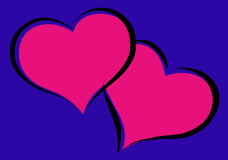
National Birth Defects Prevention Network (NBPDN)/NBDPS Annual Meeting
Feb. 26-29. 2012 Arlington, VA

Chromosome Syndromes
associated with
Congenital Heart Defects



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THE HEART AS DYSMORPHIC FEATURE

Fetus or child with multiple congenital anomalies

Face: Eyes, shape, nose, mouth → Facies?

Body parts: Proportion, number and size → Habitus?

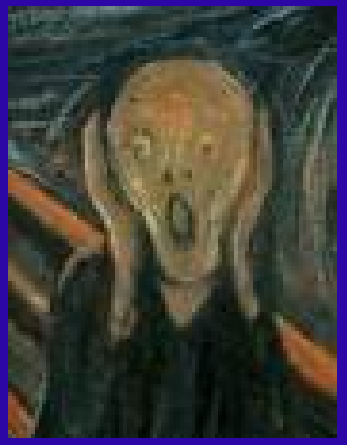
CHD (common or distinctive) → Cardiac phenotype?

Distinctive face, body, heart, other malformations, voice, behavior, growth → Syndrome

CHDs: INDIVIDUALS vs. FAMILIES

ASD VSD PDA HLHS AVC DORV COA TGA TA TA MA PA AA IAA

vs.



"EARLY" Development

1. Laterality defects, situs, heterotaxy
   Looping, complex single ventricle
2. Conotruncal, aortic arch
3. Atrioventricular canal
4. Some VSDs (conoventricular), ASDs (primum type)

"LATER"

5. Right and left heart obstruction, Ebstein
5. Most VSDs, ASDs
6. Anomalous pulmonary venous return

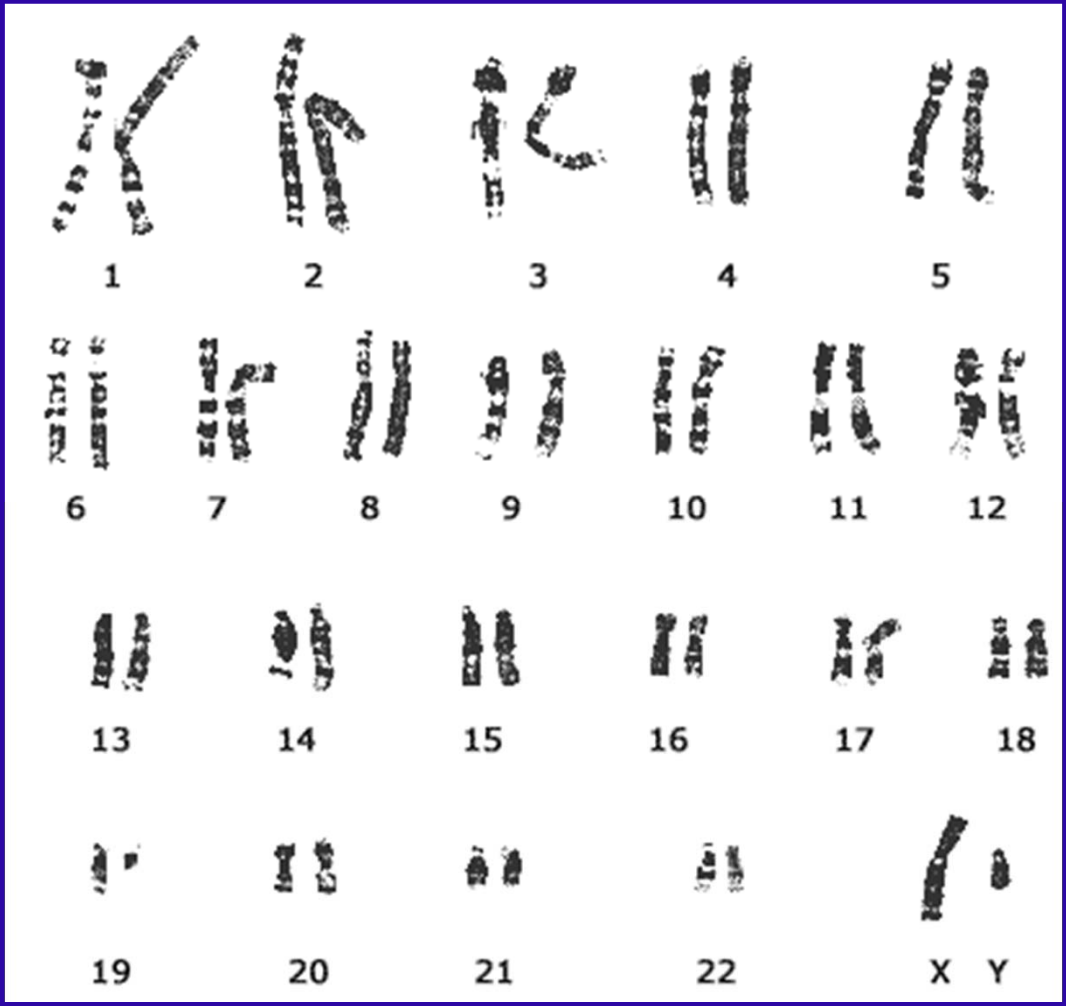
OBJECTIVES FOR TALK

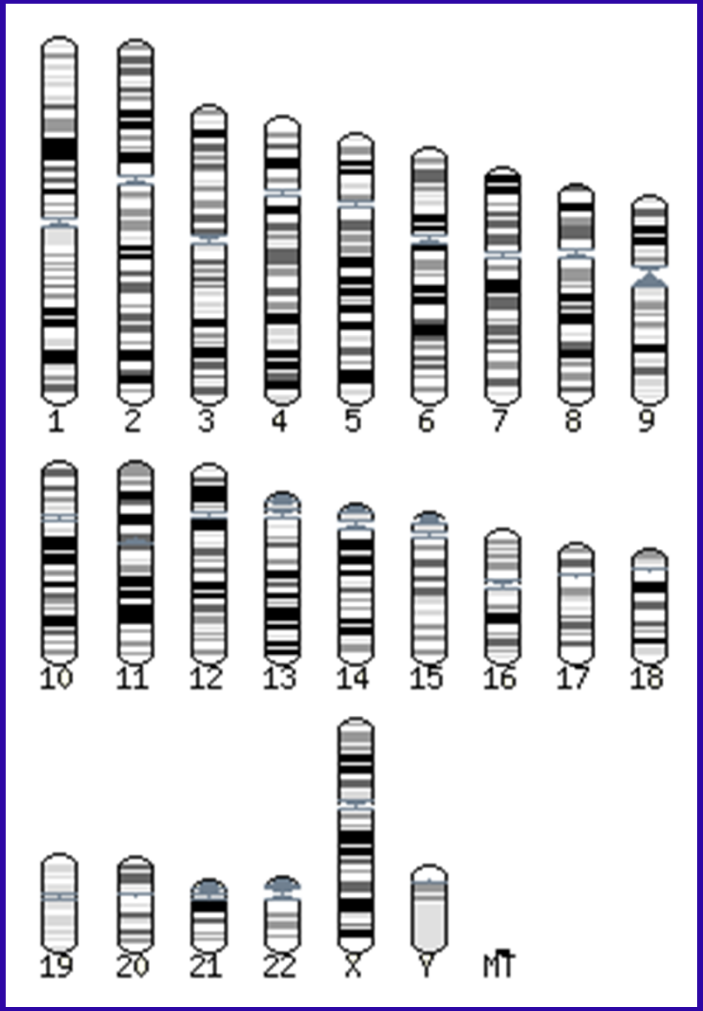
- Trade-off: Scope over detail
  (a little about many, rather than a lot about a few)
- Learn common syndromes, or distinctive ones
- Learn associated CHDs, when possible,
  patterns and CHD "families"
- Focus on phenotype (appearance) rather than
  performance, growth, development, associated
  diseases
- Focus on one or two "take home" message for each

COMMON ABBREVIATIONS

ASD	atrial septal defect
AVC	atrioventricular canal
AVSD	atrioventricular septal defect
BAV	bicuspid aortic valve
CHD	congenital heart defect
COA	coarctation
DORV	double outlet right ventricle
HLHS	hypoplastic left heart syndrome
IAA,B	interrupted aortic arch, type B
LVOTO	left ventricular outflow tract obstruction
PA	pulmonary atresia
PDA	patent ductus arteriosus
PS	pulmonary stenosis
RVOTO	right ventricular outflow tract obstruction
SI	situs inversus
SV	single ventricle
TA	truncus arteriosus
TOF	tetralogy of Fallot
TGA	transposition of great arteries
VSD	ventricular septal defect

CHROMOSOME ANALYSIS





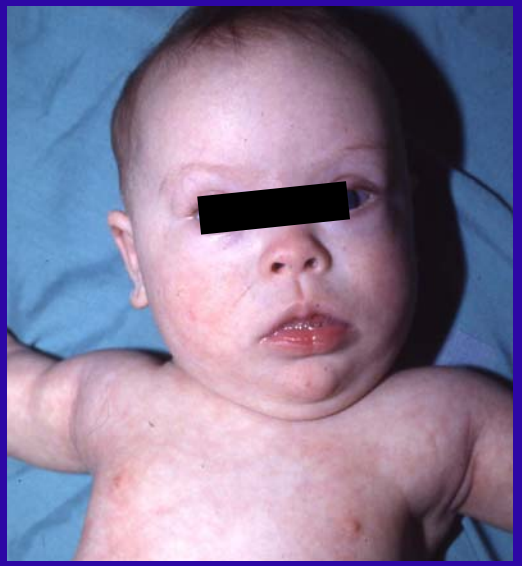
http://www.genetics.com.au/images

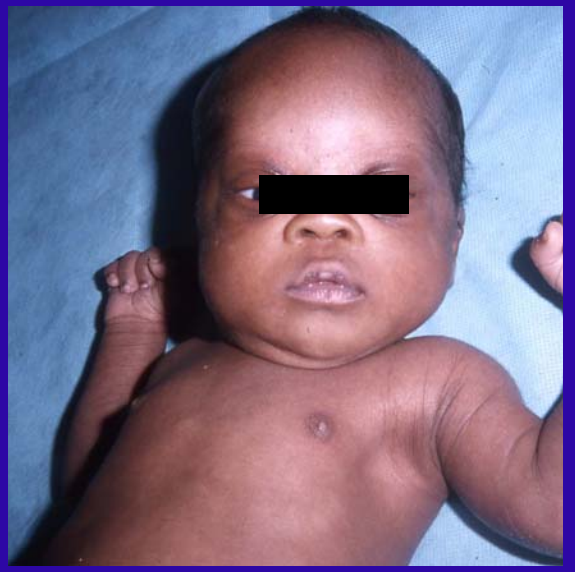
DOWN SYNDROME: Review

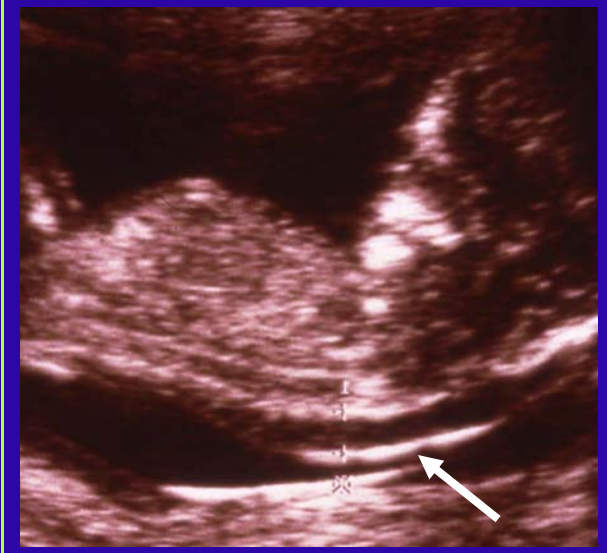
Trisomy 21
Translocation 21
Mosaicism

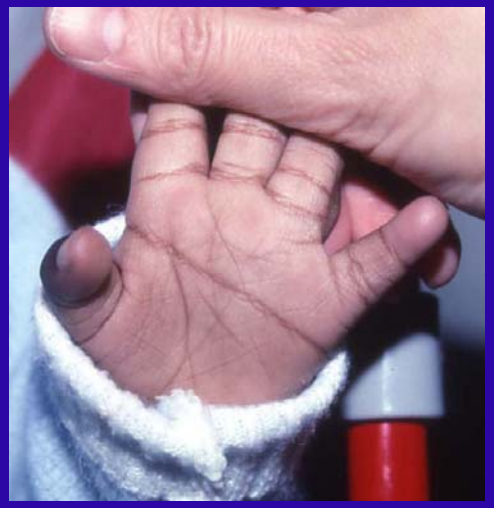
Microbrachycephaly
Sparse hair
Facial:
- Small eyes
- Upslanted eyes
- Small nose
- Small mouth
- Large tongue

Excess nuchal skin/edema
GI anomalies
Hematologic anomalies
Skeletal:
- 5th finger clinodactyly
- Joint laxity
- C1-C2 instability









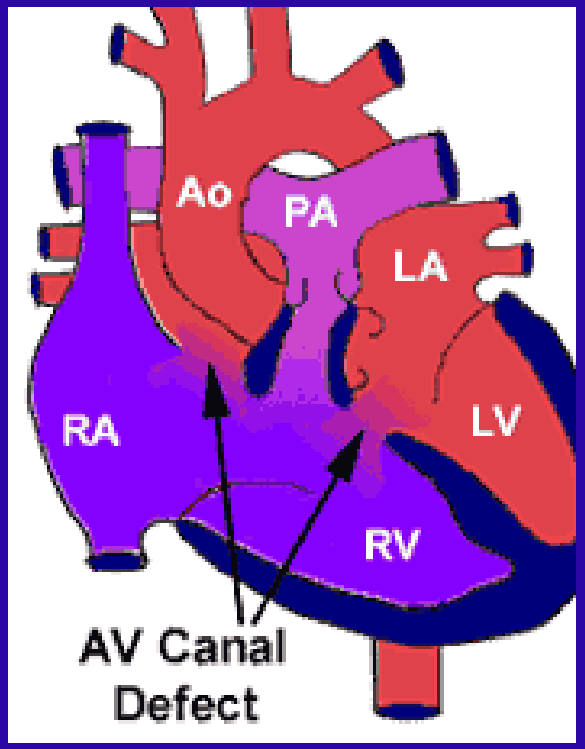
DOWN SYNDROME: Cardiac

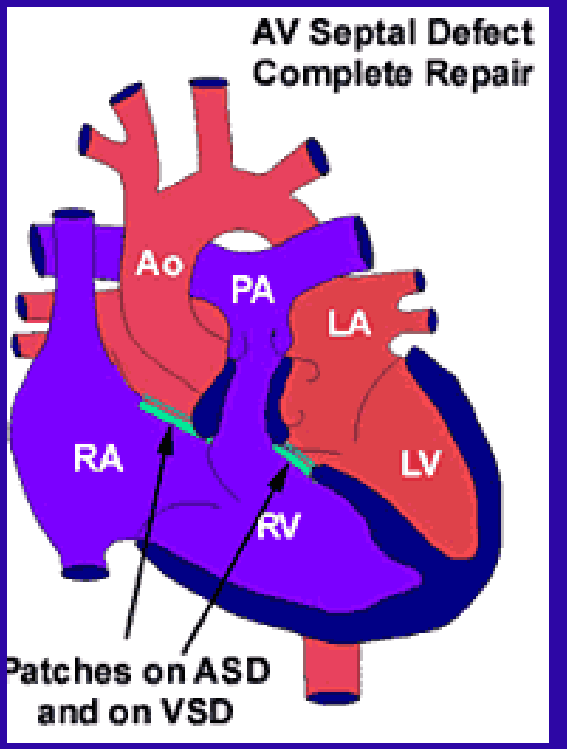
All types: 40%

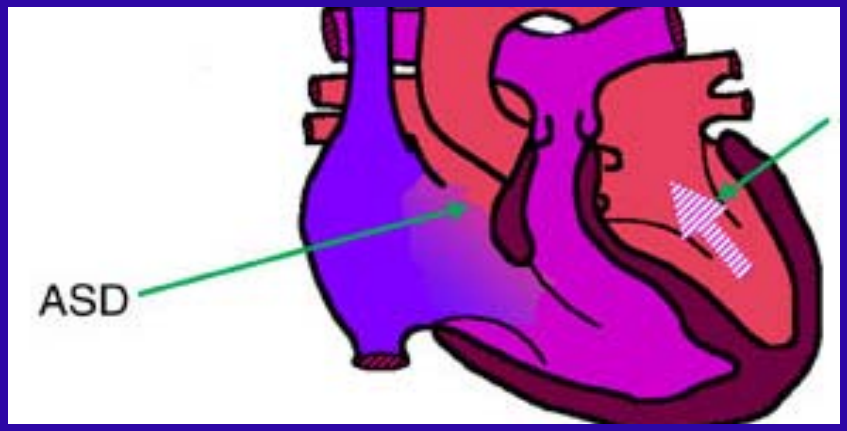
AV Canal "family"
- 40%
- Complete AVC
- Primum-type ASD

VSD, all types
ASD, secundum type
Patent ductus arteriosus
Tetralogy of Fallot

ECG Superior axis, counterclockwise loop







WHAT'S NEW: DOWN SYNDROME

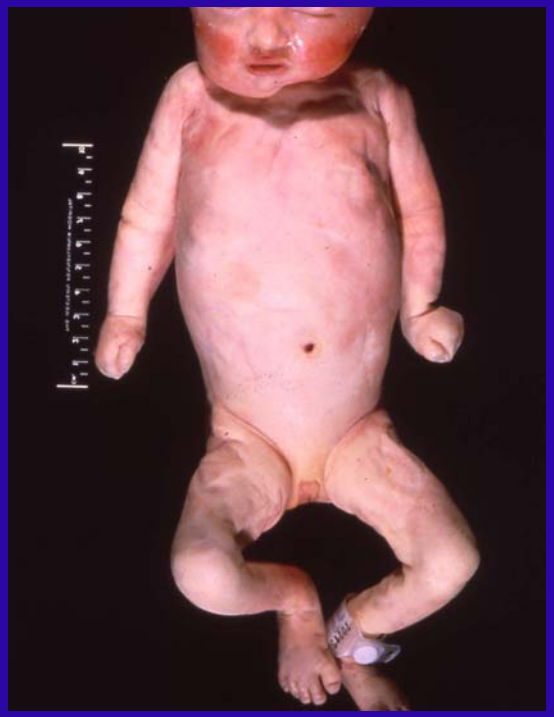
CHD surgery outcomes	BACKGROUND: Many prior studies with conflicting results about DS as a risk factor for poor outcome. **LB prevalence has increased** by 1/3 in 2 decades *(Shin M, CDC et al., Pediatrics, 2009)* Methods: National STS CHD Database 4350 DS patients (~41,000 non-DS). Results: No difference in mortality. More complications Length of stay increased ASD, VSD, TOF (not AV canal) Limitations: Society for Thoracic Surgery is a voluntary DB (includes CHB). *(Fudge JC, et al., Pediatrics, 2011)*

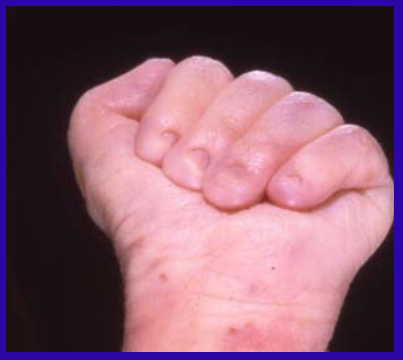
TRISOMY 18: Overall

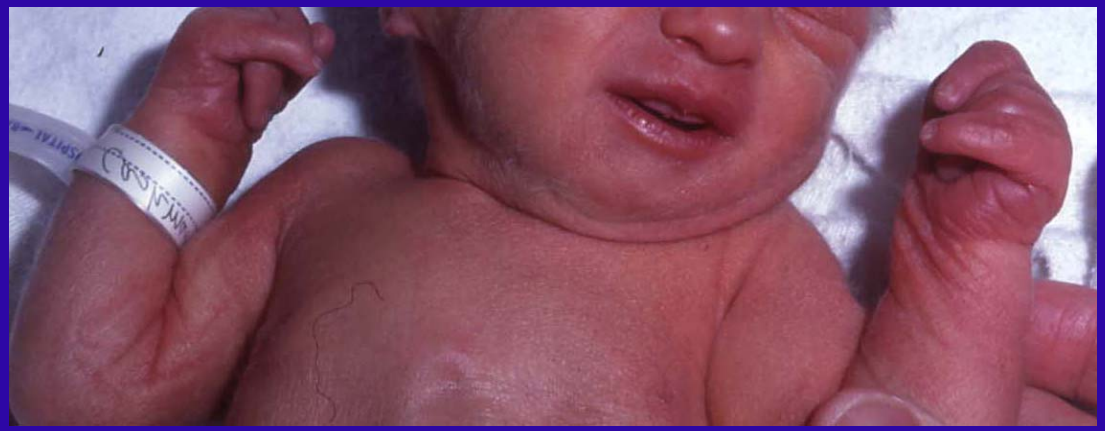
Trisomy 18
Rarely translocation

SGA, IUGR
Craniofacial
- Microcephaly
- Prominent occiput
- Small features
- “Normal”

Overlapping fingers
Short sternum
CNS (posterior fossa)
Renal anomalies
GU anomalies
Rocker bottom feet





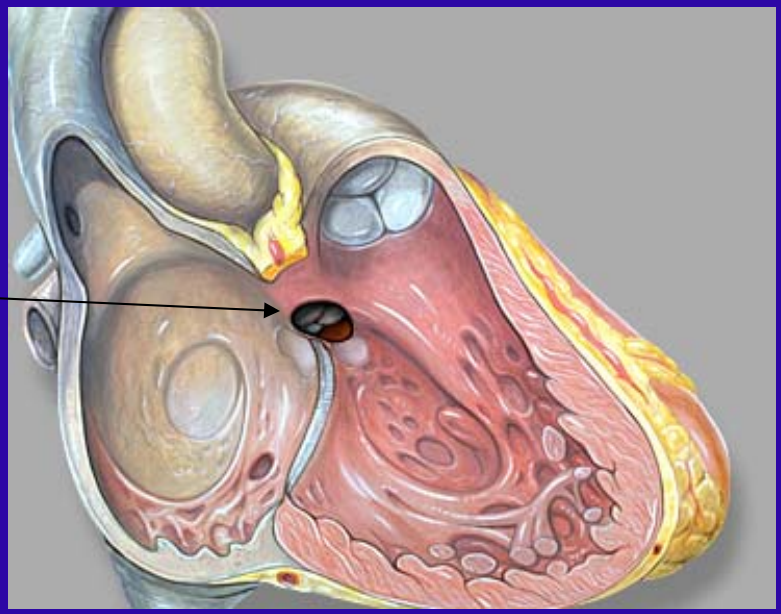


TRISOMY 18: Cardiac

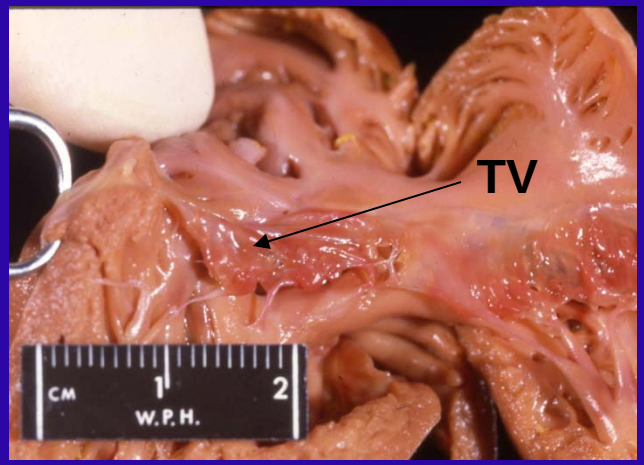
All types: 95%

Conotruncal
- VSD, conoventricular
- TOF
- DORV

Complete AV canal



95% Polyvalvar dysplasia
- Nodular, thick valves
- Bicuspid aortic valve



TRISOMY 13: Overall

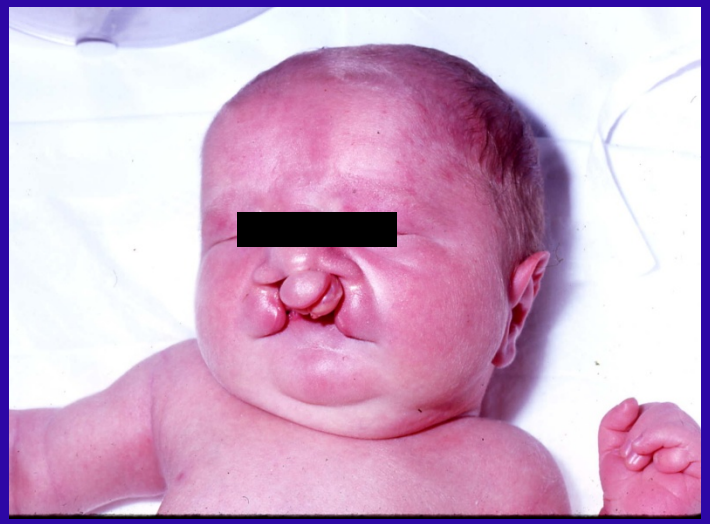
Craniofacial
- Cleft lip/palate
- Microphthalmia/ anophthalmia

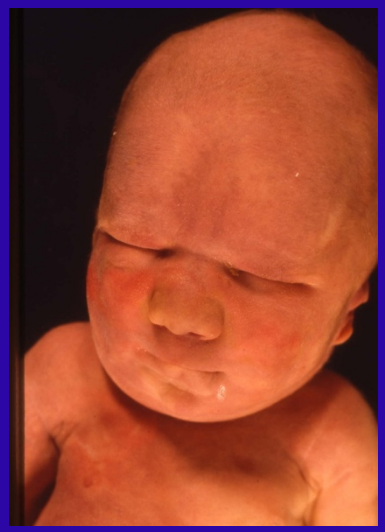
Scalp cutis aplasia

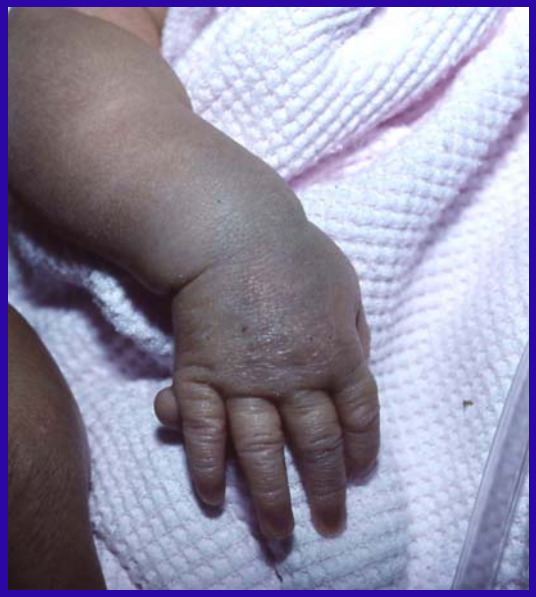
Postaxial polydactyly

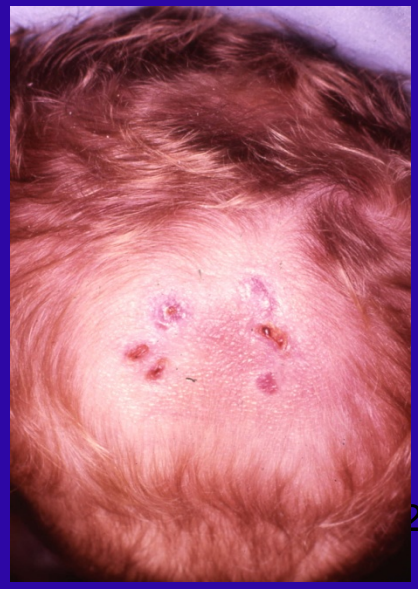
Renal/GU anomalies

CNS anomalies:
- Holoprosencephaly









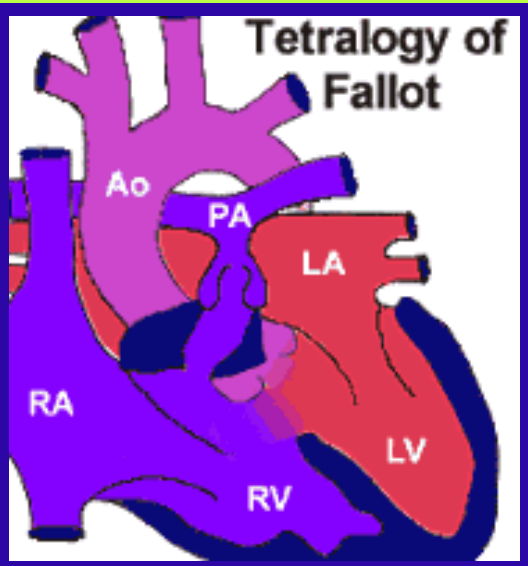
TRISOMY 13: Cardiac

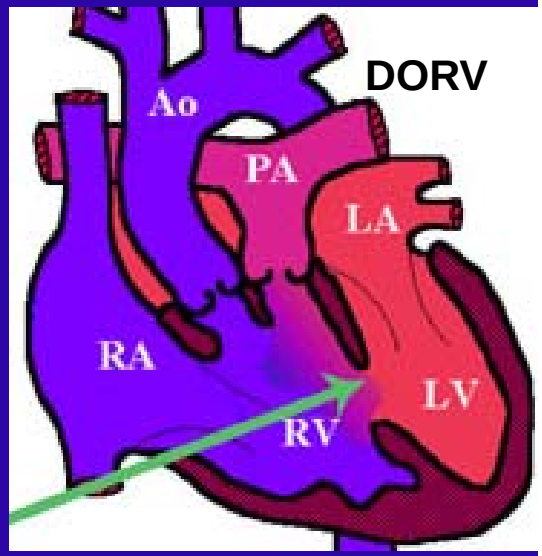
All types: 50-80%

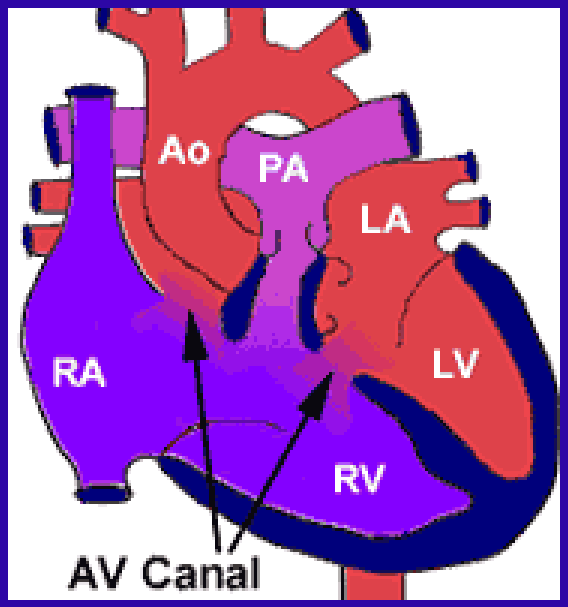
Conotruncal
- DORV
- TOF

Common AV canal
ASD
VSD
PDA

Polyvalvar dysplasia: 60%
- Less common compared to Trisomy 18







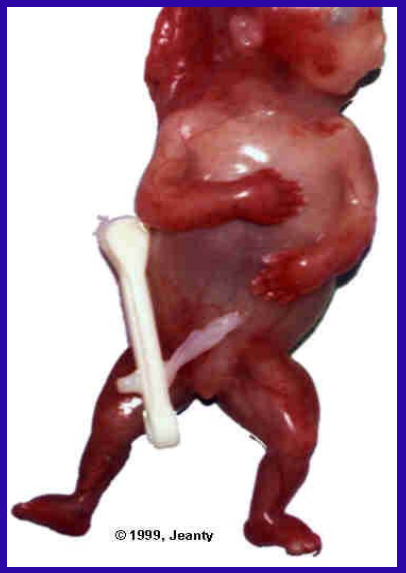
WHAT'S NEW: TRISOMY 13 TRISOMY 18

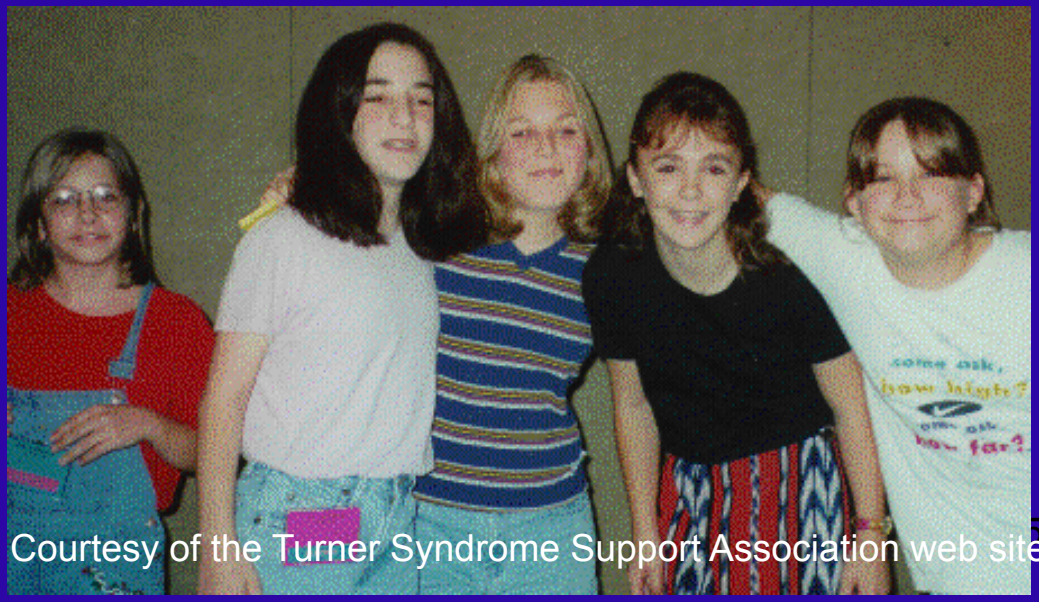
Intensive treatment		Increased survival to 1 year: 25% vs 5%. Only 2/24 survived to age 2 years. *(Kosho T et al., 2006, 2008 AJMG)*
Impact of cardiac surgery	23 pts, 6 (23%) operations, survival increases (smaller #, milder defects). *(Maeda et al., 2011 AJMG)*	34 pts, 9 (34%) operations *(Muneuchi et al., 2010, Cardiol Young)* 134 pts, 32 (25%) operations: Cardiac surgery increases survival Mosaicism contributes 25% alive at age 1 *(Maeda et al., 2011, AJMG)*
Trend in prevalence	Texas, population-based surveillance, 1999-2003. Trisomy 18: Prevalence ~1/10,000 LBs, 1 year survival 3% Trisomy 13: Prevalence ~0.8/10,000, 1 year survival 3% No ethnic difference. *(Vendola et al., 2010, AJMG)*	

TURNER SYNDROME: Overall

No single phenotype
Varies with age:
- Hydropic fetus (sab)
- Infant with CHD
- Girl with short stature
- Girl with coarctation
- Teen with delayed puberty
- Woman with infertilty
- Someone you know with short stature

Malformed pinnae
100% short stature
Most infertile
Renal: horseshoe kidney
Neck webbing, edema
Skin: nevi, keloids





TURNER SYNDROME: Cardiac

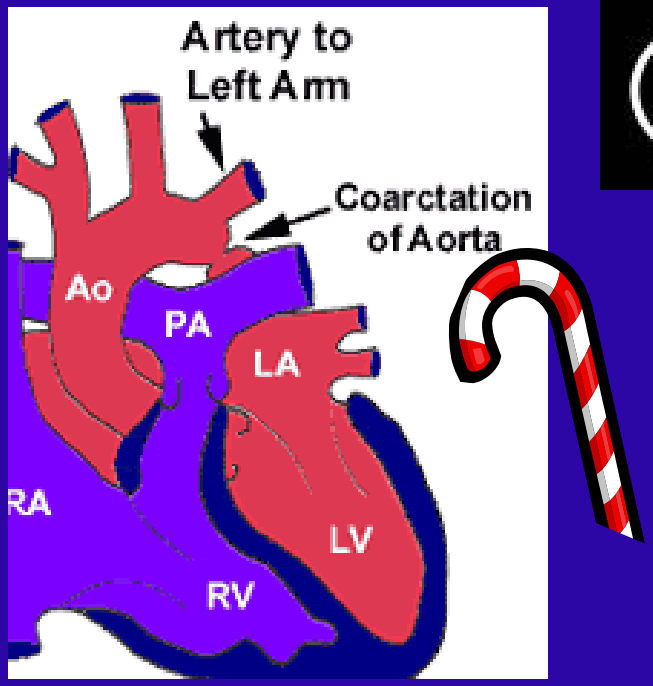
All types: 25%

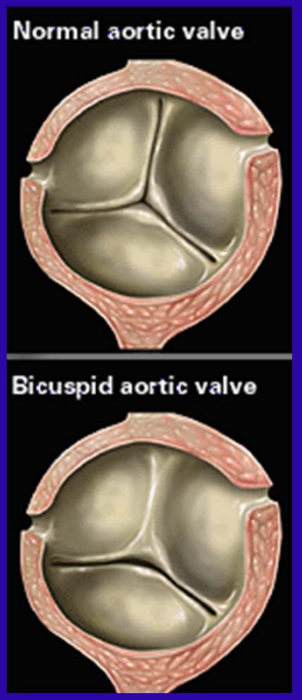
Left-sided obstruction
"LVOTO"
- Bicuspid aortic valve
- Coarctation
- Aortic stenosis
- MV anomalies
- HLHS

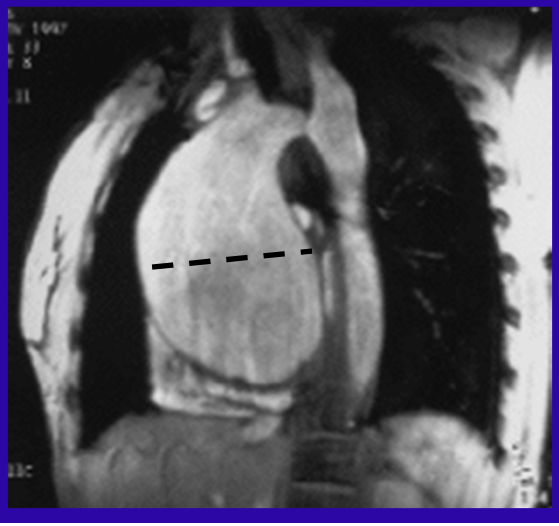
Partial APVR
ASD2, VSD

Aortic dilation, dissection

Hypertension
ECG abnormalities







WHAT'S NEW: TURNER SYNDROME

Reproduction: Assisted reproductive technology (ART)	1) Risk factors for aortic dissection: BAV, COA, HTN 5-10% have no risk factor (pregnancy itself?) 2) Spontaneous puberty ~10%; pregnancies 2-5% *(Hadnott and Bondy, Exp Rev Obstet Gynecol, 2011)* 145 pregnancies in 76 women Overall risk for major pregnancy complications ~10% Risk for maternal death ~3.5% Method of conception: ~17% ART (after 1989) More risk with ART (9/24, ~38%, vs. 6/102, ~6% spontaneous) Karyotype: 45,X more common Underlying CV abn: 100% (7/7), BAV, PIH, COA, aortic dilation.
Counseling	1) Speak of "being a mother" rather than "having a baby". Begin early, include adoption as an option. 2) Ineligible: BAV, COA, aortic stenosis, with/without surgery Pre-existing aortic dilation, hypertension Serious medical condition, 3) More conservative: View TS as having vasculopathy

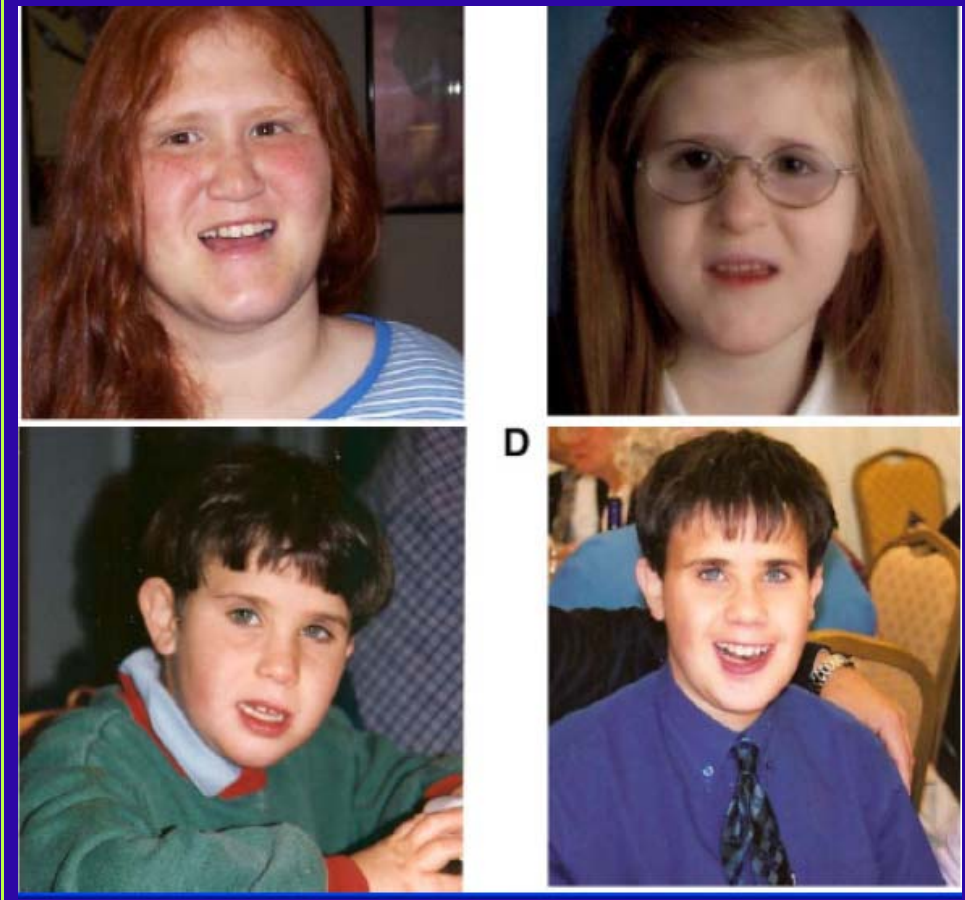
DELETION 1p36 SYNDROME: Overall

Straight eyebrows
Small, open mouth

All cardiac: 80%

CHDs 70%
Including Ebstein
Noncompaction LV 20%
Dilated cardiomyopathy 4%

(abnormality of trabecularion)



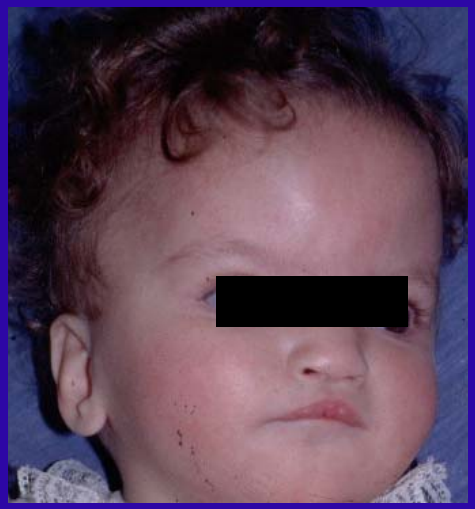
Gajecka et al., AJMG PartC 2007

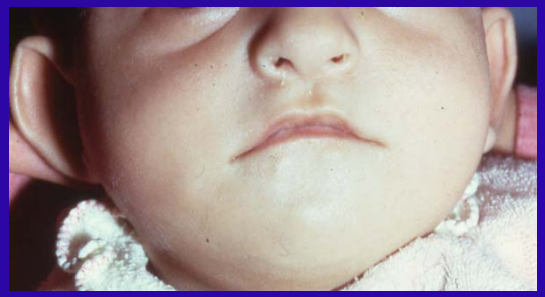
DELETION 4p SYNDROME: Overall

Wolf-Hirschorn syndrome

Craniofacial
"Greek war helmet"
- Prominent glabella
- Hypertelorism
- Downcurved mouth
- Abnormal ears
- Cleft lip/palate

GU anomalies





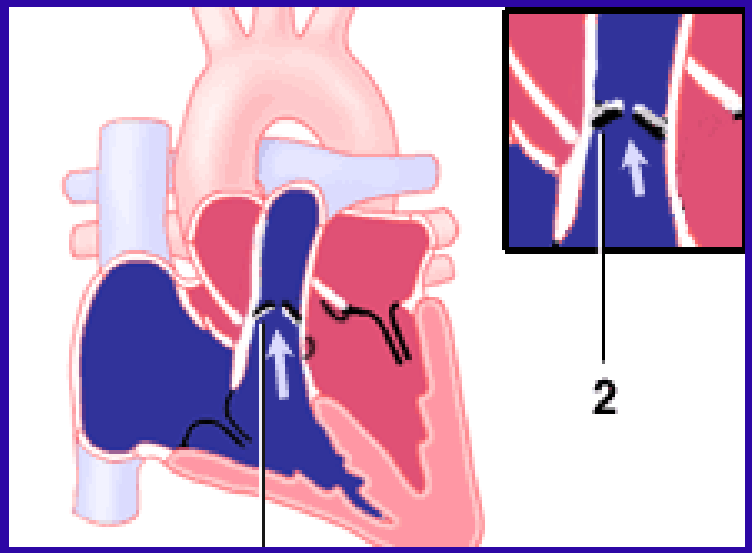
DELETION 4p SYNDROME: Cardiac

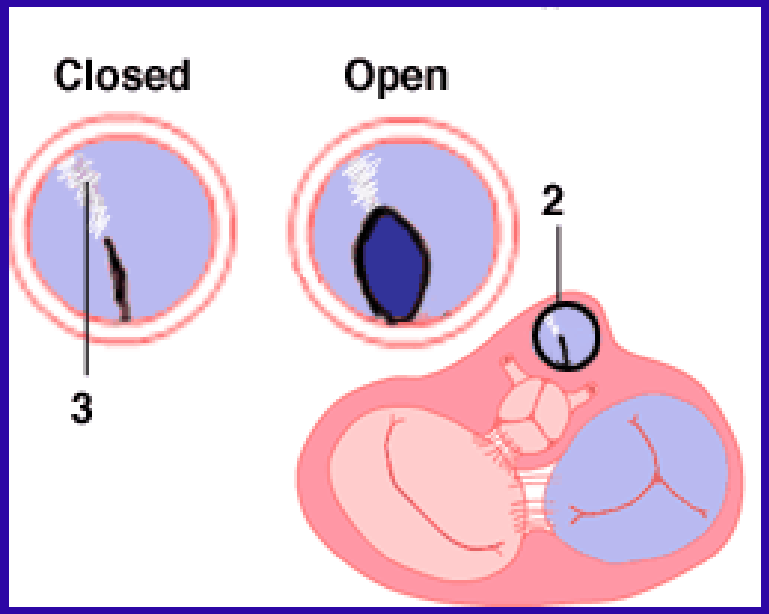
All types: 40%

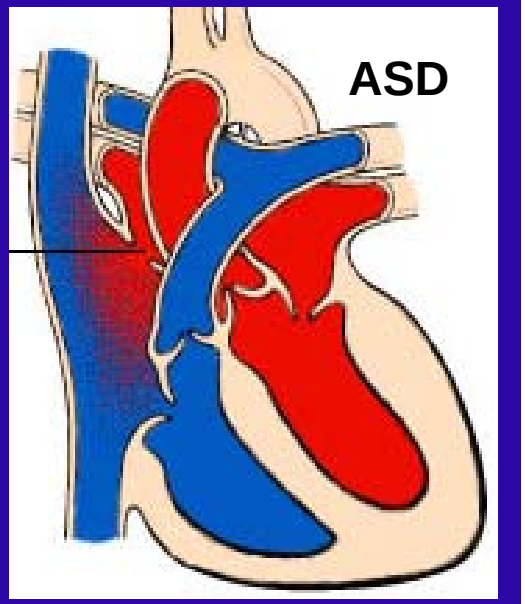
Most common:
Pulmonic stenosis

ASD

VSD







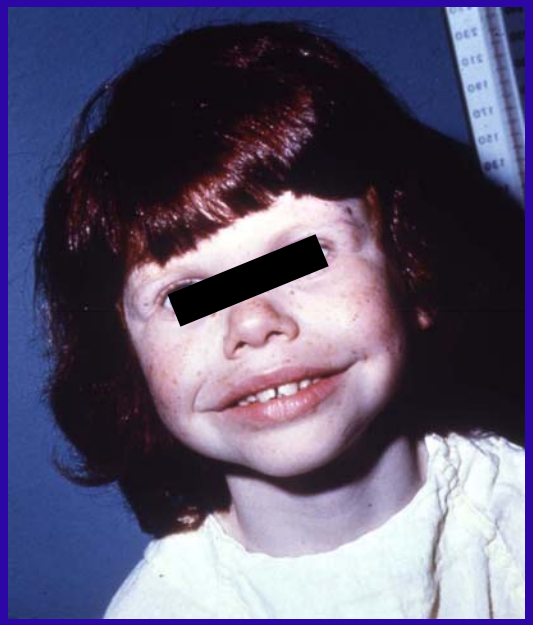
DEL 7p/ WILLIAMS SYNDROME: Overall

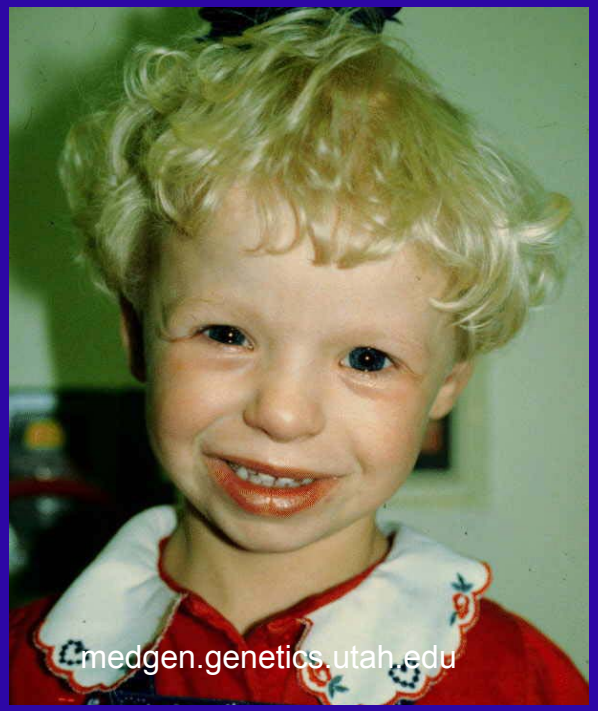
Craniofacial
- Stellate irides
- Eyebrow flare
- Periorbital fullness
- Wide mouth, full lips

Laxity, then contractures

Distinctive personality
- Irritable infancy
- Personable
- Talkative
- Anxious

Hyperacusis
Hoarse voice
Abnormal calcium levels





DEL 7p / WILLIAMS SYNDROME: Cardiac

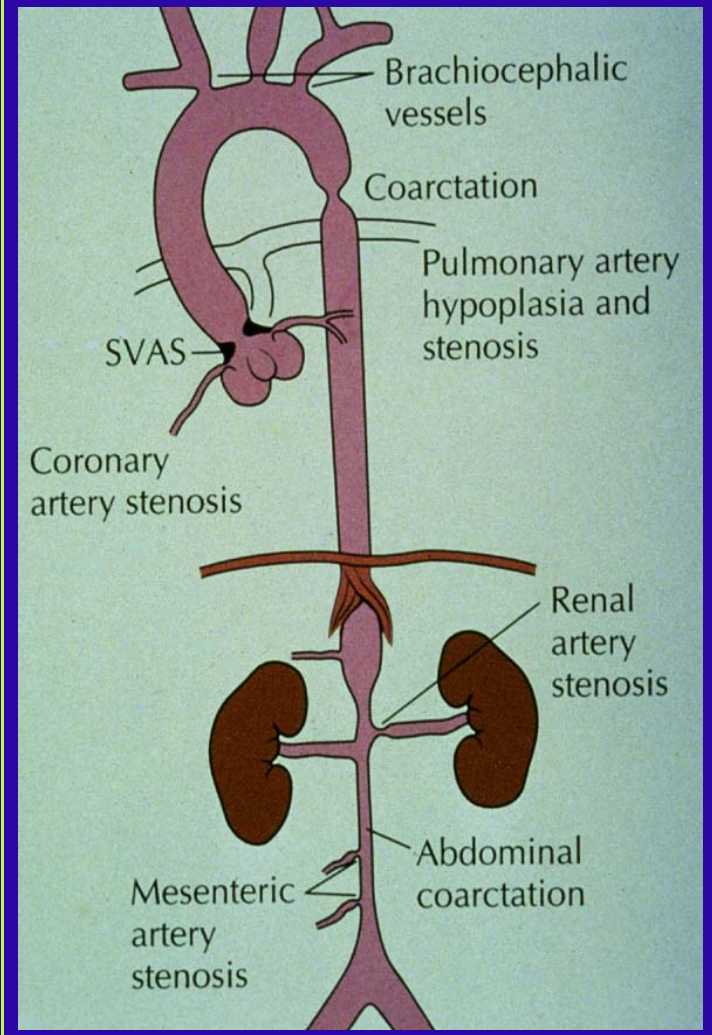
All types: 75%

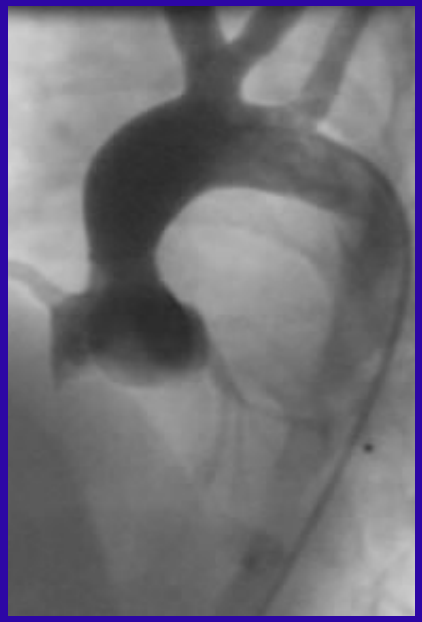
Left and right heart Obstruction:

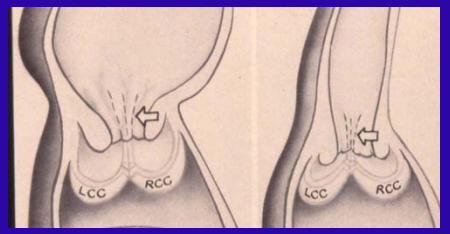
Supravalvar Ao stenosis
+/- Ao Valve stenosis
Coarctation
Aorta hypoplasia

PV stenosis
Peripheral pulmonic stenosis

ASD, VSD
Renal artery stenosis
Coronary artery stenosis







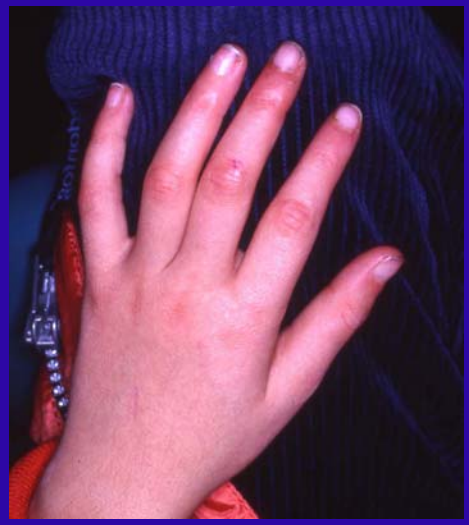
Courtesy of Drs. Leslie Smoot and Ron Lacro, CH, Boston

DELETION 22q11 SPECTRUM: Overall

DiGeorge syndrome
Velo-cardio-facial (VCFS)
CATCH-22

Craniofacial
- Narrow palpebral fissures
- Cleft palate
- Straight nose
- Wide nasal root
- Small mouth
- Thin lips

Absent thymus
Hypocalcemia
Speech problems
Psychiatric disorders



www.cardiogenetics.org

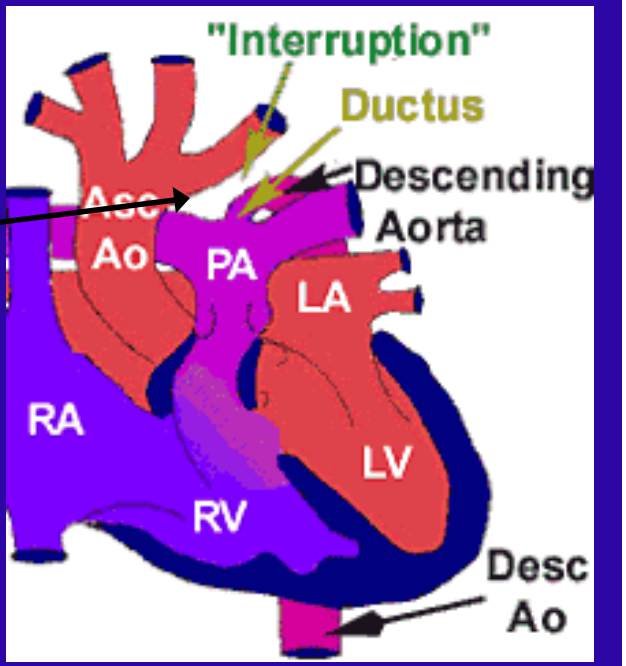
DELETION 22q11 SPECTRUM: Cardiac

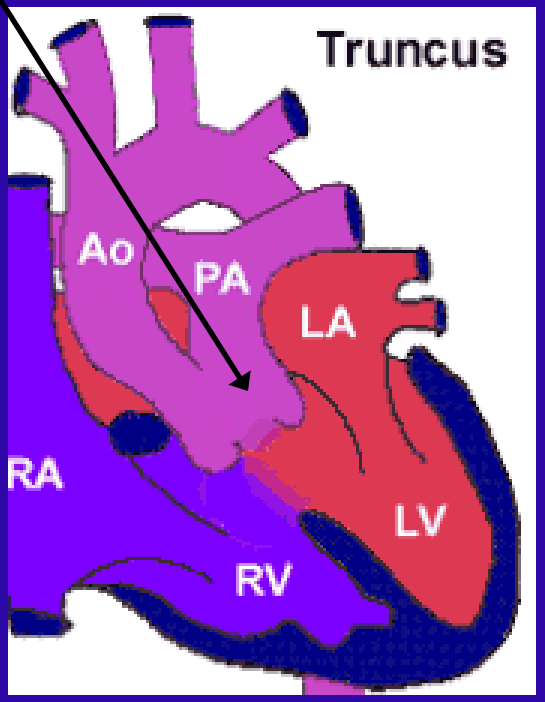
All types: 75-85%

Striking
Conotruncal
- IAA, type B
- Truncus arteriosus
- TOF
- TOF with pulmonary atresia
- VSD, malalignment
- DORV

Aortic arch anomaly
- Aberrant subclavian

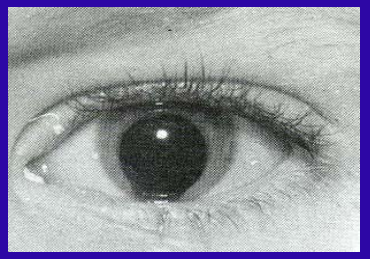
VSD, membranous
VSD, muscular





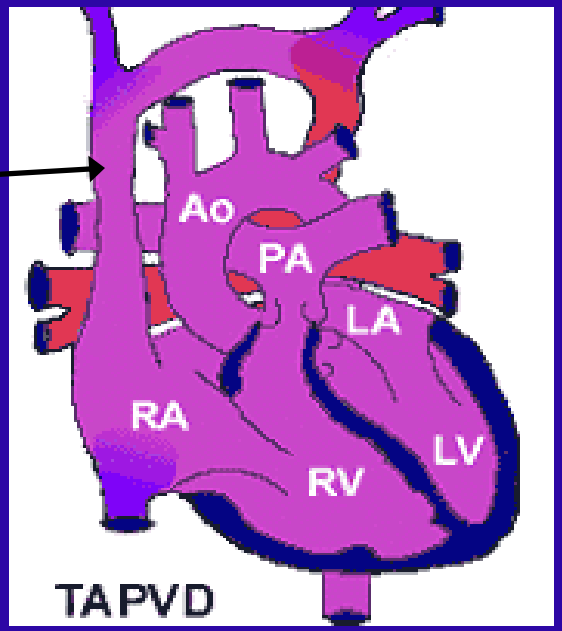
TETRASOMY 22p/ CAT-EYE SYNDROME

Iris coloboma
Pre-auricular pit/tag
Rectal anomalies
GU anomalies



CHD, all types: 50%

TAPVR
PAPVR



ACKNOWLEDGEMENTS FOR DIAGRAMS

Google the hospital, search for pediatric cardiology site:

- Children's Hospital of Boston, MA
- Children's Hospital of Philadelphia, PA
- Cincinatti Children's Hospital, OH
- Melbourne Children's Hospital, Australia
- Nemours / A.I. Du Pont Children's Hospital, DE
- Mayo Clinic, MN
- Yale Medical School, CT

http://www.rch.org.au/cardiology/
http://embryology.med.unsw.edu.au/Medicine/ILPheart.htm
http://www.mayoclinic.org/patientinfo/
http://www.heart-vessels.com/cardiovascular-diseases/
http://www.childrenshospital.org/cfapps/mml/