What new in genetics and internal medicine ?

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Everything is genetic

Genetics in internal medicine ward

- 22/3/2022 - 15 new admissions
  - Woman with PCD with mutations (AR)
  - Breast and ovarian cancer in a woman
  - Multiple organs- hearing loss, short stature, MR and family history - highly suspected to be mitochondrial
  - Woman with vestibular schwannoma and meningioma
- In ward:
  - Hereditary multiple osteochondromas (HMO) in a young woman (AD)
  - Brain AVM in a young woman
  - Man with DCM

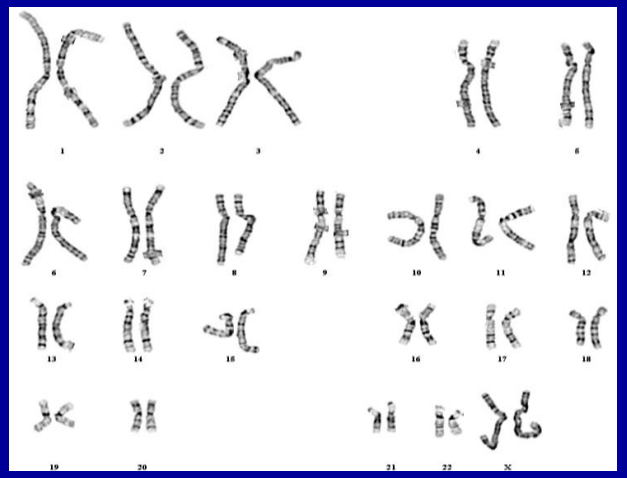
Ability to diagnose

- Phenotyping abilities improved (clinical, imaging, biopsies)
- More knowledge- Human genome project, Hap Map, mutation databases
- Bioinformatics
- Molecular understanding and targeting
- Numerous studies and development of technology for solving “common diseases”
- Collaborations between different disciplines

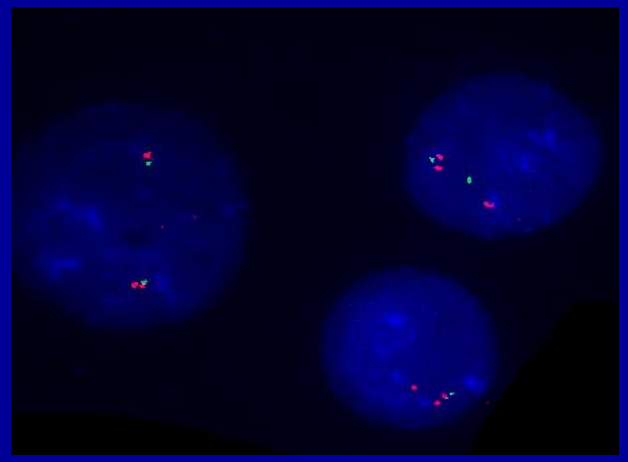
Genetics in internal medicine ward

- So many patients based only on phenotype
- Soon everyone will have their full genotype
  - Exome- prenatal or postnatal
  - Genome
  - Copy number variation
- Many tests covered by HMO – even for healthy individuals (BRCA carrier)

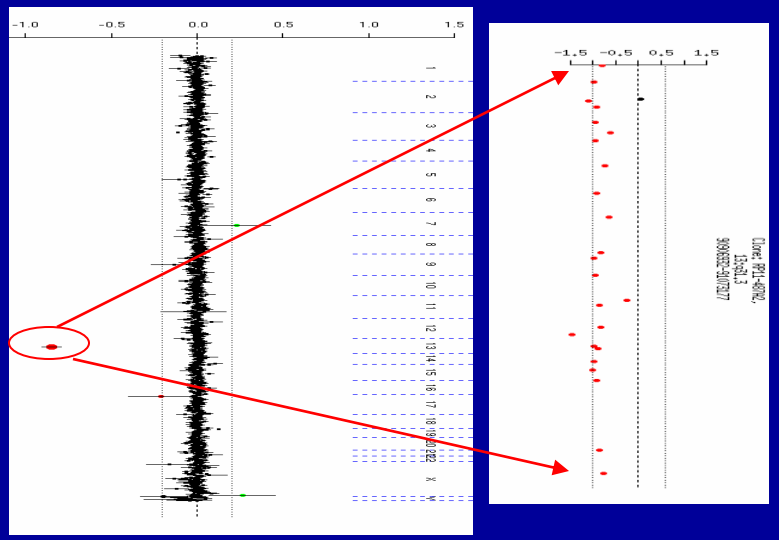
Genomic resolution 1 base pair (bp) to 10 megabase (Mb)



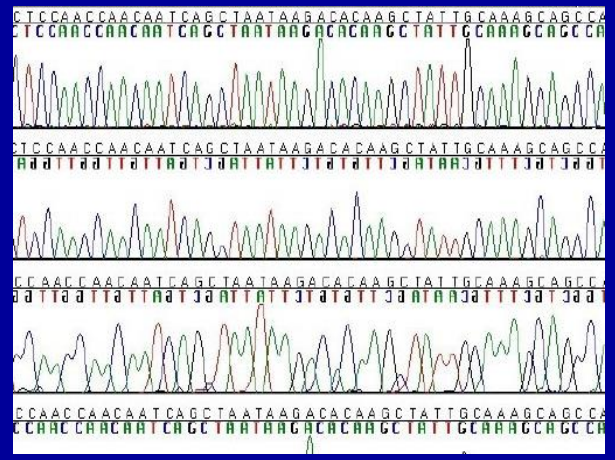
G banding > 4 Mb



FISH 40 to 250 kb /clone

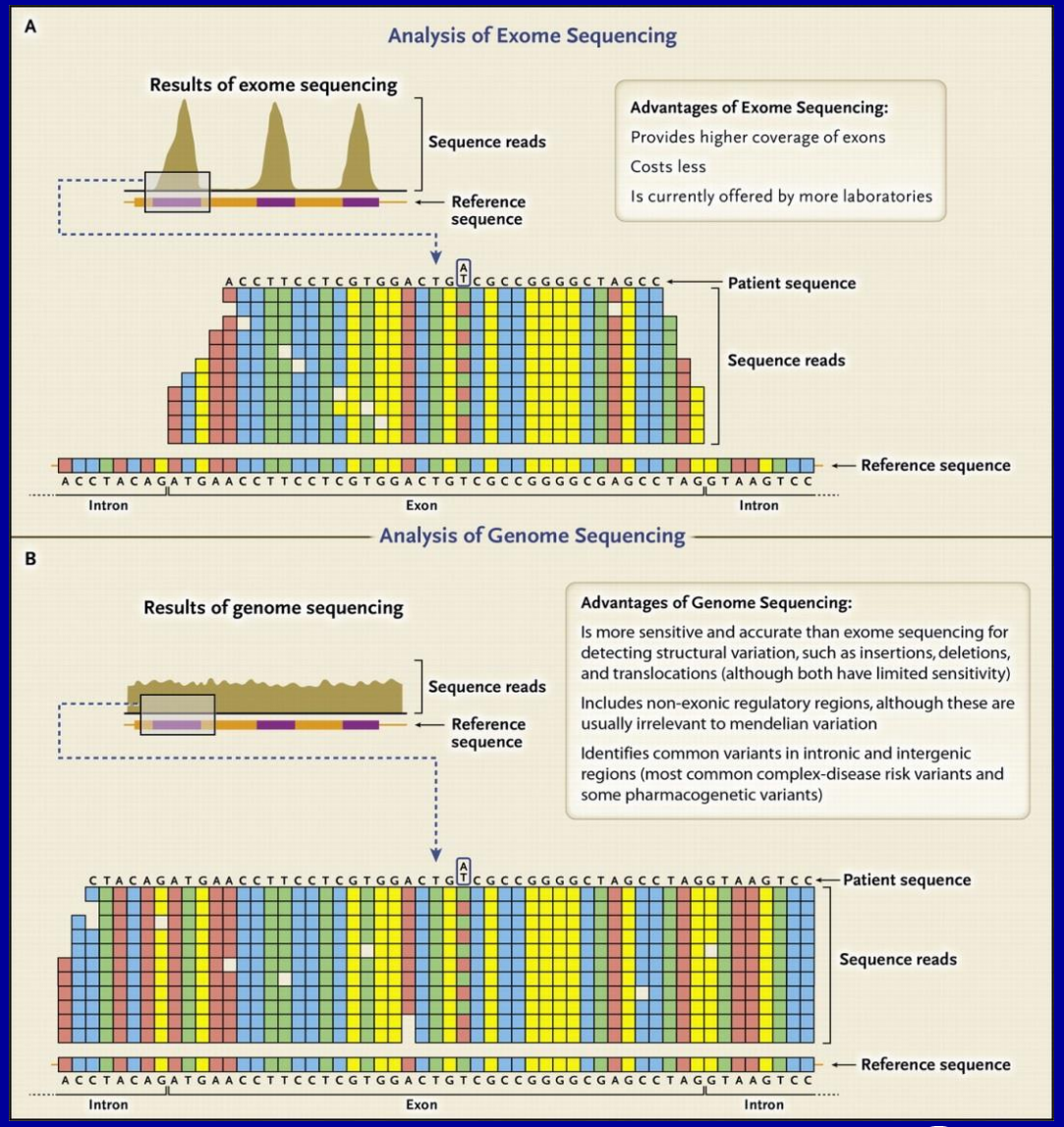


CMA 1-250 kb



DNA sequence [1 bp]

Schematic Comparison of Exome and Genome Sequencing.



Biesecker LG, Green RC. N Engl J Med 2014;370:2418-2425.

The NEW ENGLAND JOURNAL of MEDICINE

Genetic testing

- Different tests available – need to choose
- Implications for follow up and limitations
- Treatment implications
- Insurance and “life planning”
- Implications for family members
- Implication for family planning

אז איך משלבים בין סוסים לזברות?

- מרבית החולים המאושפזים בפנימית- חולים עם מחלות נפוצות עם ביטוי "קלסי"
- מרבית המחלות עם תורשה "מנדלית", ואפילו אלו המתבטאות בגילאים מבוגרים, הן נדירות.
- חלק מהחולים ששוכבים בפנימית סובלים ממחלה גנטית מנדלית- רק צריך להסתכל...
- לרוב המחלות ה"פנימיות" הקלסיות- יש בסיס גנטי משמעותי- למרות שכיום עדין קשה לאתרו.

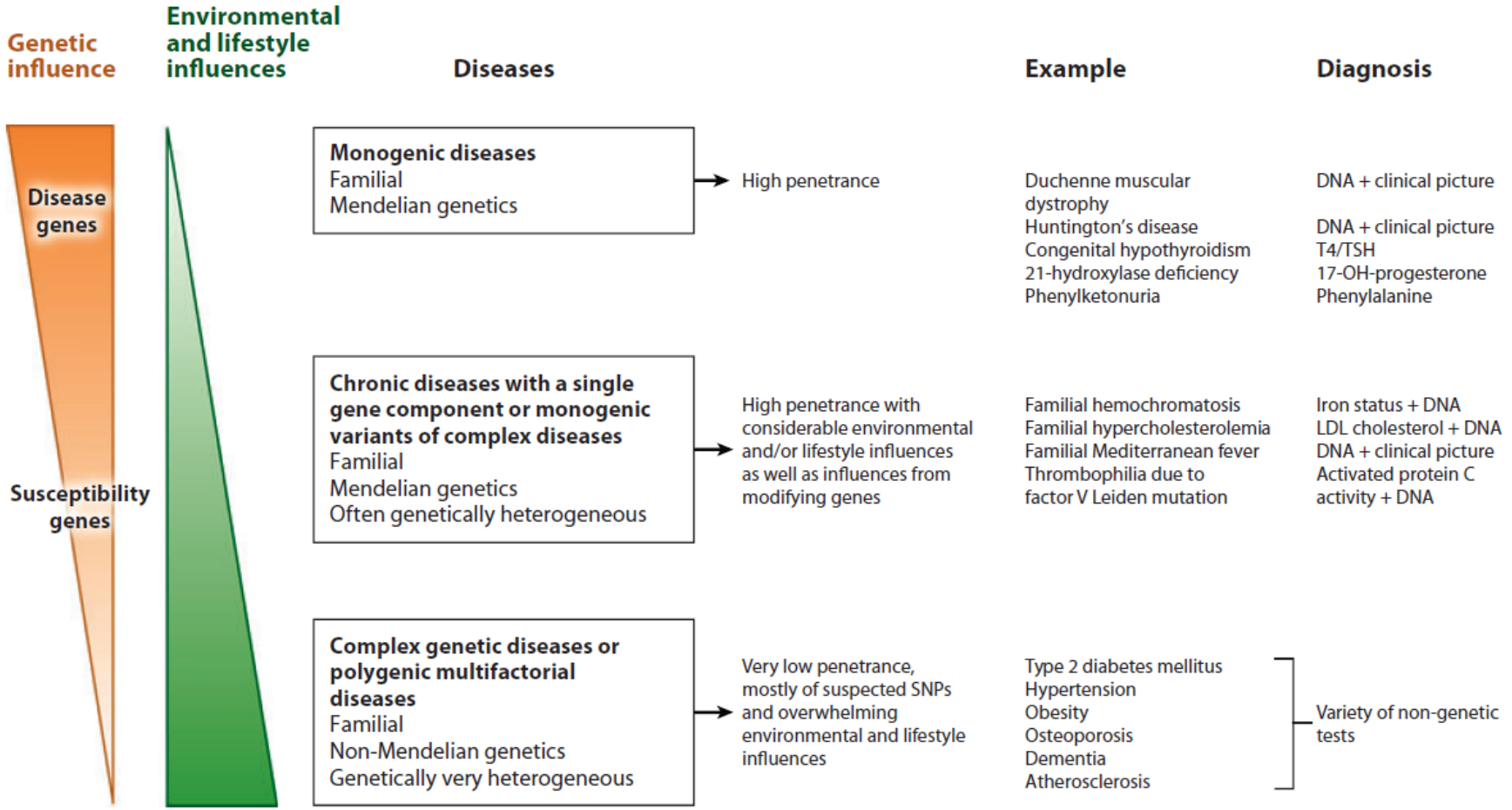


Figure 1

A classification of hereditary diseases.

Genetic Testing in Clinical Practice Lamberts and Uitterlinden. Annu. Rev. Med. 2009.

בקליניקה

- בדיקות סקר גנטי
- אבחון טרום לידתי
- מומים מולדים
- בעיות התפתחותיות
- מחלות אגירה
- מחלות גנטיות במבוגרים
- מחלות שכיחות
- גידולים
- פרמקוגנטיקה

Genetics

- Monogenic autosomal dominant
- Most have variable expression
- Most have reduced penetrance
- Causes harder interpretation and identification of the genes

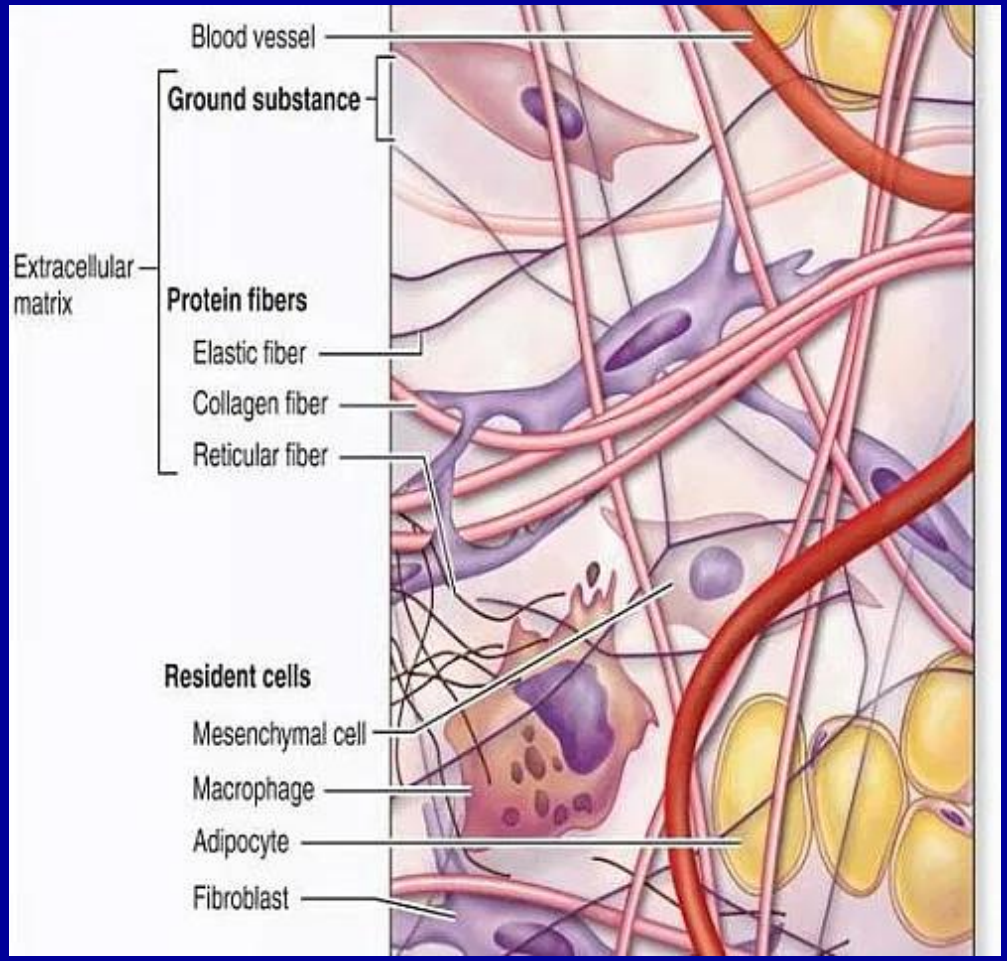
Family history

- Very important tool.
- ~20 minutes.
- Still problematic in data recording
- Ethnic background critical
- Consanguineous families
- Negative family history- *de novo*, no information (secrets and lies), small families, non paternity etc.

Aortic dilatation syndromes

- Many patients referred for evaluation of Thoracic Aortic Dilatation with or without other signs and symptoms
- Significant clinical implications- early and preventive treatment can prevent death
- Too early or misdiagnosis can impose unnecessary restrictions and stigmatize
- Many referred before the age of 18- especially before the army

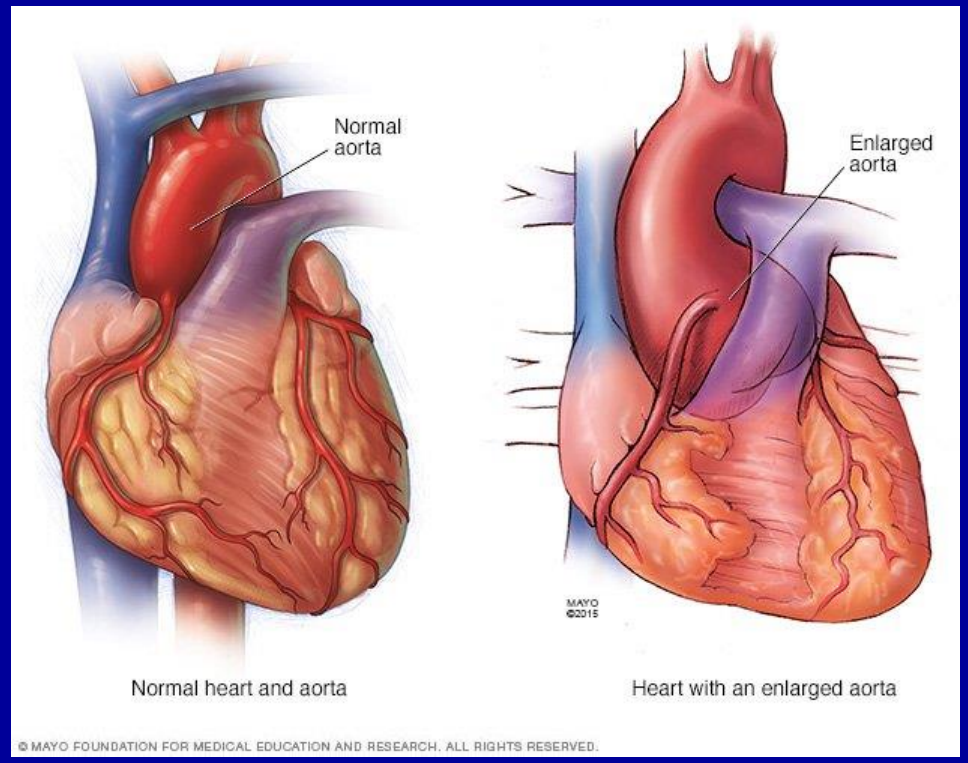
Connective tissue



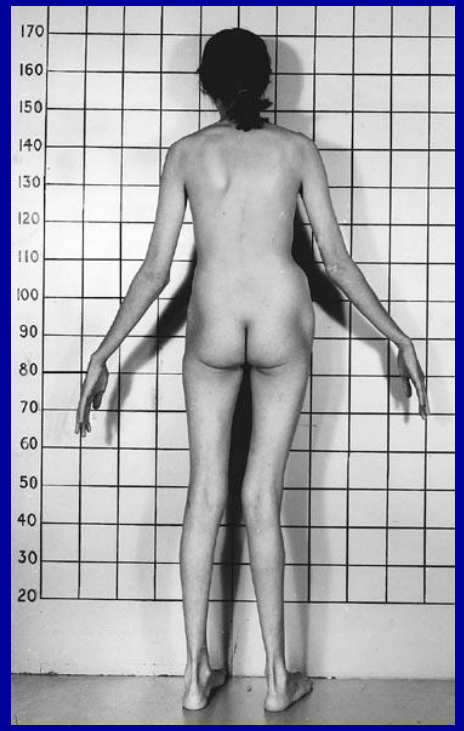
https://www.jotscroll.com/forums/11/posts/184/connective-tissue-types-structure-cells-location-functions-examples.html

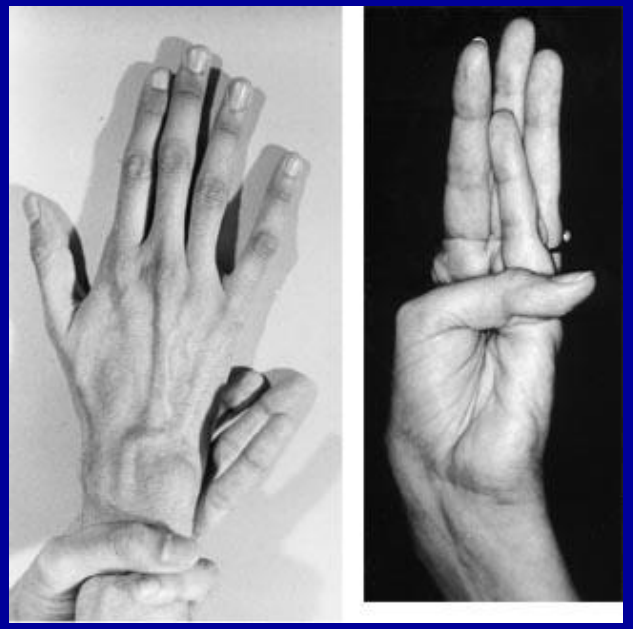
Organs affected by abnormal connective tissue

- Blood vessels- mostly large and medium sized
- Heart- mainly valves
- Eyes- myopia, lens dislocation, retinal detachment
- Skeletal – tall, long limbs and fingers, thorax
- Lungs
- Hollow organs – intestine, uterus etc

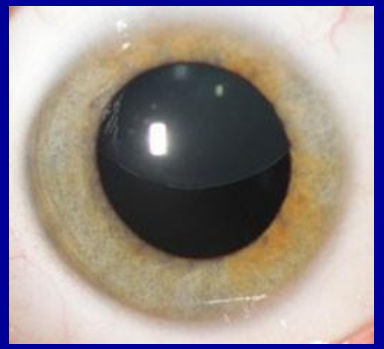


Mayoproceedings on Twitter





MMBID



https://aapos.org/glossary/marfan-syndrome

Genetic diagnosis

- Differentiation can be hard
- Evaluate for signs and symptoms in specific for each condition
- Cost of testing $600-1500 per gene
- Same as for panel or even exome or genome
- Rarer copy number variations in the genes (mostly deletions)

Gene panels

- Different panels and coverage
- Experience in sequencing and interpretation – many repeating motifs in the genes
- Cost – private companies and public health coverage
- Genes- *ACTA2, BGN, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, FOXE3, LOX, LTBP3, MAT2A, MFAP5, MED12, MYH11, MYLK, NOTCH1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, TGFBR2*

Sudden cardiac death

- Fatal or near fatal
- Decisions on AICD or medical therapy
- Prevent recurrence in individual or family members
- Collaboration with pathologists and cardiologists

Onco-genetics

- Suspect when:
  - A tumor at a younger age than common
  - Multiple tumors in same individual
  - Ovarian cancer
  - Family history of similar tumors
- Important to test the affected individual or at least extract DNA
- Might have implications for the treatment and relatives at risk

Pharmacogenetics

- Different effect of medications
- Different doses
- Different side effects
- Interaction between medications

Pharmacogenetics

- 50% of individuals with the HLA-B∗5701 gene variant (5.8% of the Caucasian population), and virtually none without it, will have a hypersensitivity reaction to abacavir
- Warfarin and *CYP2C9* and *VCOR*
- *TPMT* mutant for 6-mercaptopurine
- *UGT1A1∗28* for irinotecan
- *CYP2D6* mutants for tricyclic antidepressants
- *HLA-B∗1502* for carbamazepine

Personalized medicine

- Done all the time.
- Pharmacogenetic tailoring was done in the past (Malaria medication and G6PD)
- Genomic tailored personalized medicine is already here and will expand in the future.
- Need for more data.

Common diseases

- High frequency in general population
- Not a single disease
- Not a single gene
- Clear genetic impact/contribution. High heritability
- Previous technologies unsuccessful
- Hard to find the genetic basis
- New technologies

Common diseases

- Genome-wide association study of 14,000 cases of seven common diseases and
  3,000 shared controls. Published in Nature in 2007
- The Wellcome Trust Case Control Consortium
- British population, examined 2,000 individuals for each of 7 major diseases and a shared set of 3,000 controls.
- Case-control comparisons identified 24 independent association signals

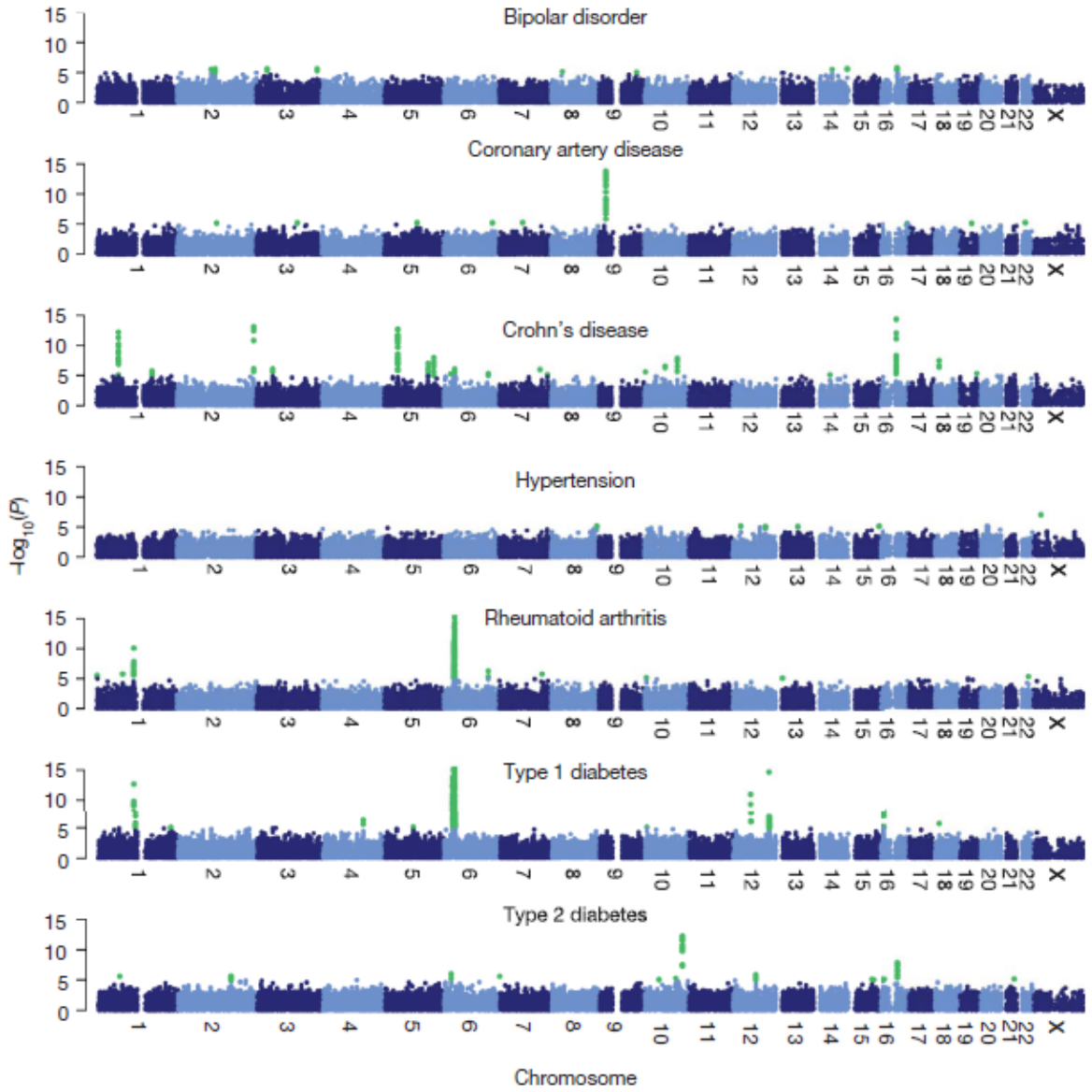


Figure 4 | Genome-wide scan for seven diseases. For each of seven diseases $-\log_{10}$ of the trend test P value for quality-control-positive SNPs, excluding those in each disease that were excluded for having poor clustering after visual inspection, are plotted against position on each chromosome. Chromosomes are shown in alternating colours for clarity, with P values $<1 \times 10^{-5}$ highlighted in green. All panels are truncated at $-\log_{10}(P\text{value}) = 15$, although some markers (for example, in the MHC in T1D and RA) exceed this significance threshold.

Resources

- Gene Reviews Gene Review
- OMIM OMIM - Online Mendelian Inheritance in Man
- Genetic Alliance http://www.geneticalliance.org/

I love INTERNAL MEDICINE

Thanks!

- Patients and families
- Colleagues
- You