

Genetic Testing for the Older Child

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Outline

- Introduction to genetic consultation
- Why do genetic testing?
- Age-based challenges to genetic consultation
- What testing was done and why?
- Questions

Introduction to Genetic Consultation

- ACMG: The application of the principles of inheritance and our knowledge of human genes **to diagnose, prevent, and treat diseases and improve health.**
- ABMS: Clinical Geneticists focus on **clinical disorders that have a genetic basis.** The specialist is trained to evaluate individuals of all ages for hereditary conditions.

Elements of Genetic Consultation

1. Gathering and interpreting information
2. Risk assessment
3. Diagnosing/Testing
4. Education
5. Counseling
6. Management and care coordination

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Why do genetic consultation / testing? For the current care of the child

- Medical
 - Better / new ways to treat on-going issues
 - Expectant screening for later onset issues
- School
 - Diagnosis may point to which services may be most helpful
 - Validating need for IEP/services
 - Extending period of schooling as appropriate
- Psychological
 - Decreases blame/guilt for child's school challenges
 - Helps child understand their condition, why they need additional care/visits

Why do genetic consultation / testing? To end the diagnostic odyssey

- Why?
 - Gives a sense of calm, knowledge, and closure to child/family
- Access
 - Patient & family support groups / foundations / resources
 - Research opportunities
- Reassessment
 - New medical conditions / findings may point to new differential
 - New conditions identified over time
 - New tests become available over time
 - Insurance coverage may have become available since last visit
 - Uncertain variants may be reclassified

Why do genetic consultation / testing? To allow for testing of relatives

- Personal health of relatives
 - Other family members may have similar symptoms and unknown etiology
 - Identifying an etiology allows for a clear diagnosis/exclusion in others
- Reproductive counseling
 - Families may want to understand their chances of having a similarly affected child
 - As some conditions are *de novo*/new to child, may be <1% chance of another affected child
 - 50% chance if also in a parent/dominant
 - 25% chance if recessive and same parent couple
 - 25% chance if XL
 - Reproductive options are available if desired

Age-based challenges to genetic consultation

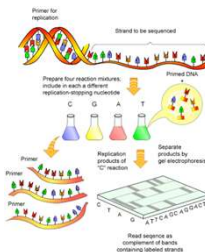
- Who is the patient?
- Consent
 - Engage children at the developmental age of 7-8+ in consent/assent
 - Helps child understand why genetic testing is helpful and how results may change their future care
- Age-appropriate information:
 - Challenges in explaining/providing an etiology for child's medical/cognitive differences
 - Avoid stigmatizing or placing limits on successes
 - Additional medical issues may need to be looked for-often presented as "we are just checking to make sure you are healthy" rather than details about what could be found
 - Balancing needs of the child and parents
 - Reassurance regarding uncertain results

Genetic Information Non-discrimination Act (GINA)

- GINA
 - Children are often unable to understand the implications of GINA
 - Only protects against medical insurance and employment discrimination
 - High risk for future medical issues may affect access to life insurance and long-term care
 - If already affected with multiple medical issues, cognitive challenges, implications on life insurance and long-term care may not be relevant

What testing was done and why?

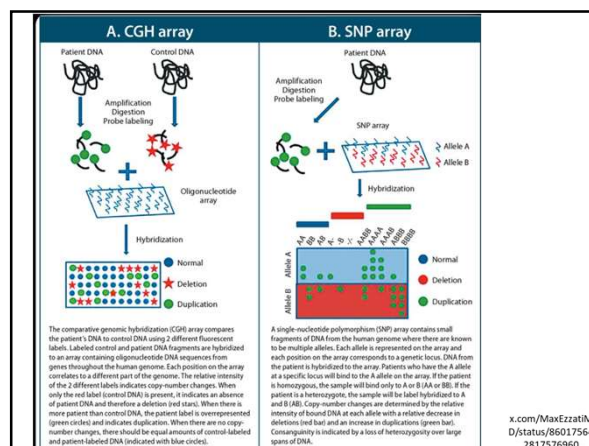
- Not all genetic conditions can be tested for using the same methods/technology
- Next Generation Sequencing (NGS):
 - Single DNA coding changes are detected by sequencing by walking down the DNA nucleotide code
 - Individual genes
 - Groups of genes (panel)
 - Exome - All coding regions of genes
 - Genome - All regions of DNA



cleanpng.com/png-human-genome-project-dna-sequencing-sanger-sequenc-2432069/#google_vignette

Chromosomal Microarray

- Purpose: detect deletions and duplications
- Comparative Genomic Hybridization (CGH)
 - Compares patient DNA quantities to control DNA
- Single Nucleotide Polymorphism array (SNP)
 - Test for the presence/absence of specific known sequences of DNA
 - Detect regions of homozygosity (identical) due to:
 - Shared ancestry / consanguinity
 - Uniparental disomy which can be associated with imprinting disorders or recessive conditions



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More methods

- Methylation- for disorders due to imprinting or uniparental disomy
 - Prader Willi syndrome/Angelman syndrome
 - Beckwith Wiedemann syndrome/Russell Silver syndrome
- Triplet repeat testing- to determine normal length versus disease-causing length (Southern blot)
 - fragile X, myotonic dystrophy, other neurologic conditions

Test Name	Purpose	Details	Caveats
Next generation sequencing (NGS)	Sequences coding regions of genes and their boundaries	Uses PCR followed by sequencing to look at DNA code	Some regions of DNA are repetitive and hard to sequence, can miss del/dup and repeat disorders
Karyotype	Counts the number of chromosomes present	Can detect deletions > 3MB and translocations	May need to request larger counts for mosaic conditions
Fluorescent in situ hybridization (FISH)	Detects deletions and duplications	Useful when testing for a specific deletion or duplication	Must have a probe available for the region in question
Chromosomal microarray (CMA)	Detects deletions and duplications of partial or entire chromosomes	Can be designed to detect very small del/dup and even SNPs	Cannot detect balanced translocations May detect unexpected relatedness
Methylation sensitive RT-PCR	Detects changes in methylation pattern, some uniparental disomy detected	Requires specific chemical to convert non-methylated C>U	Only helpful if mode of DNA variant is due to methylation issues
Southern blot	Detect variable sizes of DNA fragments such as triplet repeat disorders	Smaller fragments run faster on a gel than larger	Need specific probes to detect the DNA, cannot differentiate very small differences in size
Allele specific oligonucleotide testing (ASO)	Detects specific mutations	Must know which mutations to look for; inexpensive	Can miss variants not included on panel; Used on tests such as the NBS for CFTR
Short tandem repeat polymorphisms (STRP)	Helps differentiate individuals/samples from one another	Uses known polymorphisms to label/identify samples; used in paternity testing	Only helpful if the samples have different STRP

Resources and References

- Morphology terms: [ElementsOfMorphology.nih.gov](https://www.nlm.nih.gov/elements/morphology/)
- Mendelian Inheritance in Man: [OMIM.org](https://omim.org/)
- Atlas of diverse human malformation syndromes: research.nhgri.nih.gov/atlas
- Gene Reviews: [genereviews.org](https://www.ncbi.nlm.nih.gov/genereviews/)
- UpToDate: (limited [UpToDate.com](https://www.upToDate.com/)), full access via subscription
- MedlinePlus Genetics: medlineplus.gov/genetics
- Genetic and Rare Diseases Info Ctr (GARD): rarediseases.info.nih.gov/diseases
- Nat'l Org. for Rare Disorders (NORD): rarediseases.org
- Unique Chromosomes: rarechromo.org
- Genetic Alliance Website: geneticalliance.org Under Construction!
- GEMSS: negenetics.org/genetic-education-materials-school-success-gemss