Genomic Counseling
in the research setting

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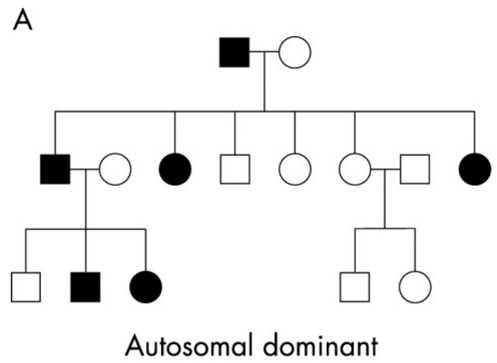
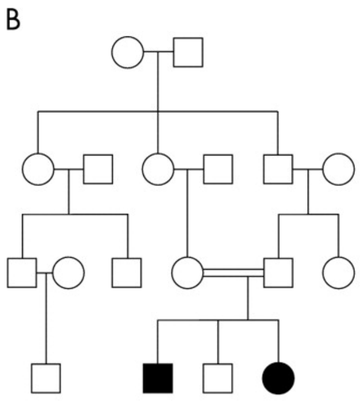
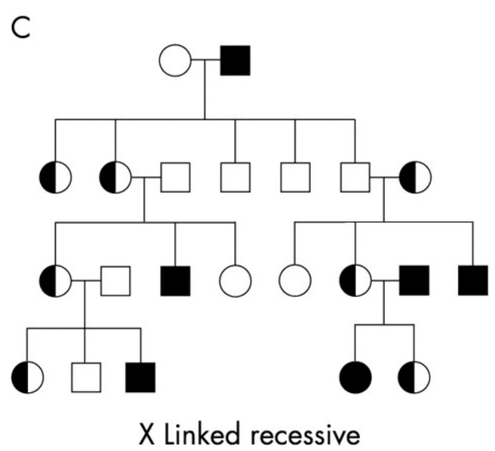
INSTITUTE FOR BIOTECHNOLOGY

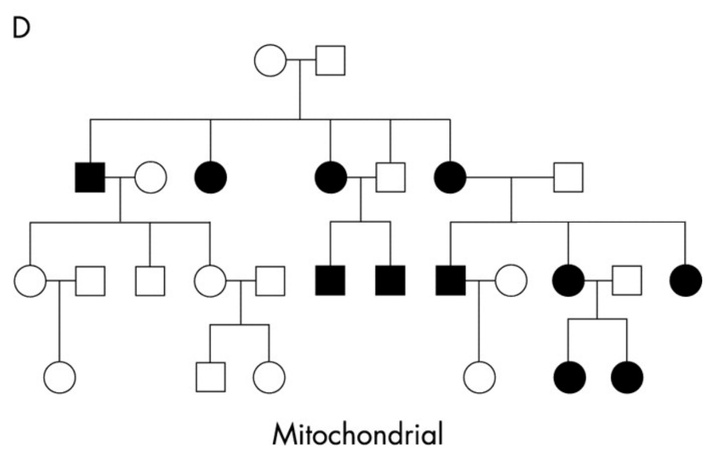
single gene disorders

- mutation in a single gene leads to disease
- often has characteristic family inheritance patterns



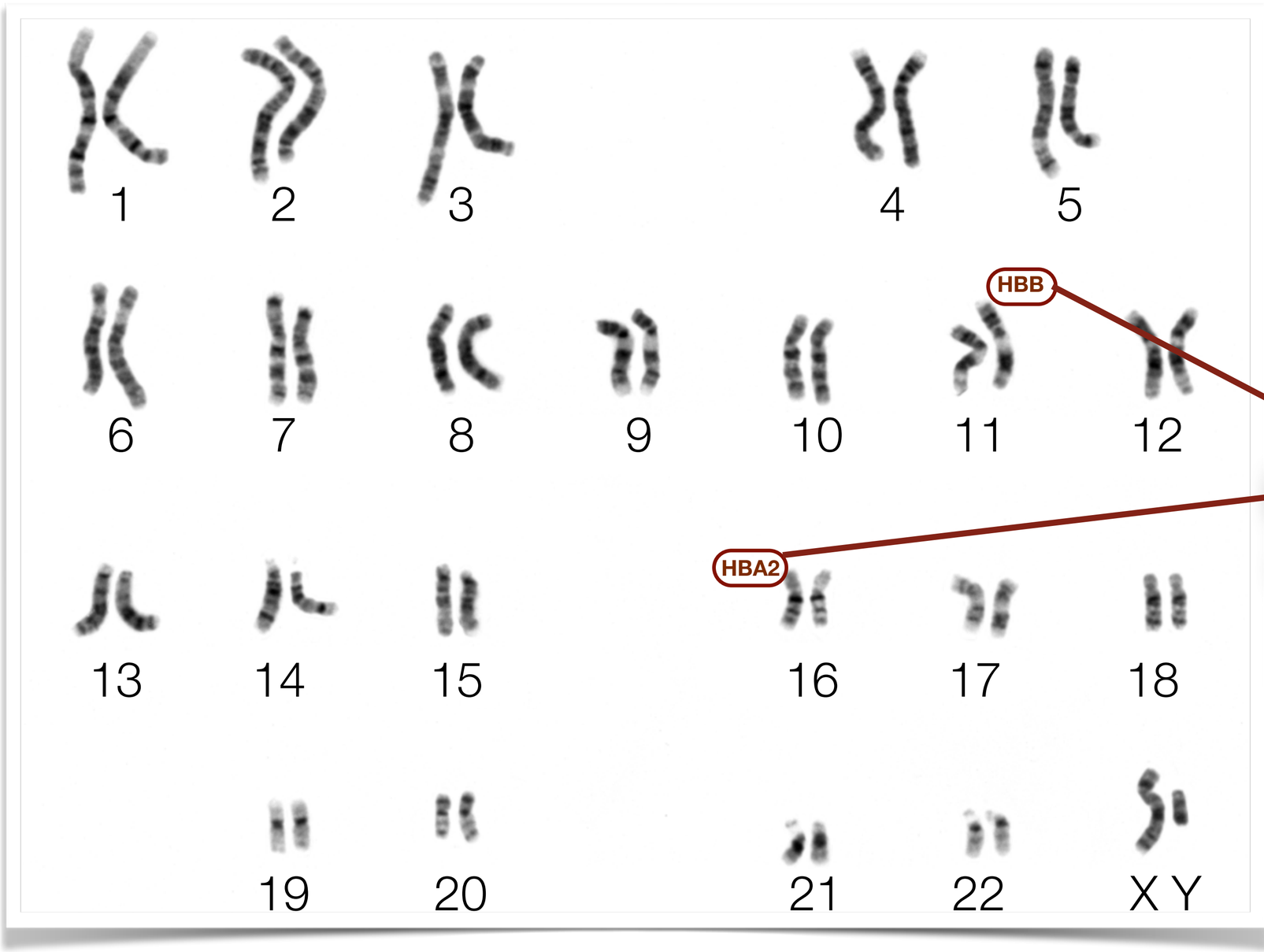


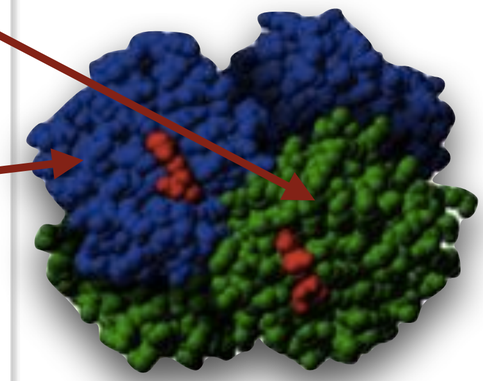




J Neurol Neurosurg Psychiatry 2002;**73**:ii5-ii11

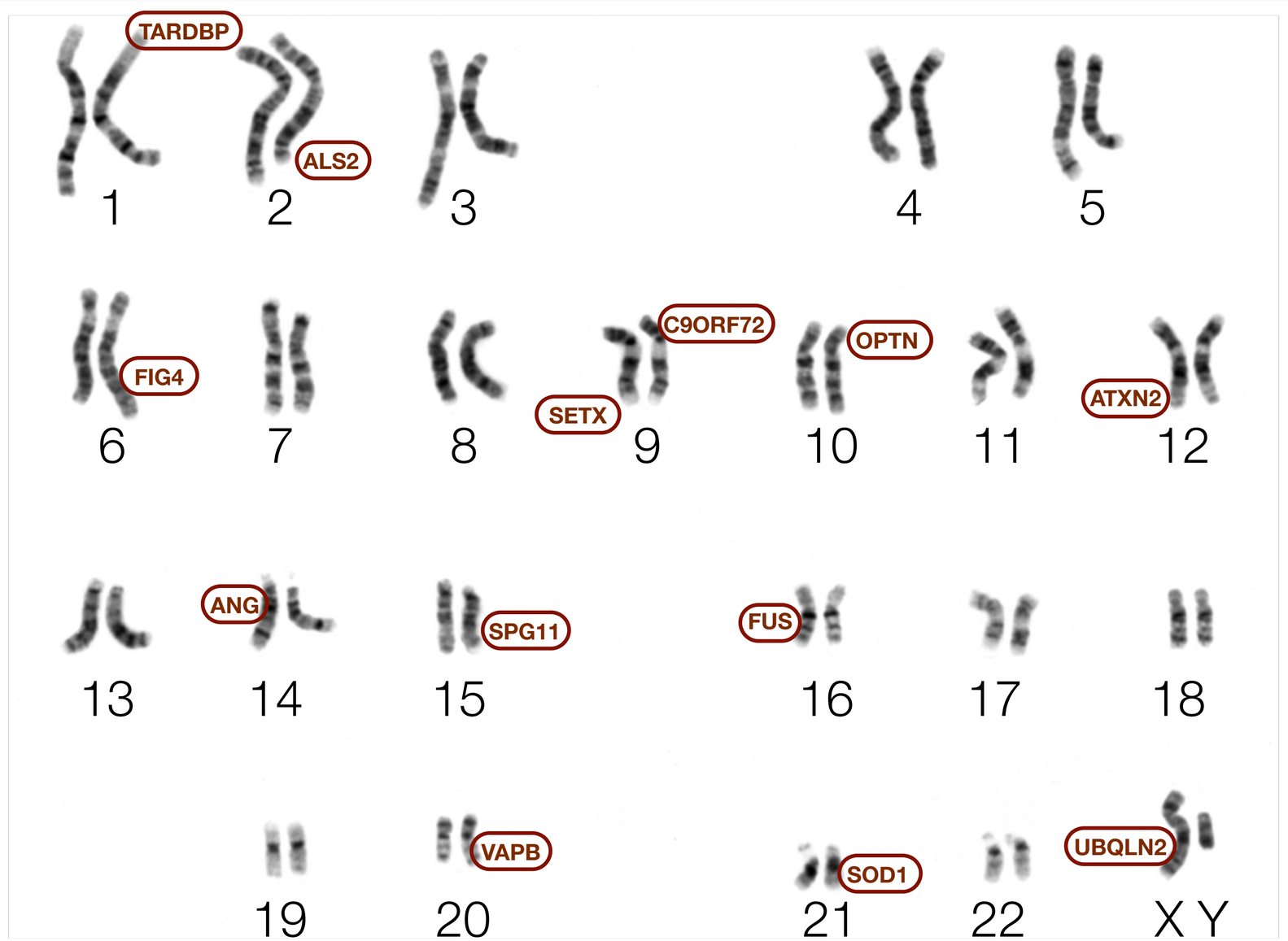
Genes that code for hemoglobin





http://www.genome.gov/glossary/resources/karyotype.pdf

Genes associated with ALS



http://www.genome.gov/glossary/resources/karyotype.pdf

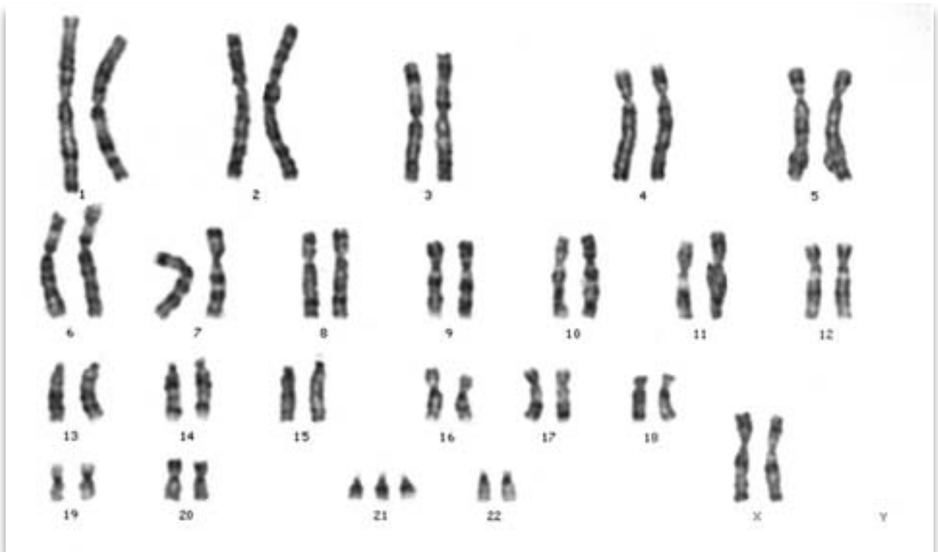
complex traits

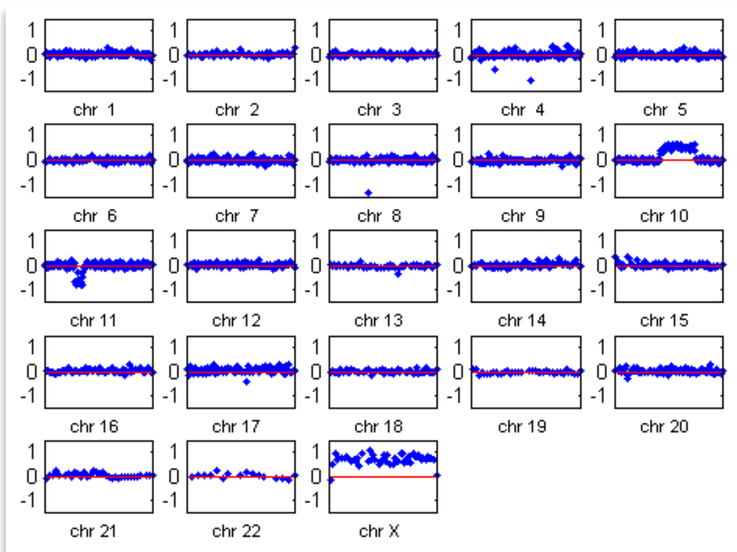
- most common traits and diseases have a complex etiology

- causative risks can include
  - genetic changes (both large and small scale)
  - environmental factors (head injury, nutrition, exposure to toxins)
  - societal factors (death of family member, abuse, hardships)

- in most cases - not triggered by a change in a single gene but rather by the interaction of several genetic, environmental and societal risks

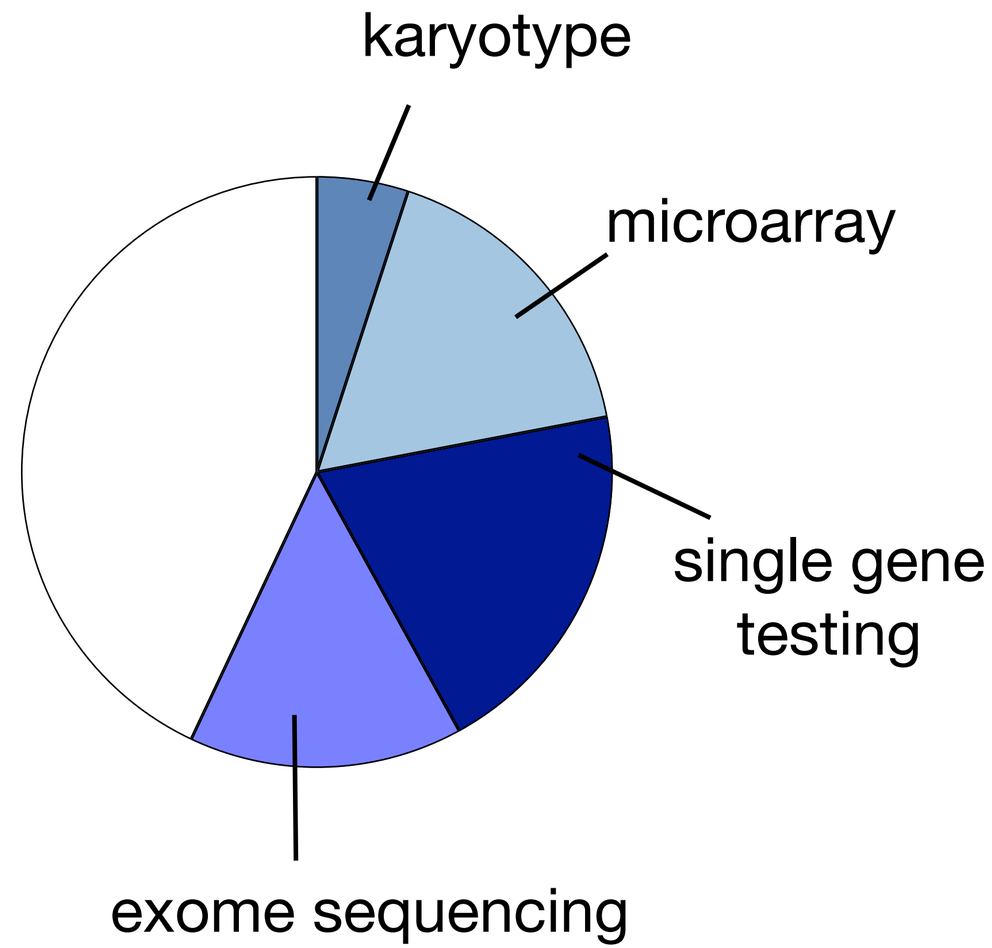
spectrum of human genetic conditions





CGTATACCGGGTCATGCACGTGTAGAGCGAGTTAGCTCGCTGGCTAAAGAGGGTCGAC
ATCCGCGAGTTTATGAGGAAGAATCGGCAGCTTGACCGAAGAGGCGTGGTAAGACCCG
TTAGGGATCGTATACCGGGTCATGCACGTGTAGAGCGAGTTAGCTCGCTGGCTAAAGA
GGGTCGACATCCGCGAGTTTATGAGGAAGAATCGGCAGCTTGACCGAAGAGGCGTGGT
AAGACCCGTTAGGGATCGTATACCGGGTCATGCACGTGTAGAGCGAGTTAGCTCGCTG
GCTAAAGAGGGTCGACATCCGCGAGTTTATGAGGAAGAATCGGCAGCTTGACCGAAGA
GGCGTGGTAAGACCCGTTAGGGATCGTATACCGGGTCATGCACGTGTAGAGCGAGTTA

in patients with a suspected genetic condition



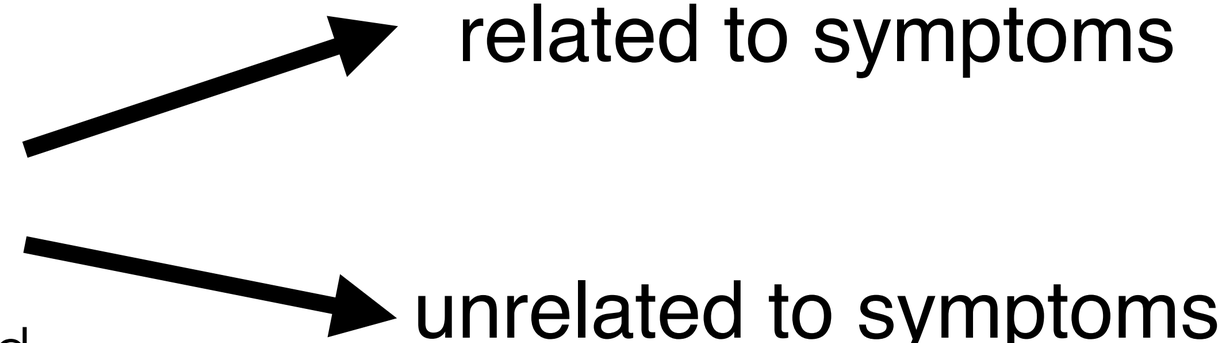
Sequence a single gene

Sequence many genes

Sequence all genes

next-generation genomic testing

- identifies variation across the genome
- wide range of possible results
- many variants cannot be understood



diagnostic odyssey

3-year-old Caucasian boy

complex set of medical symptoms with no known cause

- global developmental delay, hypotonia and epilepsy
- microcephaly and dysmorphic features, severe constipation and strabismus

Nathan

genome sequencing

next-generation sequencing of the entire genetic code

trio testing: Nathan and his healthy parents

revealed de novo mutation in TCF4 on 18q21.1

- R385X (1153C>T)

Nathan has a diagnosis of Pitt Hopkins syndrome

Pitt Hopkins syndrome

- moderate to severe ID/DD
- epilepsy
- breathing irregularities
- gastrointestinal problems
- ophthalmologic abnormalities
- microcephaly
- small hands and feet
- dysmorphic features
- often happy/excitable demeanor

Nathan

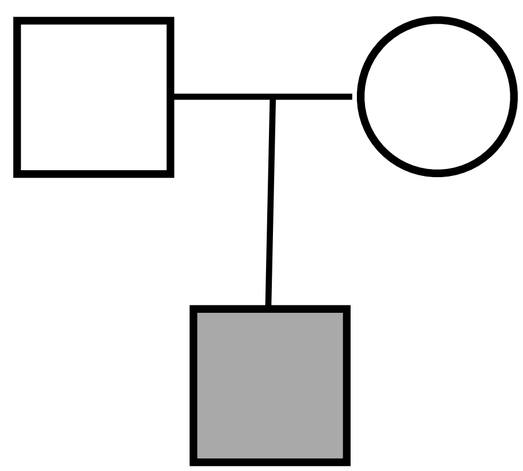
“positive for a pathogenic mutation”

now known to be a de novo (new) mutation event

recurrence risk is very low <1% for the parents to have another child with Pitt Hopkins

- not 0% because of the very small chance of gonadal mosaicism

recurrence risk for any children Nathan has in the future would be 50% (dominant condition)



Nathan

“positive for a pathogenic mutation”

family can be provided an answer, and the search for a diagnosis ends

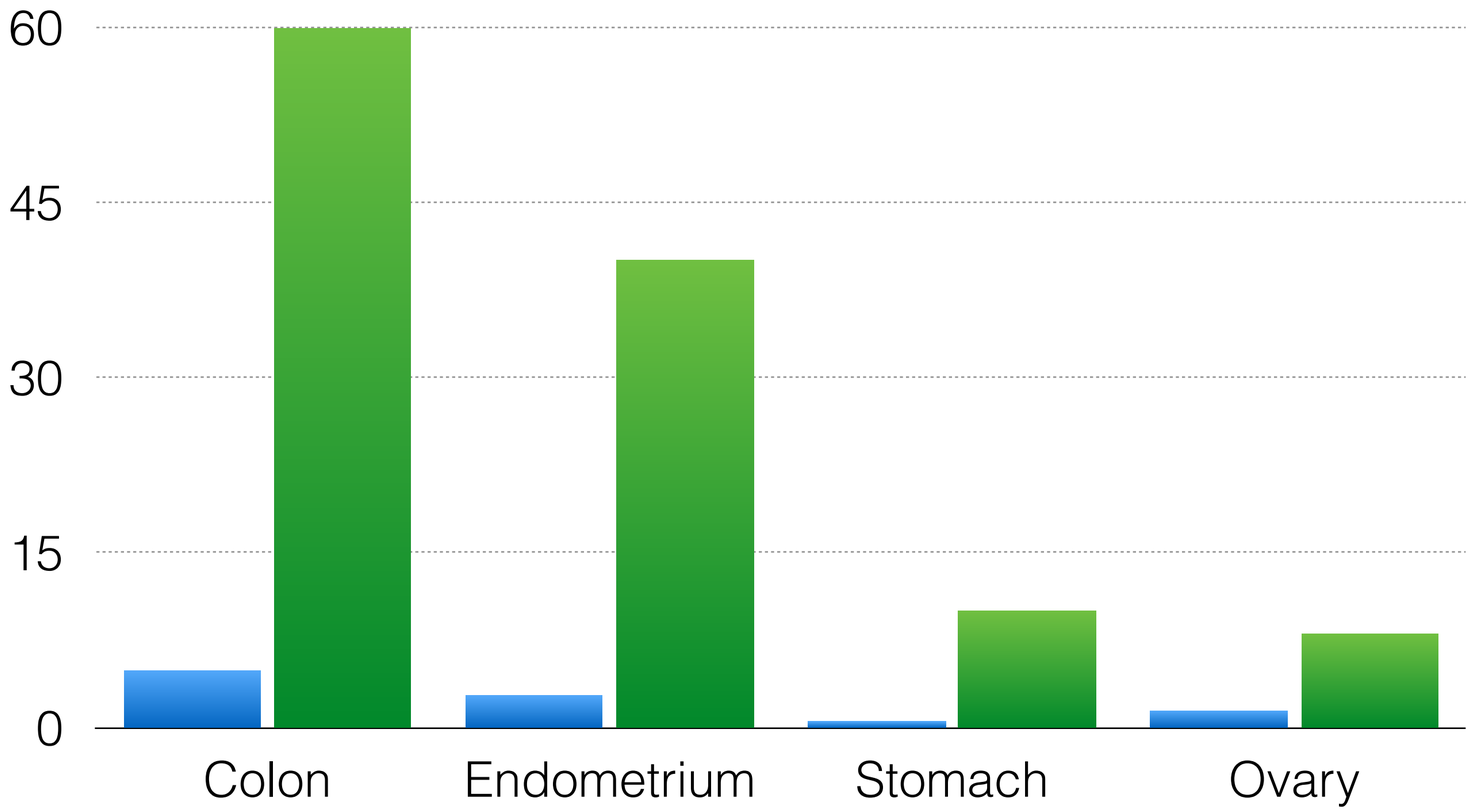
- common cause for a diverse set of symptoms
- clearer picture of what the future holds
- clearer picture of recurrence risk

diagnosis does not offer a cure or new therapeutic option

family can be plugged into support community

Nathan

oh and by the way, dad has an increased risk of colon cancer



MSH2 mutation associated with Hereditary Non Polyposis Colorectal Cancer

also increased risks of hepatobiliary tract, urinary tract, small bowel, brain and sebaceous neoplasms

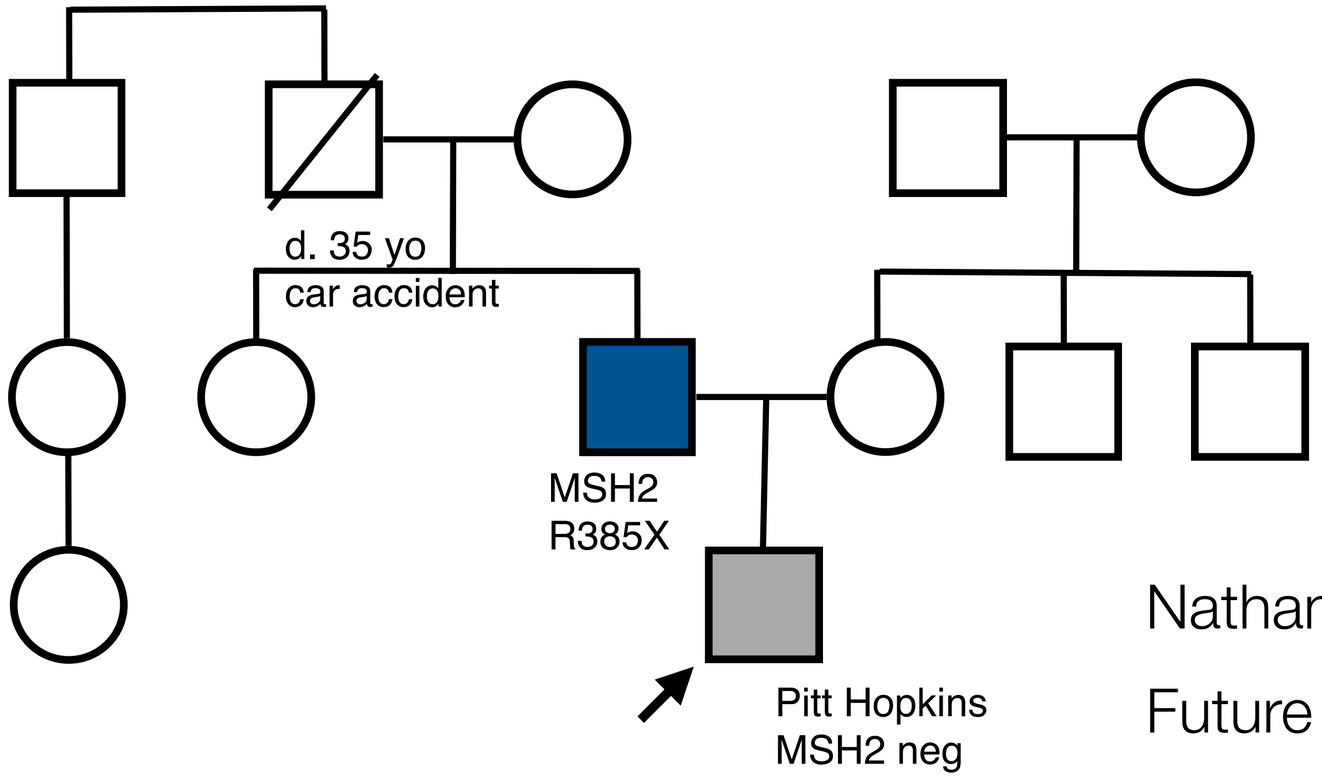
Hereditary Non Polyposis Colorectal Cancer Genereviews [Internet]

Nathan

oh and by the way….

dad should begin colonoscopies and continue every 1-2 years

share information with relatives who may pursue genetic testing for the known familial mutation



Nathan did not inherit this change

Future children at 50% risk

Nathan

informed consent

process by which the treating health care provider discloses appropriate information to a competent patient so that the patient may make a voluntary choice to accept or refuse treatment.
(Appelbaum, 2007)

informed consent for genome sequencing

Benefits

- contribution to scientific knowledge
- information on cause of condition
- information for reproductive decision-making
- possible implications for treatment decisions
- information on other disease risk

Risks

- blood draw risks
- emotional distress
- genetic discrimination
- possible identification
- possible inaccurate information

informed consent for genome sequencing

limitations

- not a perfect genetic test
- potential for unexpected and uncertain results
- results likely to not impact management or treatment options

impossible to describe every possible result that could be generated, important to capture the range of results and potential implications

categories of results

primary

secondary

- childhood onset medically actionable
- childhood onset non-medically actionable
- adult onset medically actionable
- adult onset non-medically actionable
- carrier status
- pharmacogenomics

lab or research protocol determines scope of results willing to be returned. patients/participants typically able to opt-out to receiving results

categories of results

primary

secondary

- cardiovascular disease
- cancer
- neurologic disease
- ....
- carrier status
- pharmacogenomics

lab or research protocol determines scope of results willing to be returned. patients/participants typically able to opt-out to receiving results

Below are some ways that genetic information could be helpful in the future. If this happens, how would you like your child's doctor to use the genetic information of you and your child?

I want my child's doctor, if possible, to use the genetic information to tell me about my...

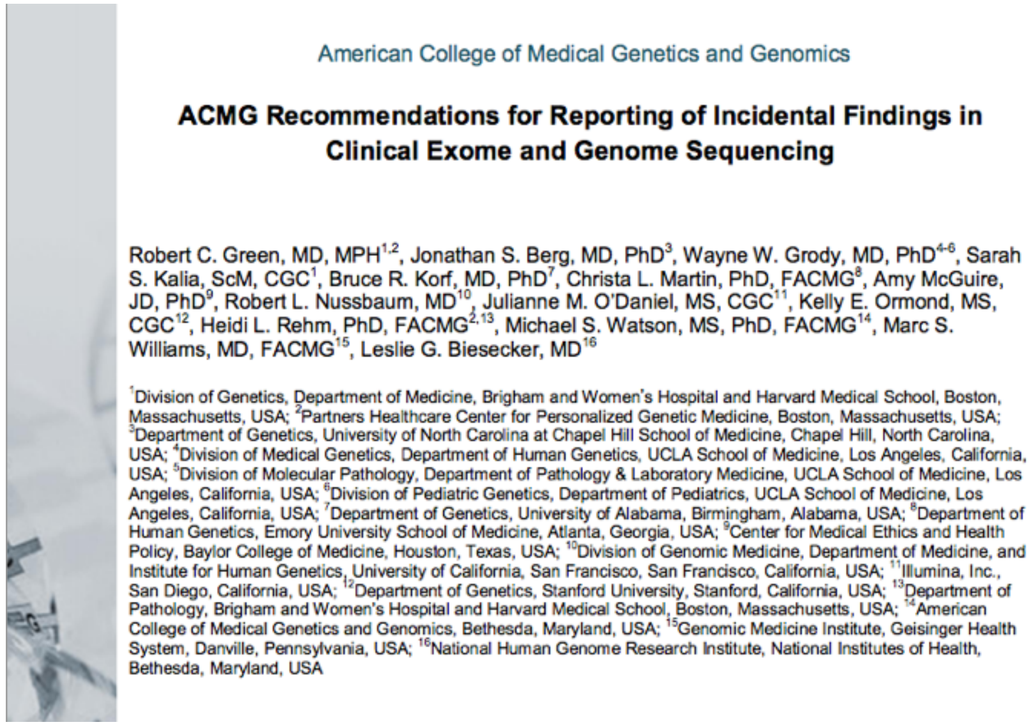
Chance of developing Obesity.	☐ Yes ☐ No ☐ Unsure
Chance of developing High Cholesterol or High Blood Pressure.	☐ Yes ☐ No ☐ Unsure
Chance of developing Diabetes.	☐ Yes ☐ No ☐ Unsure
Chance of having a Heart Attack, Heart Rhythm Problem, or Stroke.	☐ Yes ☐ No ☐ Unsure
Chance of getting Alzheimer's Disease.	☐ Yes ☐ No ☐ Unsure
Chance of getting Parkinson's Disease.	☐ Yes ☐ No ☐ Unsure
Chance of getting Bipolar Disorder, Schizophrenia, or other Mental Illnesses.	☐ Yes ☐ No ☐ Unsure
Chance of developing Breast or Ovarian Cancer (if you are a female).	☐ Yes ☐ No ☐ Unsure
Chance of developing Prostate or Testicular Cancer (if you are a male).	☐ Yes ☐ No ☐ Unsure
Chance of developing Colon, Lung, or other Cancers.	☐ Yes ☐ No ☐ Unsure
Chance of having a child with Sickle Cell Disease.	☐ Yes ☐ No ☐ Unsure
Chance of having a child with Cystic Fibrosis.	☐ Yes ☐ No ☐ Unsure
Chance of having a child with Muscular Dystrophy.	☐ Yes ☐ No ☐ Unsure
Chance of having a child with Autism	☐ Yes ☐ No ☐ Unsure

Genomic Results Patient Preferences Questionnaire

American College of Medical Genetics "56 Gene List"

List of highly penetrant, *medically actionable* genes that should be analyzed when doing exome/genome sequencing for any reason

- minimum list, additional genes can be added by laboratory
- reported regardless of age of patient



American College of Medical Genetics and Genomics

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4-6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[11], Kelly E. Ormond, MS, CGC[12], Heidi L. Rehm, PhD, FACMG[2,13], Michael S. Watson, MS, PhD, FACMG[14], Marc S. Williams, MD, FACMG[15], Leslie G. Biesecker, MD[16]

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Green, et al. ACMG, 2013.

Phenotype	Age of Onset	Gene(s)
Hereditary Breast and Ovarian Cancer	Adult	BRCA1, BRCA2
Li-Fraumeni syndrome	Child/Adult	TP53
Peutz-Jeghers syndrome	Child/Adult	STK11
Lynch syndrome	Adult	MLH1, MSH2, MSH6, PMS2
Familial Adenomatous Polyposis	Child	APC
MYH-Associated Polyposis	Adult	MUTYH
Von Hippel Lindau syndrome	Child/Adult	VHL
Multiple Endocrine Neoplasia Type 1	Child/Adult	MEN1
Multiple Endocrine Neoplasia Type 2	Child/Adult	RET
Familial Medullary Thyroid Cancer	Child/Adult	RET
PTEN Hamartoma Tumor syndrome	Child	PTEN
Retinoblastoma	Child	RB1
Hereditary Paraganglioma-Pheochromocytoma	Child/Adult	SDHD, SDHAF2, SDHC, SDHB
Tuberous Sclerosis Complex	Child	TSC1, TCS2
WT1-related Wilms Tumor	Child	WT1
Neurofibromatosis type 2	Child/Adult	NF2

Phenotype	Age of Onset	Gene(s)
EDS - Vascular Type	Child/Adult	COL3A1
Marfan syndrome, Loeys-Dietz syndrome and Familial Thoracic Aortic Aneurysms and Dissections	Child/Adult	FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11
Hypertrophic Cardiomyopathy, Dilated Cardiomyopathy	Child/Adult	MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA
Catecholaminergic polymorphic ventricular cardiomyopathy	Child/Adult	RYR2
Arrhythmogenic right ventricular cardiomyopathy	Child/Adult	PKP2, DSP, DSC2, TMEM43, DSG2
Romano-Ward Long QT syndromes, Brugada syndrome	Child/Adult	KCNQ1, KCNH2, SCN5A
Familial Hypercholesterolemia	Child	LDLR, APOB, PCSK9
Malignant Hyperthermia Susceptibility	Child/Adult	RYR1, CACNA1S

unexpected results

When sequencing an entire genome, there is a genome-worth number of possible results that could be identified

- future disease risk (cancer, heart disease, malignant hyperthermia)
- carrier status
- pharmacogenomics
- non-paternity
- consanguinity

Individual laboratories must determine how they will handle unexpected results

- what gets returned, do patients have a choice to opt-in or opt-out
- informed consent is key

misconceptions

“we have no family history, so it can’t be genetic”

“every other test has been negative, we know this one will be too”

“finally a test that will answer for once and for all whether this is genetic”

“if we identify the reason, then we will know how to treat it”

dealing with uncertainty

before a result report is generated the laboratory has to determine whether a variant is clinically relevant

There is lots of natural variation in a human genome

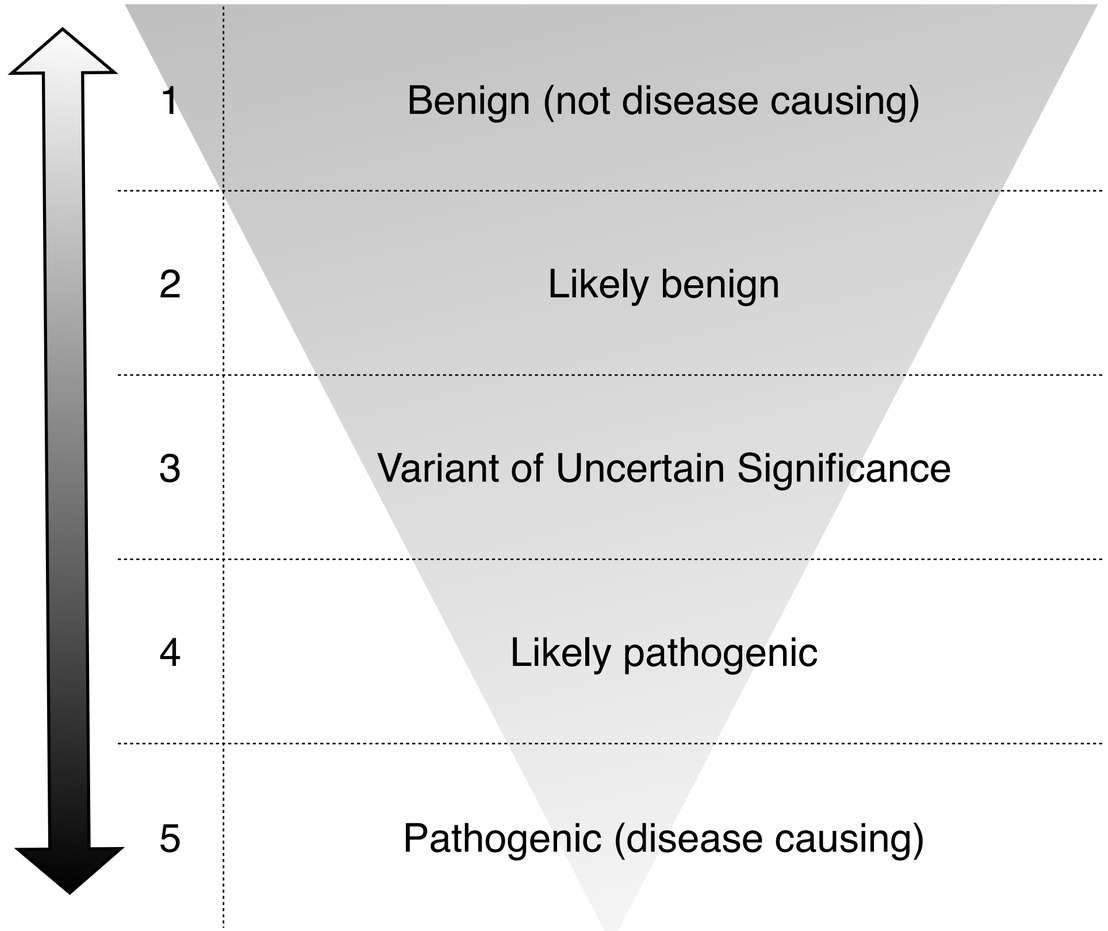
A minority of DNA changes actually cause human disease

Many changes are very rare and have never been observed before

most DNA changes have little or no clinical impact

many laboratories, including HudsonAlpha, score variants on a 5 point scale

- 1 = definitely not disease causing
- 5 = definitely disease causing
- 3 = we have no idea



evidence for pathogenicity

gene has been associated with patient's symptoms

specific variant has been seen in patients with similar symptoms

- and variant has not been seen in healthy populations

type of mutation expected to cause a loss of protein function

- nonsense or frameshift mutations
- computer models predict effect on protein

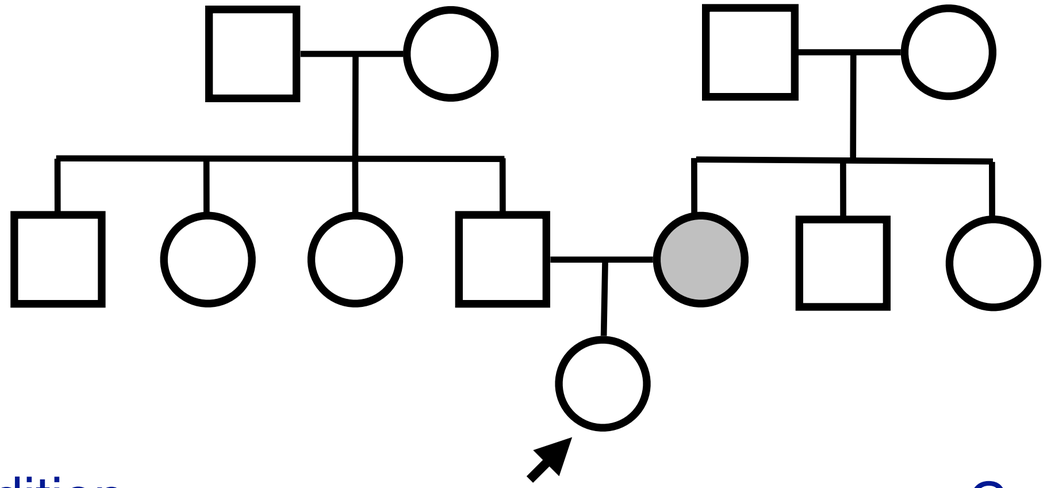
makes sense in light of the patient's family history

key components of a family health history

- three generations
- relationship to patient, gender
- current age or age (and cause) of death
- medical conditions and age at diagnosis
- ancestry/ethnicity
- **inclusion of affected AND unaffected relatives

family members share genetic information and often environment

knowing family health history information about an individual can help inform risk assessment



Dominant Mendelian condition, 50% risk

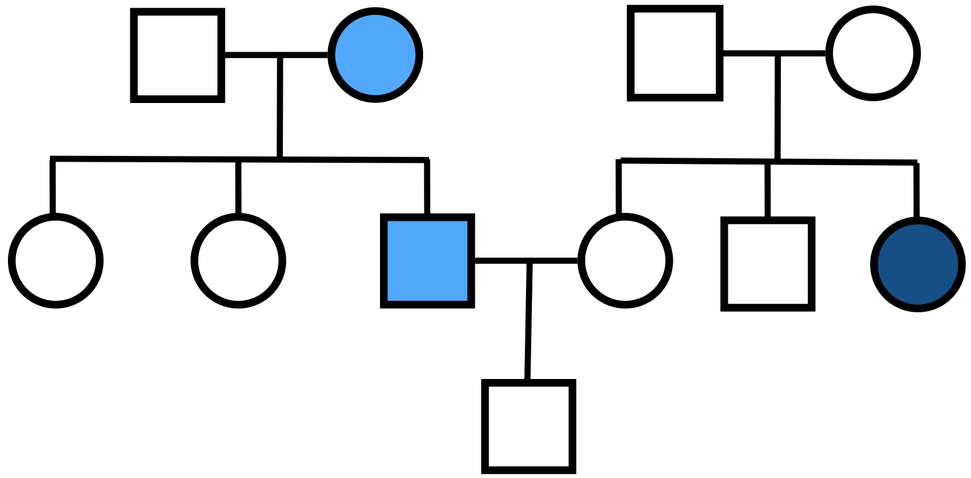
Crohn’s disease, ~5%

Russell & Satsangi. Epidemiology, 2008

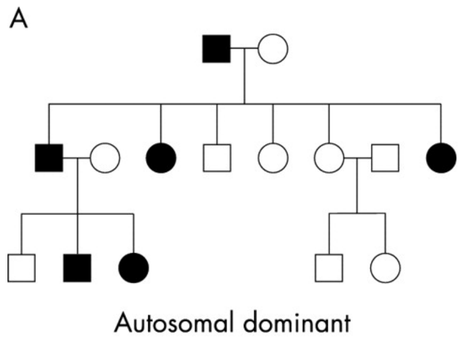
clinical pedigree

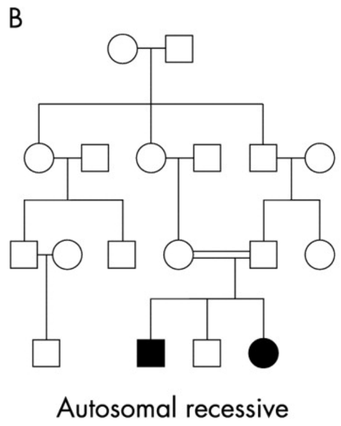
visual representation of family structure and disease

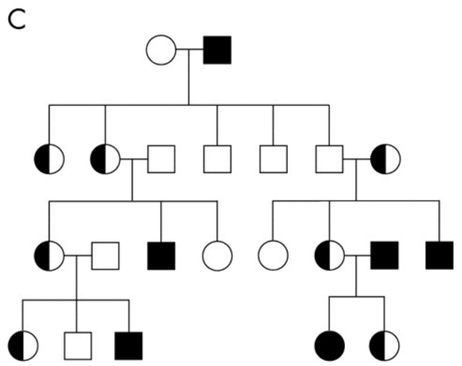
- standard symbols for universal readability
- visibly differentiate maternal and paternal lines and affected and unaffected relatives
- easily see the relatedness between individuals and strength of family history
- multiple conditions can be tracked using different colors/shading

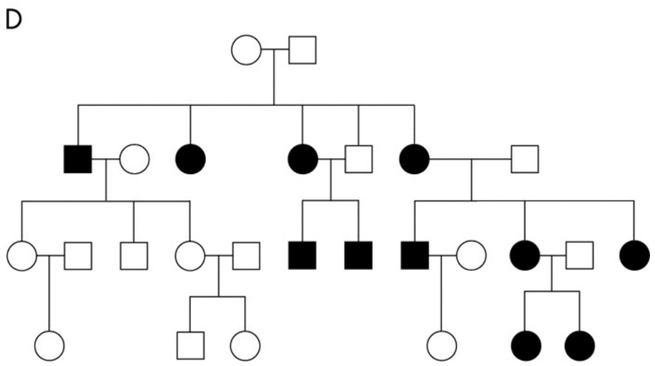


with a quick glance one can get a comprehensive picture of who is at risk and may benefit from genetic counseling, testing or medical management changes









for classic Mendelian (single-gene) conditions, pedigrees can help identify at risk family members and calculate numerical risks

J Neurol Neurosurg Psychiatry 2002;73:ii5-ii11

limitations of family history

only as good as the historian giving the information

- some patients have little or no information about their relatives health
- patients may choose to not disclose information because of cultural or personal reasons or misconceptions about genetics

takes time and skill to collect *and analyze*

- only useful if the information is interpreted

individual variants are scored and discussed

1	Benign (not disease causing)	no report
2	Likely benign	no report
3	Variant of Uncertain Significance	validate and report **primary only**
4	Likely pathogenic	validate and report primary and secondary
5	Pathogenic (disease causing)	validate and report primary and secondary

return of results

primary

positive

uncertain

negative

secondary

positive

~~uncertain~~

~~negative~~

positive for a pathogenic mutation

genetic variant that is the definite or likely cause for the reason for testing (primary) or potential future disease (secondary)

Based on mutation and inheritance pattern, may initiate a cascade of testing among family members

May or may not lead to changes in medical management

- many of the more common genetic conditions and susceptibility syndromes have established guidelines for management
- referral to a genetics specialist may be indicated if testing was done elsewhere

value of a genetic diagnosis

(Late Infantile) Batten Disease

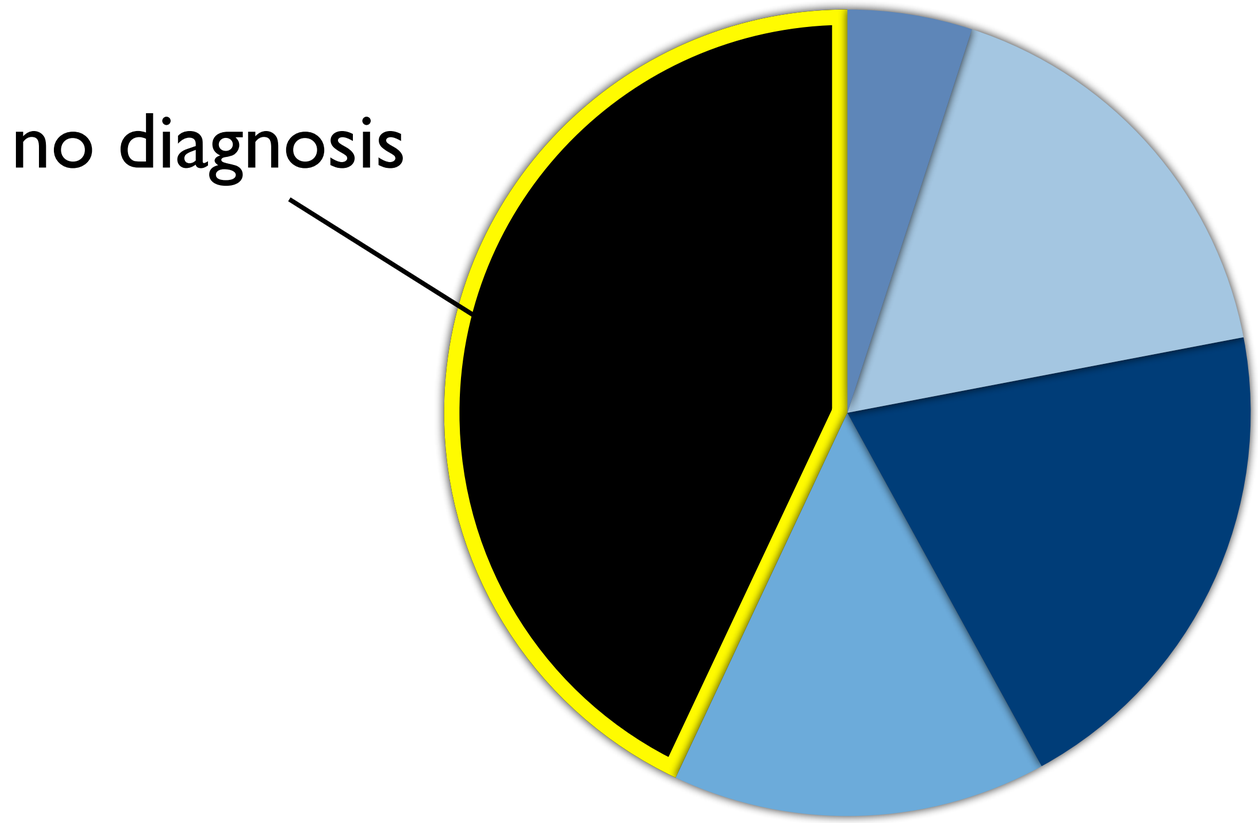
- Progressive neurodegenerative disorder
- Onset between ages 2 and 4
- Initial symptoms of loss of muscle coordination and seizures
- Rapid progression resulting in death between 8 and 12

“It’s not quite the result we were hoping for, but at the same time I’m very grateful that we do know. I don’t know how much longer we would have been searching...The not knowing is harder than knowing.”

-Jacob and Dylan’s mom

http://www.bio-itworld.com/2013/1/24/batten-disease-finding-ends-diagnostic-odyssey-california-family.html

in patients with a suspected genetic condition



sometimes a diagnosis does not provide lots of information…

atypical presentation of well known disorders

Mutation Spectrum in Patients With Rett Syndrome in the German Population: Evidence of Hot Spot Regions

F. Laccone,[1]* P. Huppke,[2] F. Hanefeld,[2] and M. Meins[1]
[1]*Institute of Human Genetics, Georg-August-University Göttingen, Göttingen, Germany*
[2]*Neuropediatric Department, School of Medicine, Georg-August-University Göttingen, Göttingen, Germany*

atypical Rett syndrome
unclear prognosis,
recurrence risk

new gene/phenotype associations

handling the inevitable VUS

VUS = “variant of uncertain significance”

Laboratory did not have enough data to determine whether variant is benign or pathogenic.

Clinically, should be treated like an uninformative result. Management dictated by personal and family history.

- request re-interpretation of the variant periodically by the testing laboratory
- some, but not all, clinical labs routinely try to reclassify VUS’s and automatically update reports

burden of re-analysis and re-interpretation by research laboratories?

true negative vs uninformative negative

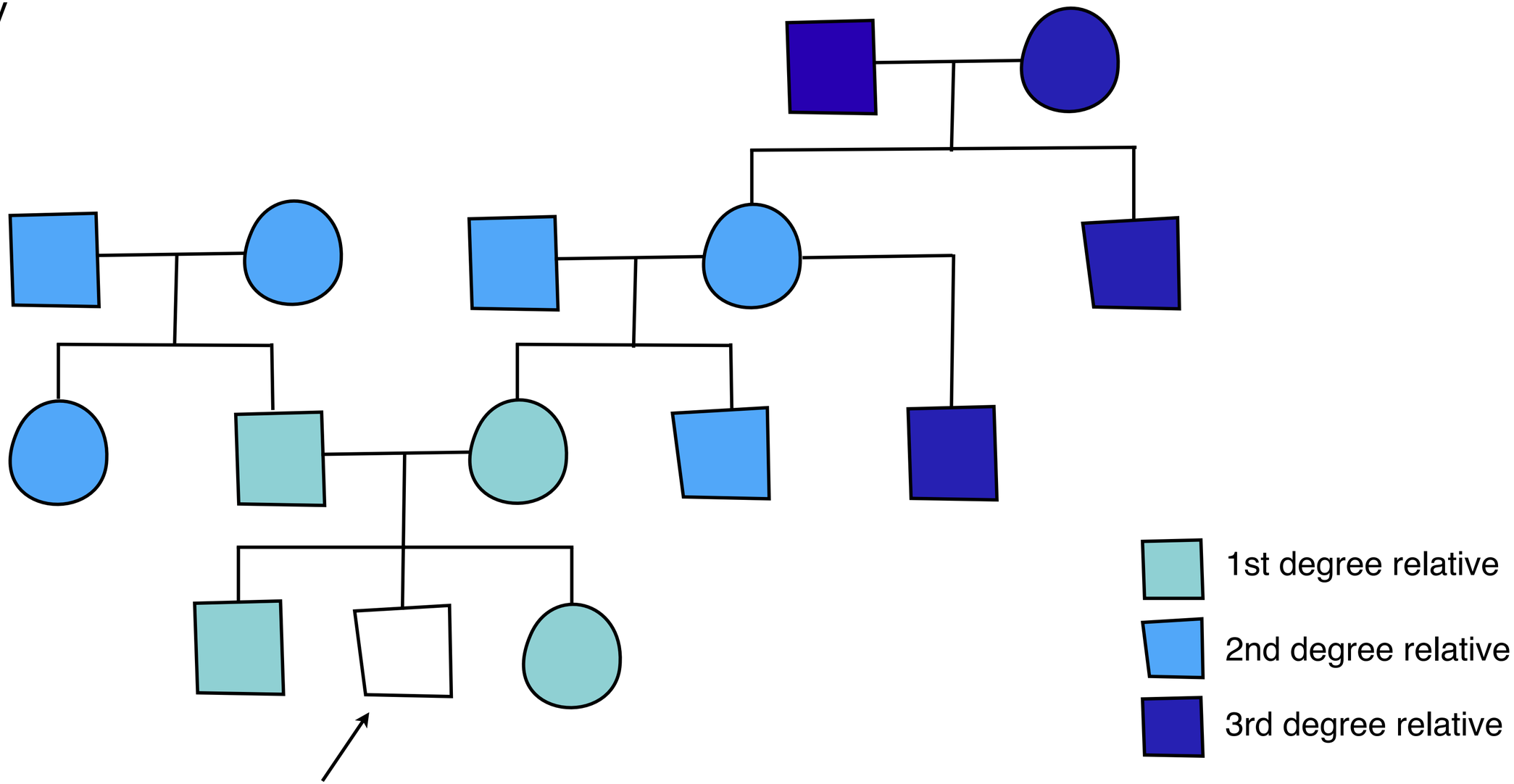
A negative genetic test result does not necessarily mean the patient does not have a condition or is not at risk for developing disease

A negative result in a family member where there is a known familial mutation is a true negative result. That individual does not have the risk factor causing disease in the family.

A negative result in an individual where a mutation has not been identified in the family, does not mean a genetic risk factor is not present.

- could be undetectable by current testing technologies

following an uninformative negative result, risk and management assessment should be made in light of medical and family history



population based empiric risk estimates

while not necessarily applicable to a specific person or family, empiric risk estimates from population studies can be helpful to estimate disease risk based on family history

Genetic Risk in Idiopathic Epilepsy	
Affected Individual	**Risk**
monozygotic twin	60%
dizygotic twin	10%
sibling (onset <10)	6%
parent	4%
parent and sib	10%

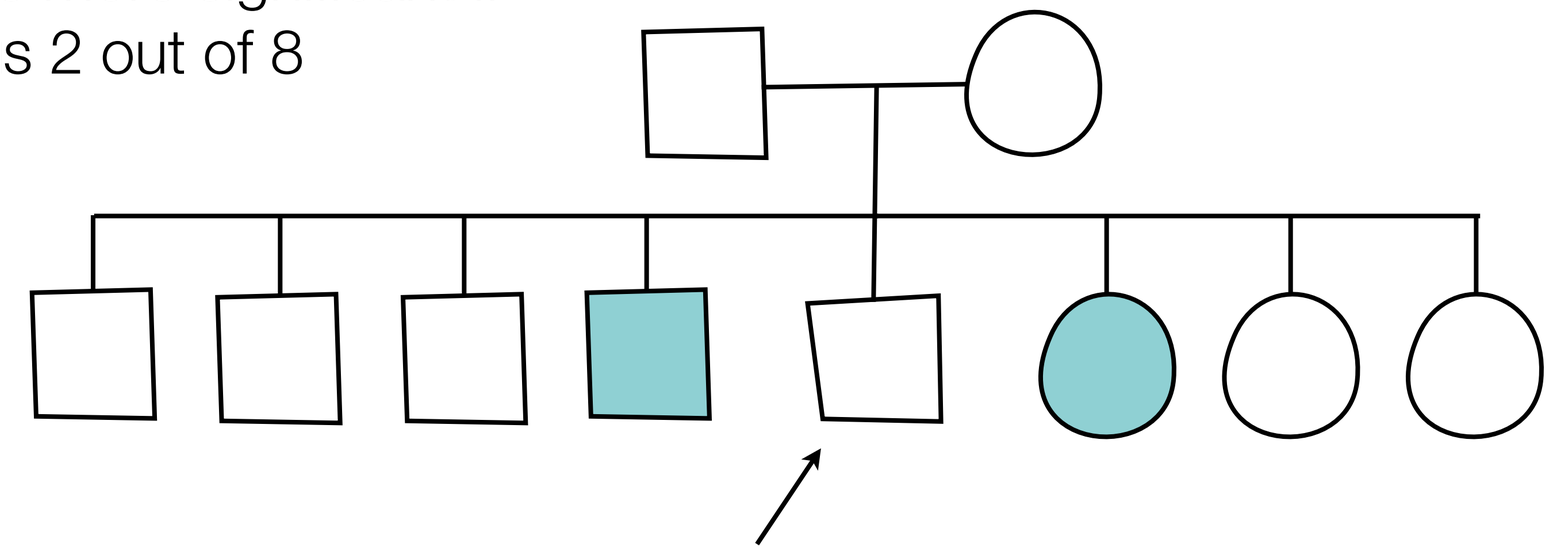
Genetic Risk in Schizophrenia	
Affected Individual	**Risk**
monozygotic twin	40%
dizygotic twin	10%
sibling	9%
parent	13%
parent and sib	15%

Harper. Practical Genetic Counselling, 6th Ed, 2004.

value of a negative family history

consider the number of unaffected family members

having 2 siblings with diabetes is more significant if they are your only siblings versus 2 out of 8



misconceptions

negative result: “now we know it is not genetic”

negative result: “whew, glad to know I don’t have any genetic risk factors”

VUS result: “genetic mutations have to be bad”

positive result: “can’t you just go in and fix the mutation?”

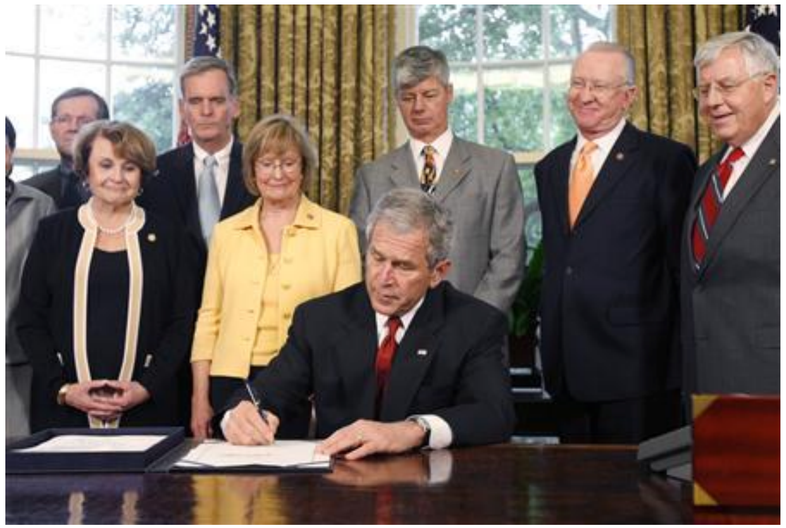
before results disclosure: “ok, tell me how I am going to die”

genetic discrimination

Genetic Information Nondiscrimination Act, 2008

Makes it illegal for genetic information (genetic test results, family history) to be used against you in the following arenas

- health insurance
- employment



Does not cover life, disability or long term care insurance

Does not apply if symptomatic

Credit: Reuters/Jason Reed, http://www.reuters.com/article/2008/05/21/us-genetics-bush-idUSN2143439320080521

testing minors for adult onset conditions

Hereditary cancer, heart disease, Huntington disease

Management changes (if available) do not start until adulthood

- historical position to not test minors for adult onset conditions
- this position is being challenged by large scale genome sequencing

Whose autonomy is respected: parental versus child

access to genome sequencing

most insurance companies do not currently provide reimbursement for exome/genome sequencing

- limiting access to these services to those who can afford to pay out of pocket or are able to participate in research based testing

Questions?