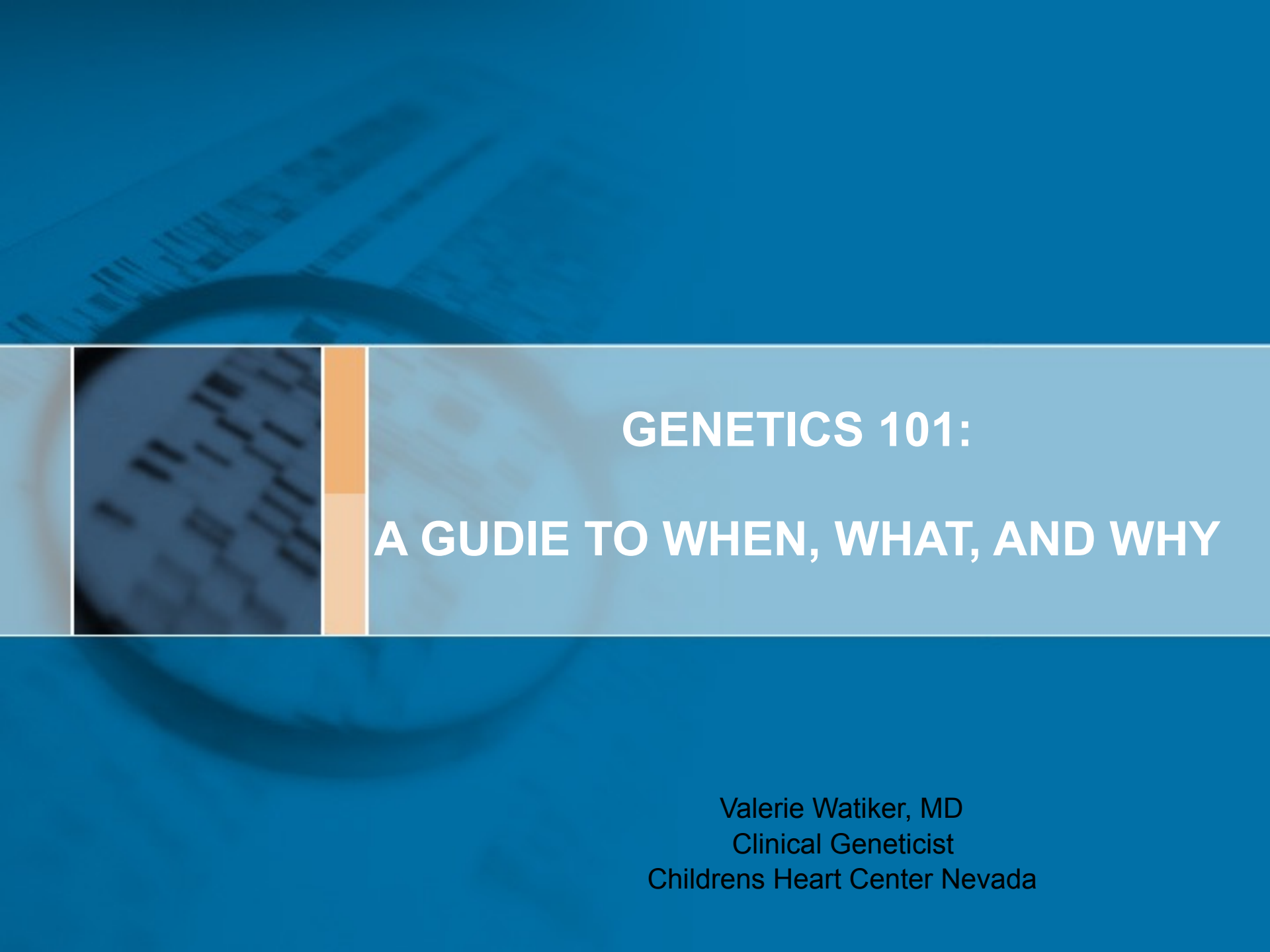




GENETICS 101:

A GUIDE TO WHEN, WHAT, AND WHY

Valerie Watiker, MD
Clinical Geneticist
Childrens Heart Center Nevada

Disclosures

▶ NONE



GENETICS: 101

- » Who: Genetics Team/Patients
- » WHAT: Are the Tests
- » WHEN: ToTest
- » WHY: Why Test
- » WHERE: Labs we use
- » HOW: TO GET more INFORMATION

WHO: Pediatric Genetics Team

- Clinical geneticist- MD
 - Clinical
 - Metabolic
 - Adult
 - Prenatal
- Genetic counselor- MS
- Nurse
- Social Worker
- Nutritionist

Referral

- Typical pediatric referrals include:
 - Developmental delay
 - Hypotonia (low muscle tone)
 - Dysmorphic features
 - Short stature
 - Multiple congenital anomalies
 - Failure to thrive
 - Unusual constellations of findings
 - Family history

Referral

- Typical Adult referrals include:
 - Pregnancy
 - Abnormal Screening
 - Sudden Cardiac arrest
 - Cardiomyopathy
 - Cancer at young age/unusual Cancer
 - Adult with a Genetic disorder (Marfan)
 - Family history

Genetics101: What to Know

- No single test will evaluate all types of Genetic Disorders
- 1DNA= Many RNA= Many Proteins

WHAT: TO ORDER

» NO TEST DETECTS ALL SYNDROMES

» CHROMOSOME

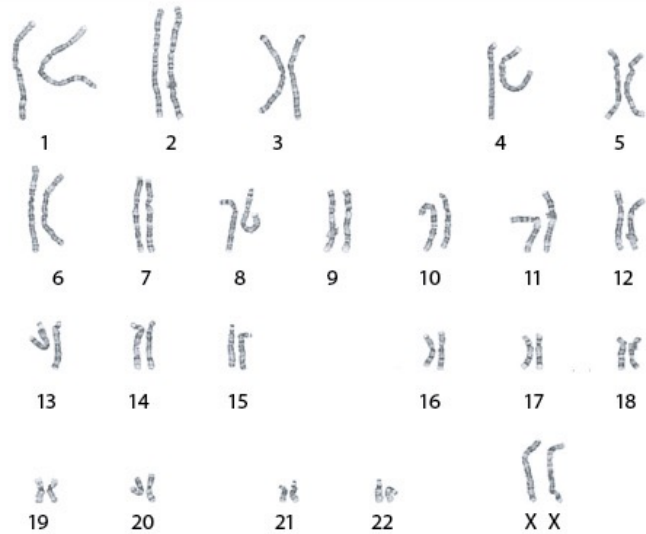
» MICROARRAY

» SINGLE GENE/PANEL

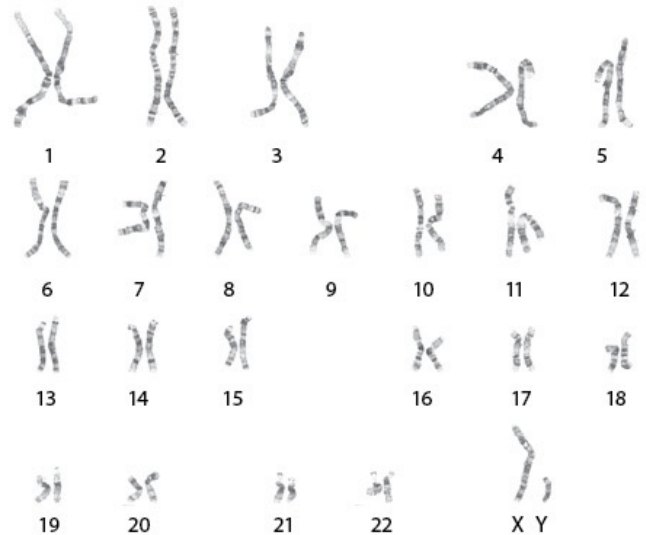
» WHOLE EXOME

TYPICAL FEMALE AND MALE KARYOGRAMS

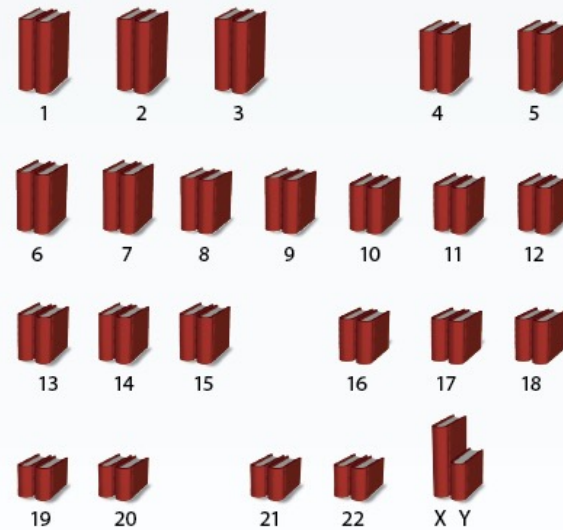
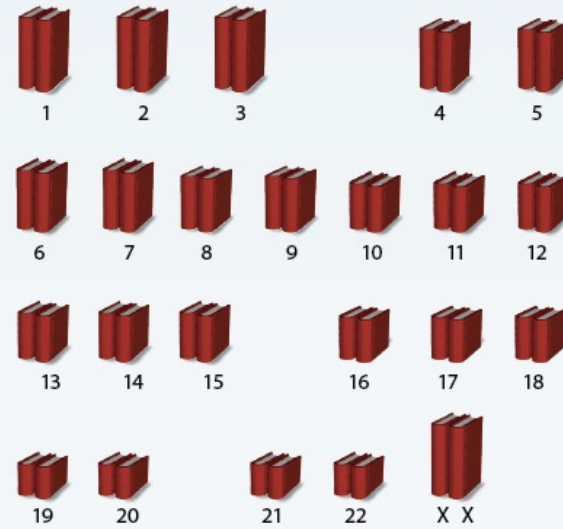
♀ female



♂ male

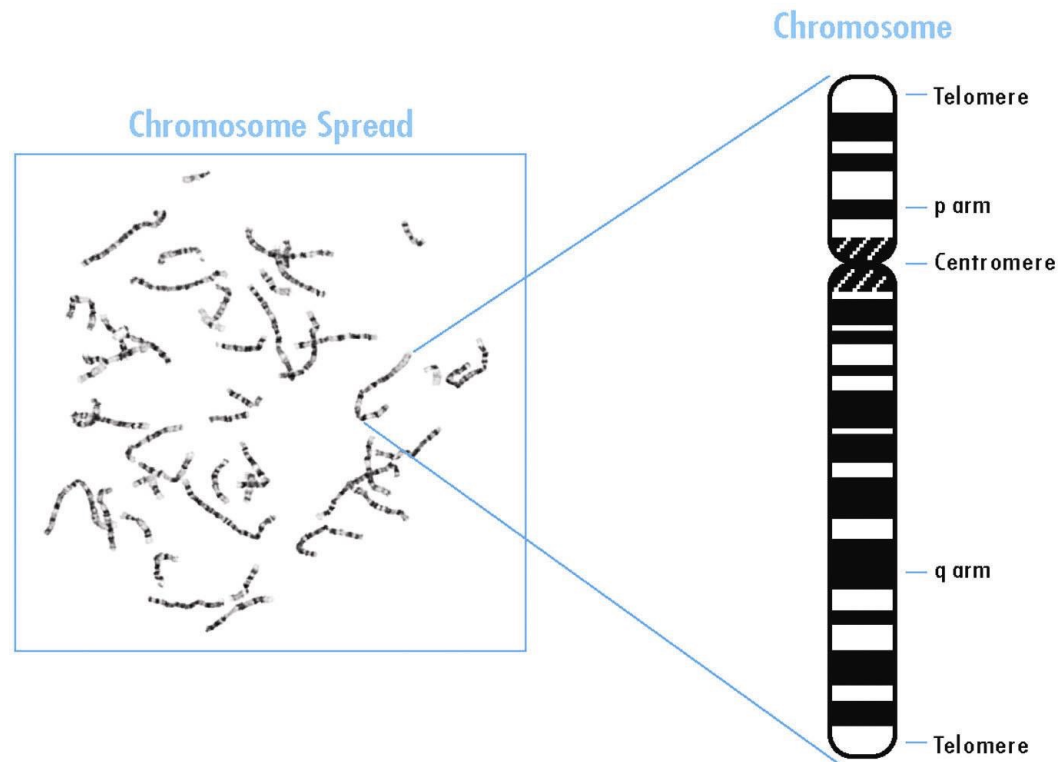


COMPLETE ENCYCLOPEDIA SET



Anatomy of a Chromosome

Anatomy of a Chromosome



Trisomy 21

- » Hypotonia
- » Flat mid face
- » Low small ears
- » Inc. Nuchal skin
- » VSD
- » Simian Crease
- » Protruding tongue



Trisomy 13

- » Holoprosencephaly
- » Scalp defect
- » Microphthalmia
- » Low set ears
- » Cleft lip +/- palate
- » Polydactyly
- » Clenched hand (thumb over fingers)
- » Cardiac: VSD, PDA
ASD, Dextroposition



diseasespictures.com



Trisomy 18

- » IUGR
- » Weak cry
- » Low set ears
- » Short pf.
- » Small mouth
- » Clenched hand
(index finger over 3rd finger)
- » Cardiac: VSD,
ASD,PDA



newborn and 1 year of age

Common Chromosomal Disorders

- » Turner Syndrome , (45, X)
- » Klinefelter, (47XXY)
- » Deletion 1p36
- » Wolf Hirschhorn (4p-)
- » Cri Du Chat (5p-<https://>



<https://missingxchromosome.wordpress.com/>

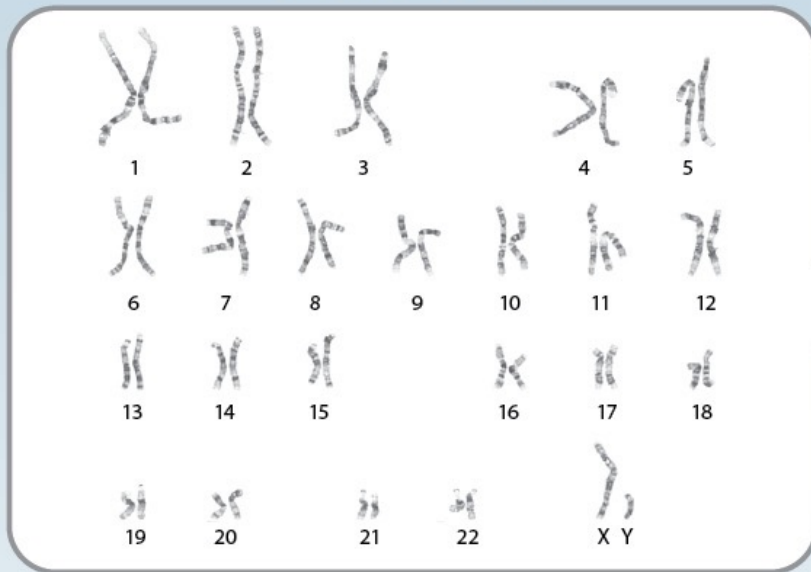


wikipedia

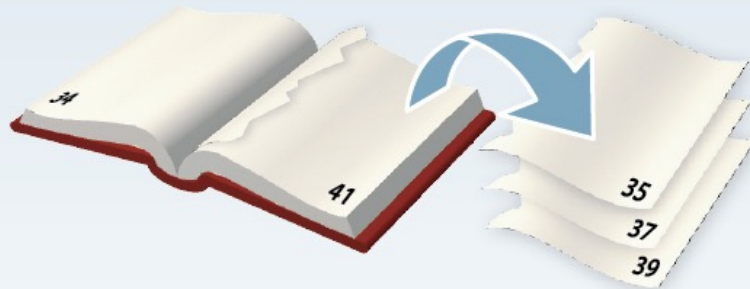
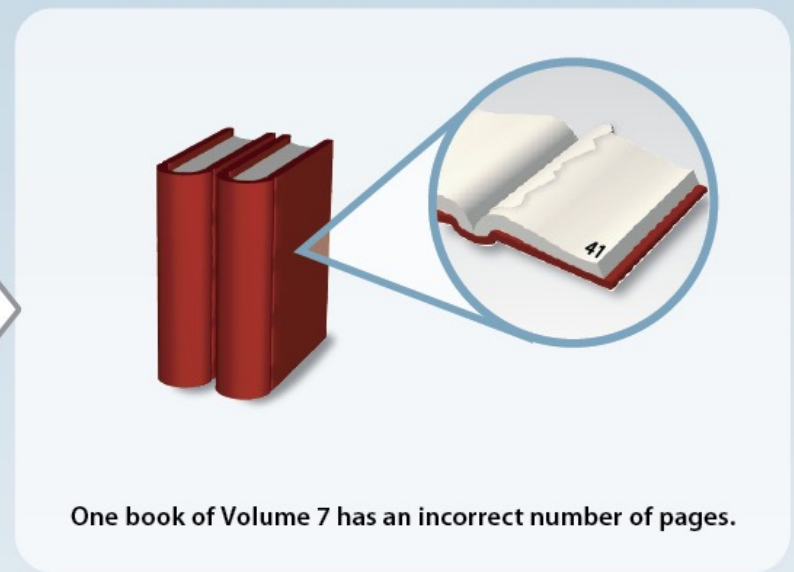


» [emedicine.medscape.com/
article/950480-overview](https://emedicine.medscape.com/article/950480-overview)

NORMAL KARYOGRAM



ABNORMAL ENCYCLOPEDIA VOLUME (INSIDE)



Pages within the chromosome or encyclopedia volume are removed or *deleted*.

OR



Pages within the chromosome or encyclopedia volume are present in multiple copies or *gained*.



Am. J. Hum. Genet. 76:865–876, 2005

22q11.2 Duplication



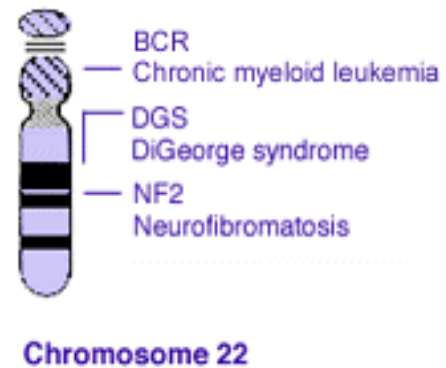
Am. J. Hum. Genet. 76:865–876, 2005

22q11.2 Triplication



22q11.2 deletion

<http://dempsterfamilyfoundation.org>



22q11.2 deletion

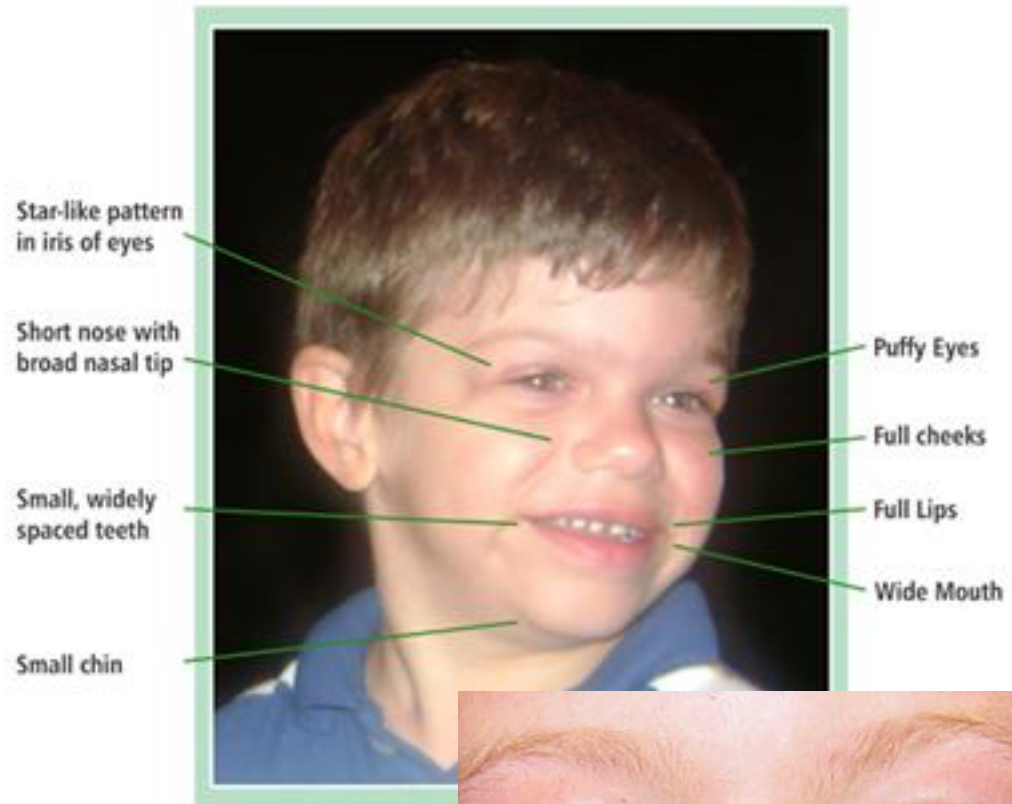
- IQ variable
- Learning disabilities
- Hypernasal speech
- cleft palate
- Facial features
 - hooded eyes
 - tubular nose
- Short stature
- Cardiac: TOF



Williams Syndrome

- » Developmental delay
- » Cocktail party personality
- » Cardiac: 60-80%
- » Supervalvular AS
- » Supervalvular PS

Facial Features of Williams Syndrome



<http://www.forgottendiseases.org/assets/WilliamsSyn.html>

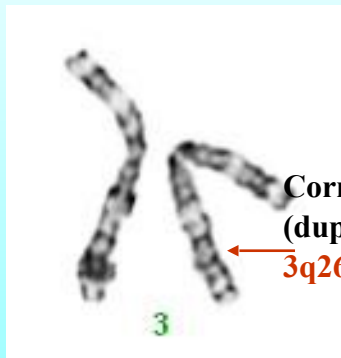
<https://infograph.venngage.com/p/106191/williams-syndrome-infographic>



1



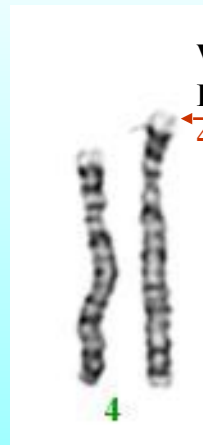
2



3

Cornelia de Lange
(duplication)

3q26.1



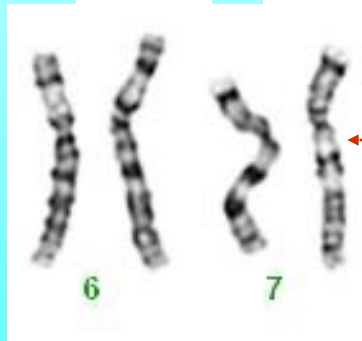
4

Wolf-
Hirschhorn

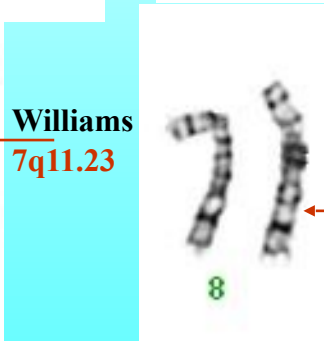
4p16.3



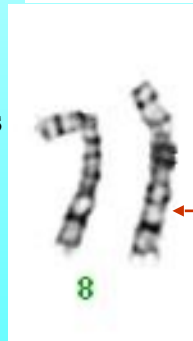
5

cru-du-chat
5p15

6



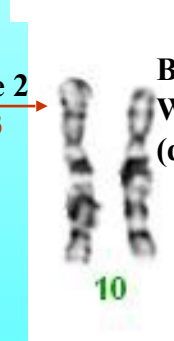
7

Williams
7q11.23

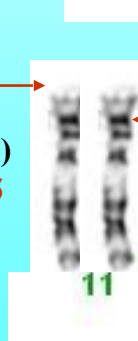
8

Langer
Gideon
8q24.11

9

DiGeorge 2
10p13

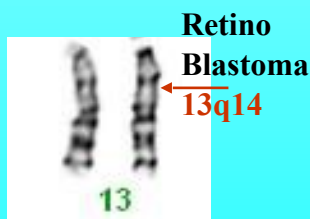
10

Beckwith-
Wiedemann
(duplication)
11p15.5

11

Aniridia
11p13

12



13

Retino
Blastoma
13q14

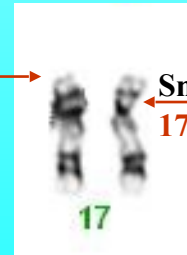
14

Angelman/
Prader-Willi
15q12

15

Rubenstein-
Taybi
16p13.3

16

Miller-Dieker
Lissencephaly
17p13.3

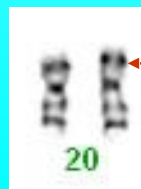
17

Smith-Magenis
17p11.2

18



19



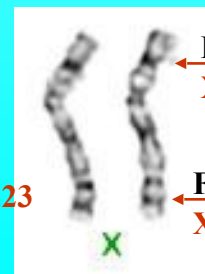
20

Alagille
20p11.23-12.1

21

Down Syndrome
Critical region
21q22.3

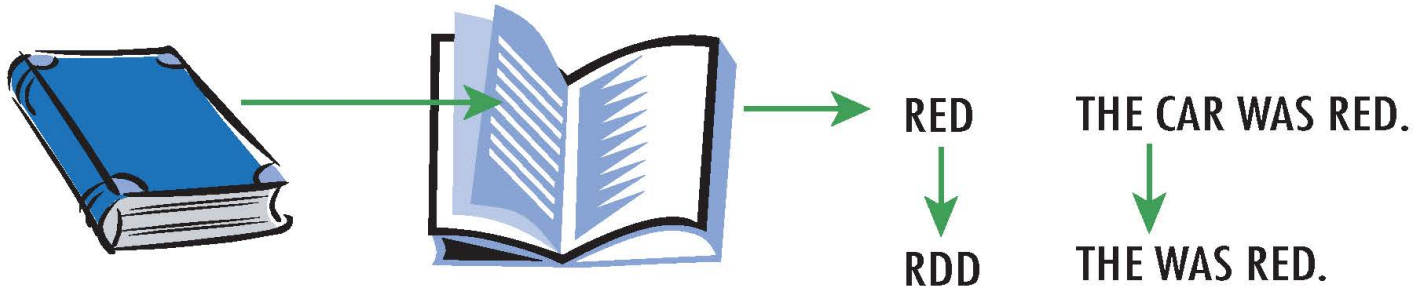
22

DiGeorge
22q11.21-11.23

X

Duchenne
Xp21Fragile X
Xq27.3

Types of Gene Mutations



Chromosomes are like chapters in a book; one set is from the mother, one set is from the father.

Genes are like sentences in a chapter.

Mutations are like misspelled words or the disruption of a sentence.

Missense Mutations change one word or letter

THE CAR WAS RED. → THE CAR WAS HAT.
→ THE CAR WAS RDD.

Insertion Mutations add one word or letter

THE CAR WAS RED. → THE CAR WAS RED RED.
→ THE CAR WAS ERED.

Nonsense Mutations end the instructions too soon

THE CAR WAS RED. → THE CAR. _____

Deletion Mutations change the meaning by subtracting words or letters

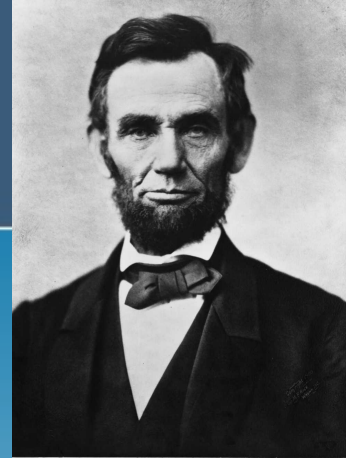
THE CAR WAS RED. → THE ___ WAS RED.
→ THE _AR WAS RED.

Holt Oram

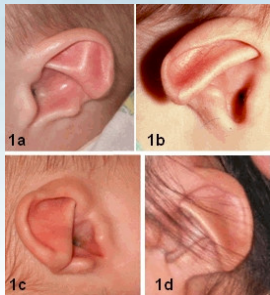
- » Thumb abnormalities
- » Absent radius/
Ulna
- » Cardiac: ASD
VSD



Single Gene Disorders



- » Marfan Syndrome (AD) FBN1 gene
- » Tuberous Sclerosis (AD), TSC1 and TSC2
- » Charge Syndrome (AD), CHD7,
- » TAR syndrome (AR) , unknown, some del 1q21
- » Alagille Syndrome (AD) - JAG1, NOTCH2



WHEN: TO TEST

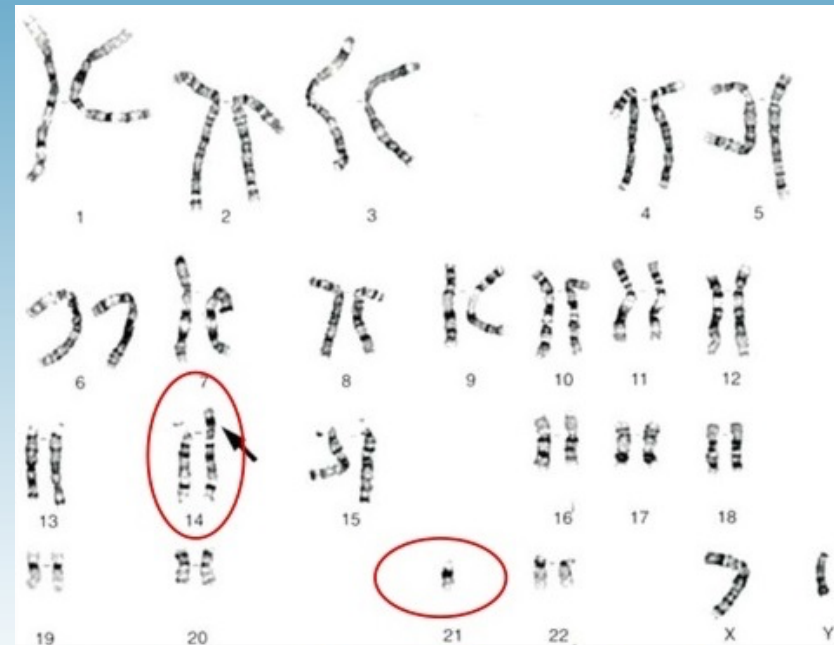
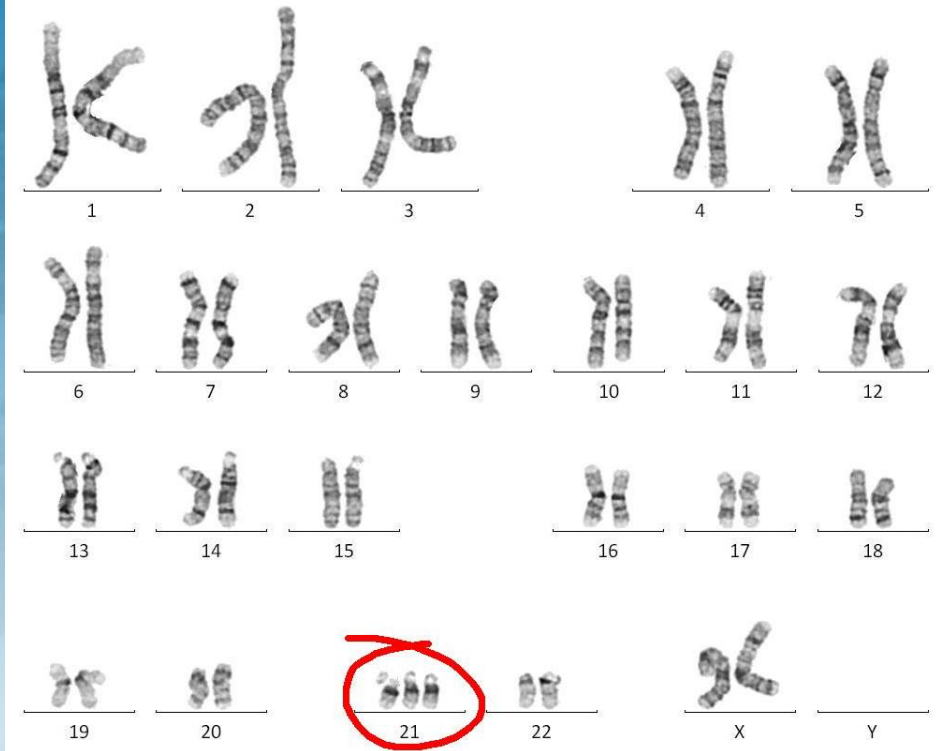
- » MORE THAN 1 BIRTH DEFECT
- » DYSMORPHIC FEATURES
- » UNEXPLAINED DEVELOPMENTAL DELAY/MR
- » RECOGNIZE A SYNDROME
- » Family History

If Unsure:

Chromosomal Microarray is First Line Test

Microarray / Chromosomes

Down syndrome karyotype



Translocation Karyotyping

WHY: TEST

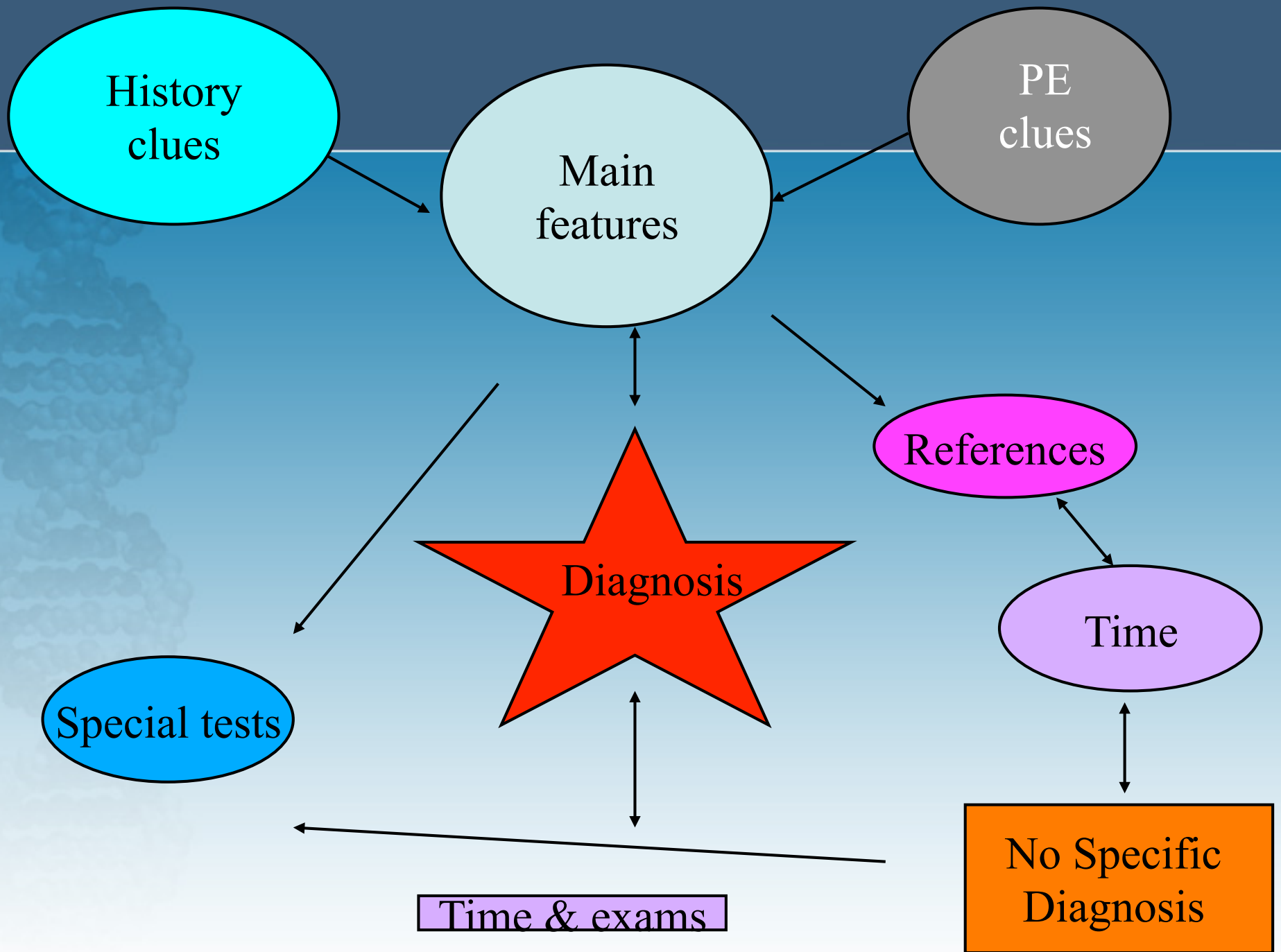
- » Provide a Diagnosis
- » Provide Prognosis
- » Medical Management Improved
- » Recurrence Risks

* Insurance: Impact medical management

WHERE

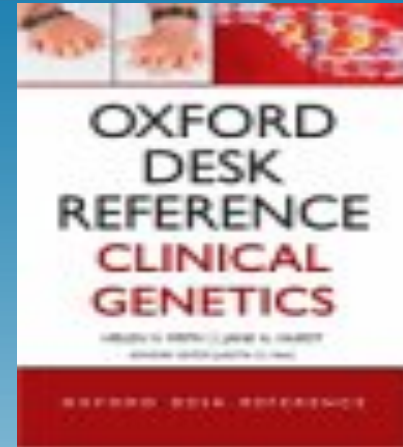
- » SNP MICROARRAY
 - » CONTRACTED LAB
 - » LAB CORP/INTEGRATED GENETICS
 - » QUEST DIAGNOSTICS
- » SPECIALTY LABS
 - » GENETESTS.ORG

* Insurance: labs may /may not contract with insurance



HOW TO GET MORE INFORMATION

- **Genereviews:** <https://www.ncbi.nlm.nih.gov/books/NBK1116/>
- **OMIM:** <http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM&itool=toolbar>
- **ACMG**
- **NSGC**
- **ACOG**
- **Laboratory websites**



GeneReviews[®] [Internet]. < Prev Next >

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Noonan Syndrome

Judith E Allanson, MD and Amy E Roberts, MD.

[Author Information](#)

Initial Posting: November 15, 2001; Last Update: February 25, 2016.

Summary Go to: ☒

Clinical characteristics. Noonan syndrome (NS) is characterized by characteristic facies, short stature, [congenital](#) heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities. Although birth length is usually normal, final adult height approaches the lower limit of normal. Congenital heart disease occurs in 50%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. Other structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Up to one fourth of [affected](#) individuals have mild intellectual disability, and language impairments in general are more common in NS than in the general population.

Diagnosis/testing. NS is diagnosed on clinical grounds by observation of key features. Affected individuals have normal [chromosome](#) studies. Molecular genetic testing identifies a [pathogenic variant](#) in *PTPN11* in 50% of [affected](#) individuals. *SOS1* in approximately 13%. *RAF1* and *RIT1* each in 5%. and *KRAS* in fewer than 5%. Other genes in

