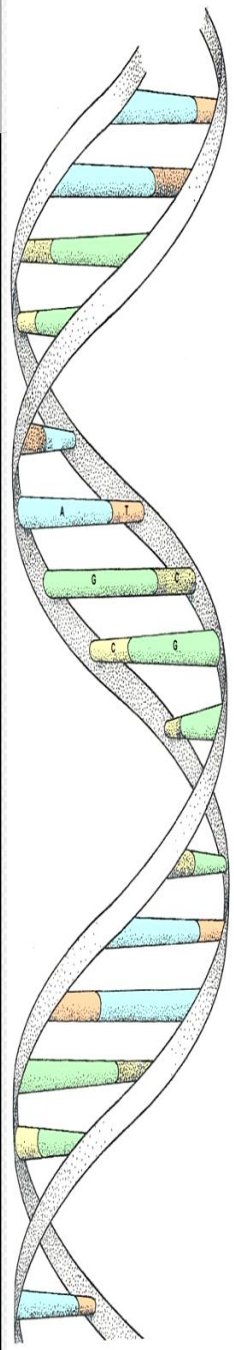
d	D**d**	D**d**

Autosomal recessive disorders







Autosomal recessive disorders

- Both copies of a gene should be mutated to produce disease phenotype
- Parents of an affected individual, though usually asymptomatic, are obligate carriers
- Horizontal pedigree pattern with 1 or more siblings affected
- Both males and females are equally affected
- Risk of recurrence in siblings is 25%

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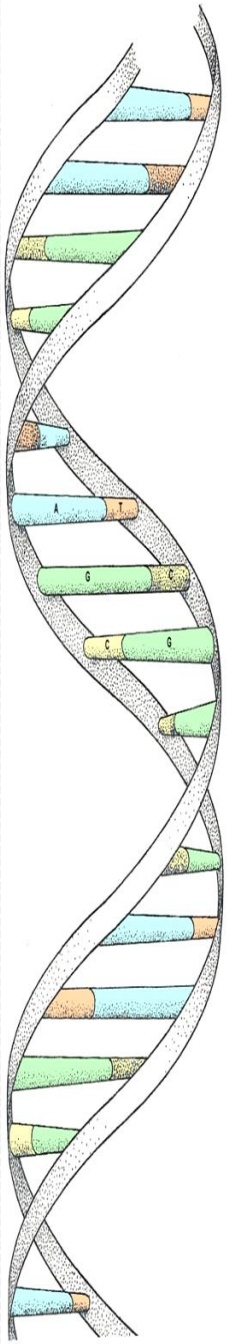
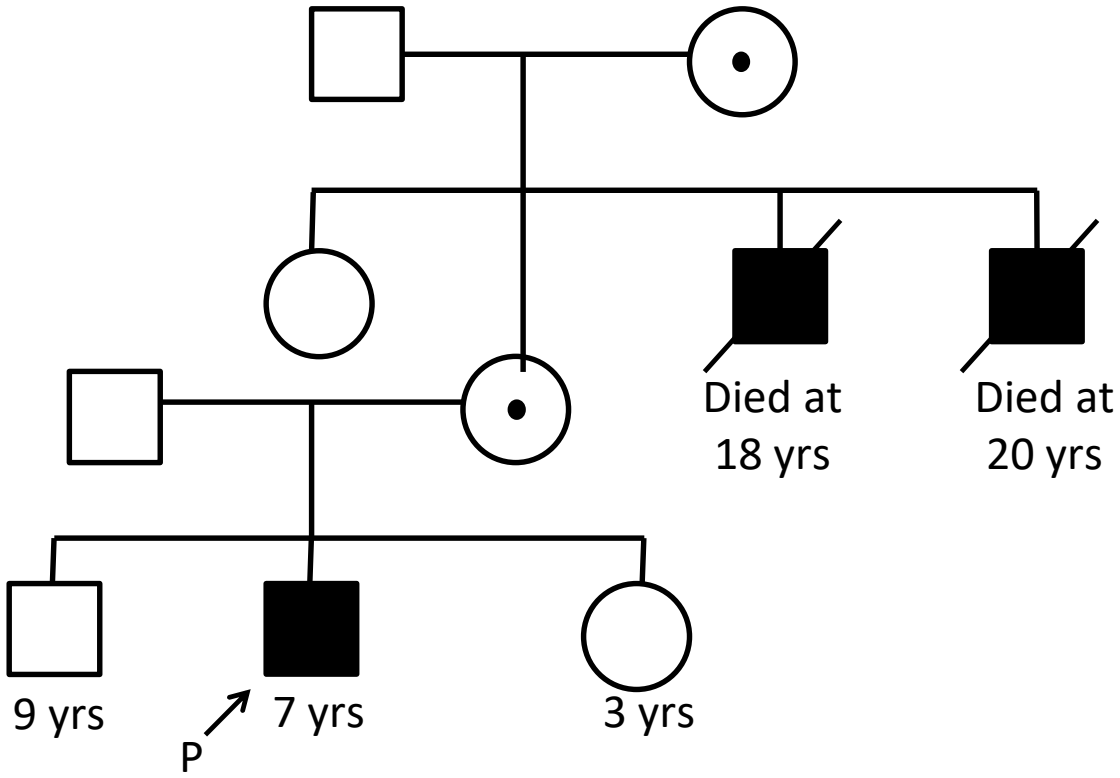
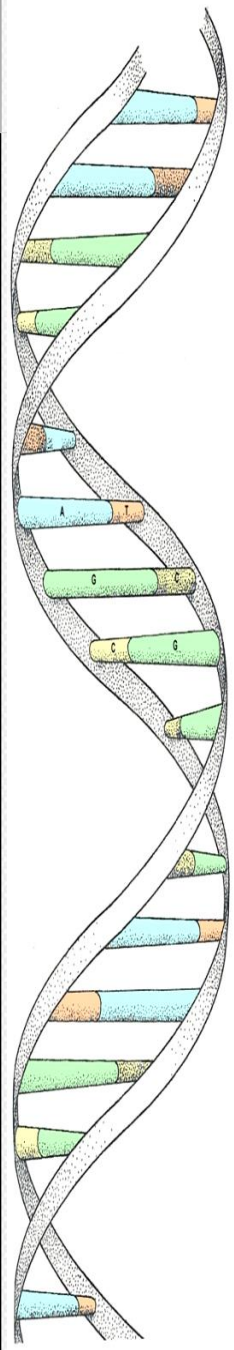
d	D**d**	**dd**

X-linked recessive disorders



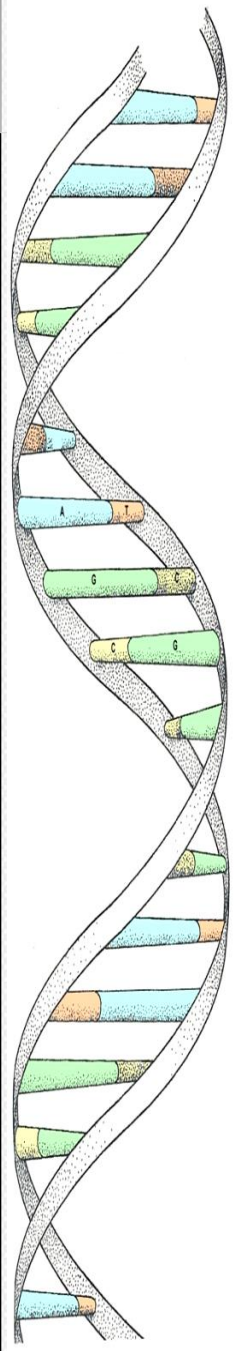




X-linked recessive disorders

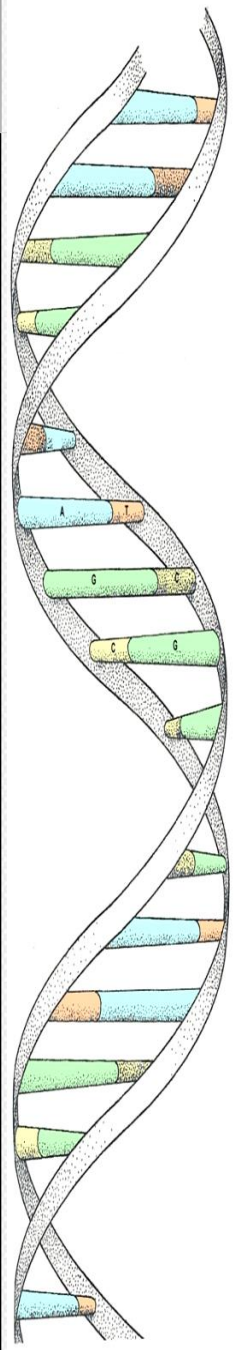
- Mostly males affected; females usually normal carriers or only mildly affected
- For a carrier mother, risk of male offspring being affected is 50% and chance of female offspring being carrier is 50%.

	X_A	X_a
X_A	X_AX_A	X_AX_a
Y	X_AY	X_aY



Summing up....

- *Congenital heart disease can be a component of many genetic syndromes*
- *Detailed family history and thorough dysmorphology evaluation essential in every case with CHD*
- *Genetic test to be done depends on clinical diagnosis – no single test for all types of genetic disorders*
- *Karyotyping informative only for chromosomal disorders*
- *Accurate genetic diagnosis essential for appropriate management, genetic counseling and prenatal diagnosis*



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