Random Pearls in Dysmorphology and Genetics

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Evolution of Diagnostic Criteria

- Berlin nosology 1986
  - Beighton et al. International nosology of heritable disorders of connective tissue, Berlin 1986. Am J Med Genet 29:581-594, 1988
- FBN1 identified 1991
- Ghent criteria 1996
  - De Paepe et al. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 62:417-426, 1996

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Original Ghent Criteria
major criteria in 2 systems + involvement of 3rd

System	Diagnostic Criteria	
	Major	*Minor*
Skeletal system	pectus carinatum	pectus excavatum of moderate severity
	pectus excavatum requiring surgery	joint hypermobility
	reduced upper-to-lower segment ratio or arm span-to-height ratio greater than 1.05	highly arched palate with crowding of teeth
		facial appearance (dolichocephaly, malar hypoplasia, down-slanting palpebral fissures, retrognathia)
	wrist and thumb signs	
	scoliosis of > 20° or spondylolisthesis	
	reduced extension at the elbows (< 170°)	enophthalmos
	medial displacement of the medial malleolus causing pes planus	
	protrusio acetabulae of any degree (ascertained on radiographs)	
For skeletal system to be considered involved, at least 2 of the components comprising the major criterion or 1 component comprising the major criterion plus 2 of the minor criteria must be present.		
Ocular system	ectopia lentis	abnormally flat cornea
		increased axial length of globe
		hypoplastic iris or hypoplastic ciliary muscle
For ocular system to be involved, at least 2 of the minor criteria must be present.		
Cardiovascular system	dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva	mitral valve prolapse with or without mitral valve regurgitation
		dilatation of the main pulmonary artery
	dissection of the ascending aorta	calcification of mitral annulus
		dilatation or dissection of the descending thoracic or abdominal aorta
For the cardiovascular system to be involved, a major criterion or only one of the minor criteria must be present.		
Pulmonary system	none	spontaneous pneumothorax, or apical blebs (ascertained by chest radiography)
For the pulmonary system to be involved, one of the minor criteria must be present.		

System	Diagnostic Criteria	
	Major	*Minor*
Skin and integument	none	striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy, or repetitive stress, or
		recurrent or incisional herniae
For the skin and integument to be involved, one of the minor criteria must be present.		
Dura	lumbosacral dural ectasia by CT or MR image	none
For the dura to be involved, the major criterion must be present.		
Family/Genetic History	having parent, child, or sibling who meets these diagnostic criteria independently	none
	presence of mutation in *FBN1*, known to cause Marfan syndrome; or	
	presence of haplotype around *FBN1* inherited by descendent known to be associated with unequivocally diagnosed Marfan syndrome in the family	
For the family/genetic history to be contributory, one of the major criteria must be present.		

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Revised Ghent Criteria

Loeys BL, et al.
J Med Genet. 2010 Jul;47(7):476-85. doi: 10.1136/jmg.2009.072785.

- Criteria in absence of family history
  - Ao (Z ≥ 2) + ectopia lentis
  - Ao (Z ≥ 2) + FBN1 mutation
  - Ao (Z ≥ 2) + systemic features (≥ 7 points)
  - Ectopia lentis + FBN1 mutation with known aortic involvement

Ao = aortic diameter above indicated Z score or aortic dissection

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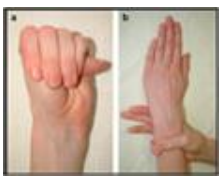
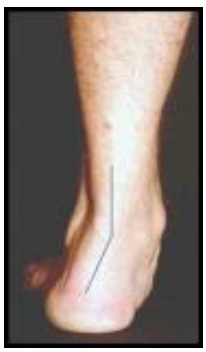
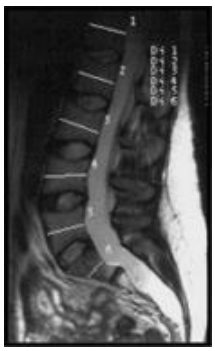
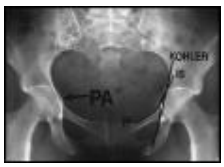
https://www.marfan.org/dx/score

Positive wrist and thumb	3
Positive wrist or thumb	1
Pectus carinatum	2
Pectus excavatum/asymmetry	1
Hindfoot deformity	2
Flat feet	1
Spontaneous pneumothorax	2
Dural ectasia	2
Protrusio acetabulae	2
Scoliosis/kyphosis	1
Reduced elbow extension	1
3 of 5 facial features	1
Skin striae	1
Severe myopia	1
Mitral valve prolapse	1
Reduced U/L segment ratio & Increased span to height	1









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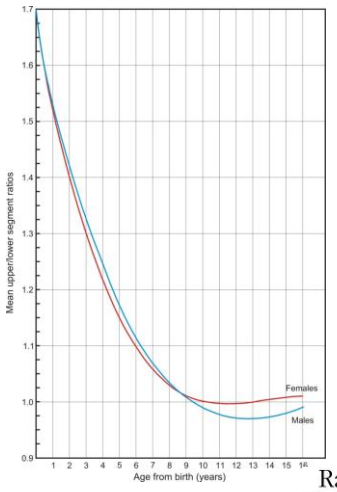
Upper/lower segment ratio

- Measure height
- Measure lower segment
  - Top of symphysis to heel
- Derive upper segment
- Measure span
- Divide

- www.marfan.org/dx/score



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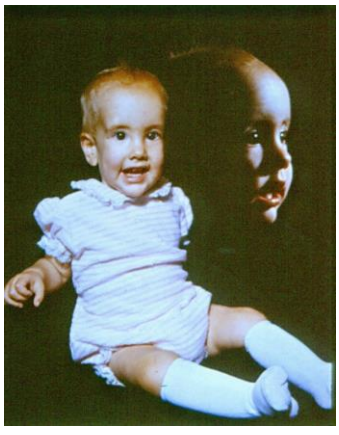
Special case for young children

- Systemic features are age related
- Hypotonia
- Contractures
- Joint laxity
- Motor delays



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Management of Marfan syndrome

- Ophalmologic follow up
  - Avoid LASIK
- Cardiac follow up
  - No competitive sports
  - Beta blockers
  - Losartan
  - Elective replacement aortic root
  - Avoid decongestants and caffeine
- Orthotics

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Other diagnoses

- Loeys-Dietz syndrome
- Vascular Ehlers-Danlos
- Shprintzen-Goldberg
- Familial thoracic aortic aneurysms
- Homocystinuria
- Stickler syndrome
- Fragile X

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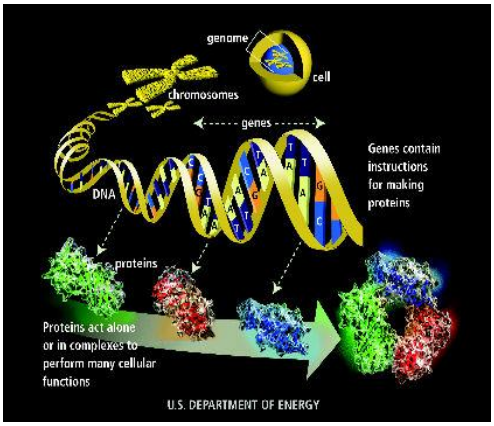
Content of the Human Genome

- 46 chromosomes (23 pairs)
  - 1956
- 20-25,000 protein coding genes
  - disease causing mutation in ~5000
- 3+ billion base pairs (A,G,T,C)
  - 16569 mitochondrial
  - double helix 1953
  - draft of sequence June 2000
  - completed sequence Spring 2003
- First Genome Sequenced 2007



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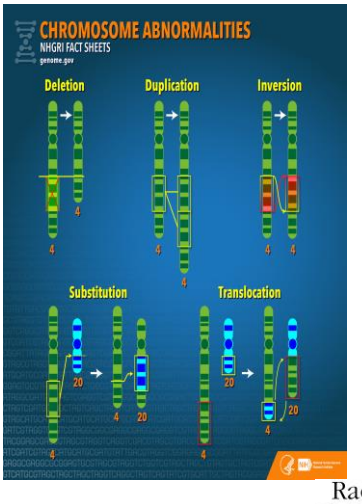
Packaging Problems

- Aneuploidy
- Translocation
- Deletion
- Duplication
- Inversions
- Markers



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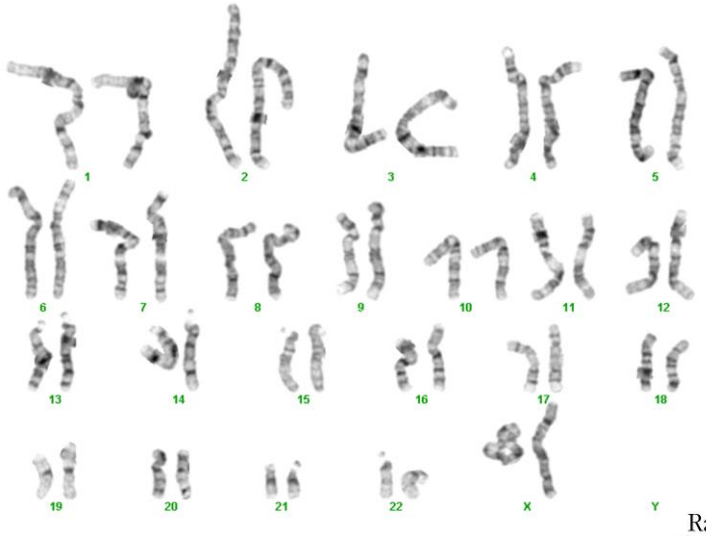
Chromosomes



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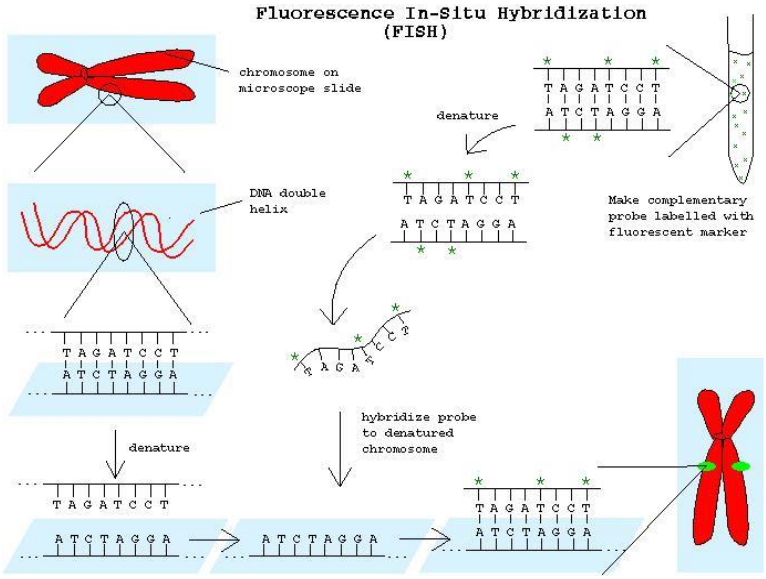
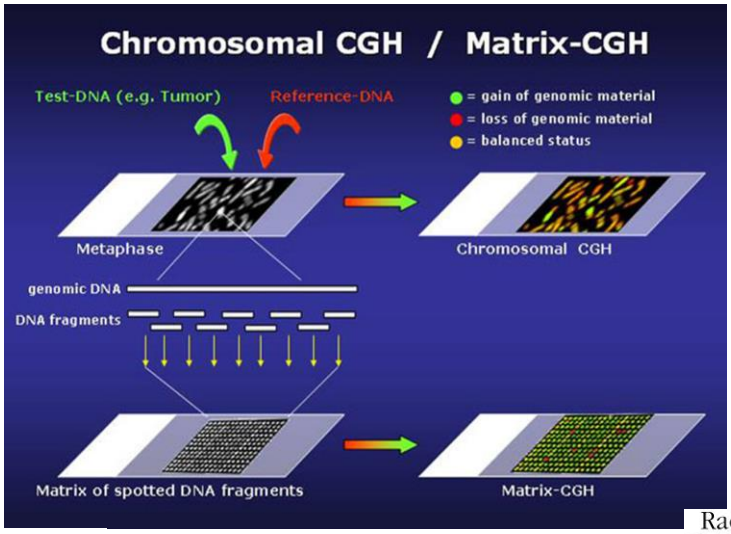
Fluorescence in-situ hybridization



Comparative Genomic Hybridization Array



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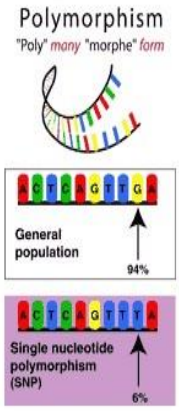
Single Nucleotide Polymorphism

- Coding/non-coding regions
- 1:1000 to 1:100-300 base pairs
- SNP close to gene is marker for gene
- SNP in coding region may alter protein structure



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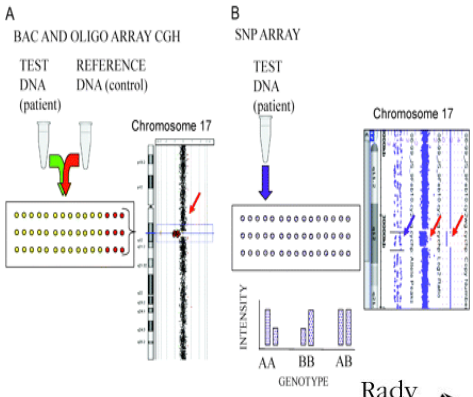
CGH-SNP Array

- Copy number abnormalities
- Identity by descent
- Consanguinity
- Incest
- Uniparental disomy



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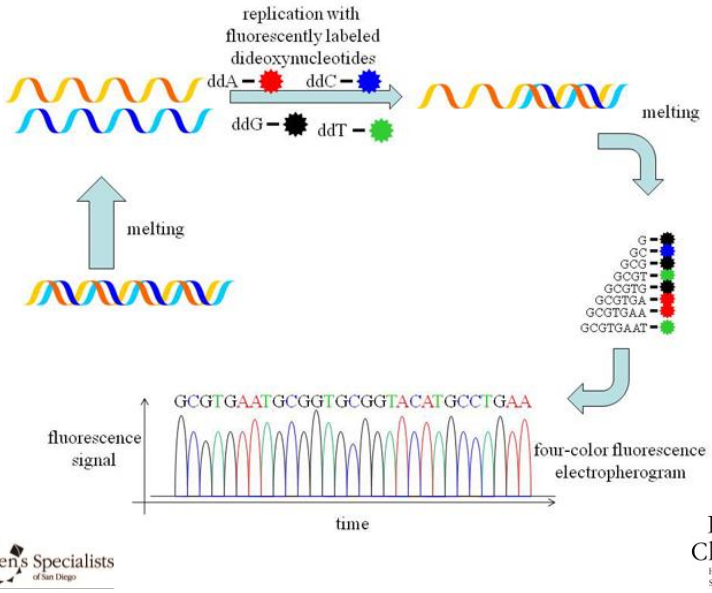
Sanger sequencing



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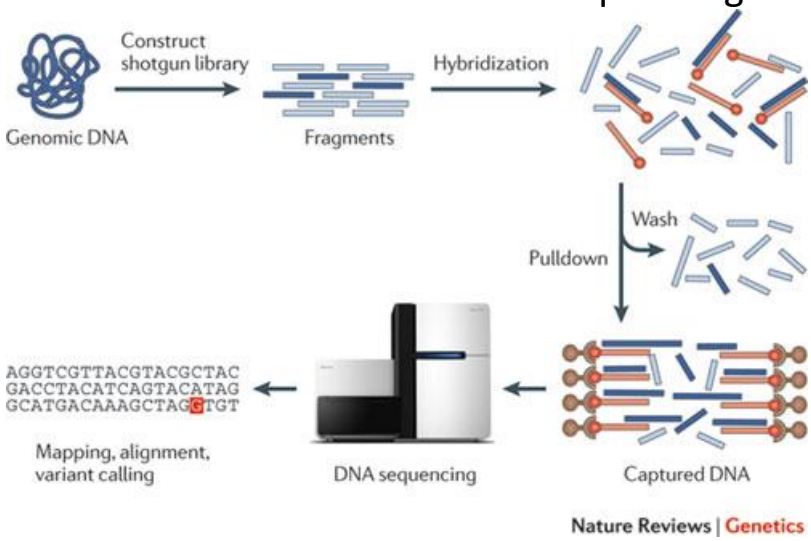
Exome and Whole Genome Sequencing



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Issues with Genome Sequencing

- Patient autonomy
  - Right to know or not
  - Adult vs. Children
- Laboratory: NOT
  - Structural variants
  - Repeat expansion
  - Copy number variants
  - Imprinting abnormalities

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Green RC, et al: Genet Med. 2013 Jul;15(7):565-74.

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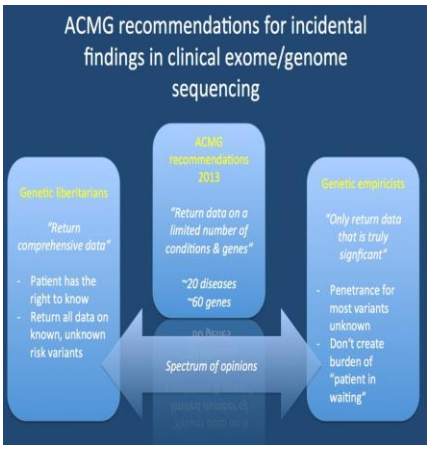
Issues with Genome Sequencing

- Pathogenic findings
- Incidental findings
- Laboratory
  - Point mutations
  - Small insertions/deletions
- VUS



Green RC, et al: Genet Med. 2013 Jul;15(7):565-74.

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Variants of Uncertain Significance (VUS)

- Evaluate in context of family history
- Test other family members
- Review literature relative to gene function

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Direct to Consumer Testing

- Traits
- Carrier screening
- Wellness
- Ancestry
  - Validated
  - FDA approved
  - Exploring pharmacogenomics

- Interpretome
- GeneticGenie
- Promethease

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MTHFR

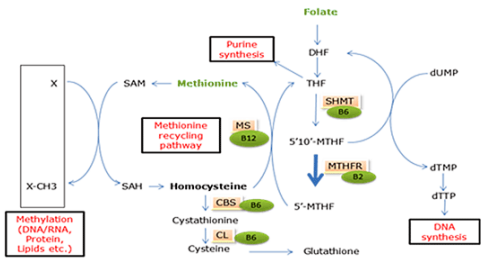
Two common polymorphisms

c.665C>T (C677T)

>25% Hispanics

10-15% Caucasians

c.1286A>C



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MTHFR

- Do not order genotyping
- If known homozygote, fasting homocysteine
- If homocysteine is normal, reassure
- If elevated, suggest a multivitamin

Hickey SE, et al. ACMG practice guideline: lack of evidence for MTHFR polymorphism testing. Gen Med 15:153-156, 2013

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Question

Chromosomal microarrays have obviated the need to do chromosome testing

- True
- False

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Question

Whole exome sequencing can detect triplet repeat and methylation abnormalities

- True
- False

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Thank You!

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