Understanding the Fundamentals: The Language of Genetics

Genetics Webinar Series for Blue Plans

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Agenda

I. Case Study

II. Genetic Terminology

III. Types of Genetic Alterations

IV. Inheritance

V. Case Study Discussion
I. Case Study: Roger

• **Patient history**
A 6 y/o boy is brought by his mother because he is struggling in first grade. His growth has fallen off and he is the shortest in his class (3rd %ile). He has had one seizure. His head circumference is normal, 95%ile.

• **Family history**
Mother and father have normal intelligence, but father is unemployed due to generalized weakness and pain. Mother is average stature, father is 5’4” tall, and stocky. Mother is pregnant.

• **Lab tests and Differential Diagnosis**
Tests for Thyroid and Growth Hormone deficiency are normal.

Pediatrician wonders if he has an intellectual disability “syndrome” even though his appearance is normal.
Genetics consultant detects mild brachydactyly and borderline upper/lower segment and armspan to height ratios, indicating mild limb shortness and suspects a skeletal dysplasia.
I. Case Study: Roger

- **Genetic testing**

FGFR3 gene sequencing is ordered. The ordered test sequences only exon 13; it is targeted to detect two variants, c.1620C>A and c.1620C>G. It does not examine other FGFR3 exons, including exon 10, where the fully penetrant pathogenic variant responsible for Achondroplasia is located.

I. Case Study Discussion: Preview

1. Why do the cDNA variants c.1620C>A and c.1620C>G both result in protein variant p.Asn540Lys?

2. How many copies of the hypochondroplasia variant allele were found? Is this a dominant or recessive disorder?

3. How can Roger’s diagnosis possibly help his father?

4. Only some persons with hypochondroplasia have intellectual disability. What two phenomena explain this?

5. The doctor could have ordered a complete radiographic survey including skull, pelvis, AP and lateral spine, legs, arms, and hands, instead of a genetic test, to diagnose hypochondroplasia. Give three reasons why she might have chosen the genetic test over the radiographic diagnostic approach. What did she risk by choosing the genetic test?
II. Genetic Terminology: DNA

All the genetic material in the nucleus, plus the mitochondrial genome

Molecules of DNA that contain the coded instructions for how to build, maintain, and replicate a human being

Is not identical in anyone but identical twins

Always contains both benign variation and variation that can cause or contribute to disease(s)

It’s big! 3,300,000,000 base pairs
II. Genetic Terminology: Chromosomes

- 23 pairs (pairs!)
  - 22 pairs of autosomes
  - 1 pair of sex chromosomes
- Packages of DNA
- Consistent structure
II. Genetic Terminology: Structure

- Exons are segments of genes that contain code for proteins
- Introns are spacers that get cut out after transcription
- Gene coding regions are about 1% of the genome
II. Genetic Terminology: Transcription

- DNA copied to RNA
- "Sense" strand
II. Genetic Terminology: Translation

- DNA
- Transcription
- RNA
- Transport to cytoplasm
- mRNA
- Ribosome
- Amino Acid chain
- tRNA
- Translation

Amino acids:
- Met
- Thr
- Asp
- Gln
- Pro
- Gln
- Ala
- Glu
- Leu
- Ala
- Phe
- Thr
- Tyr
- Asp
- Ala
- Pro

Codons:
- Codon 1
- Codon 2
- Codon 3
- Stop Codon
II. Genetic Terminology: Genotype and Phenotype

Genotype

- The *genetic code* describing an individual

Phenotype

- The *physical manifestations* of genotype in an individual
II. Genetic Terminology: Genetic Heterogeneity

- **Allelic Heterogeneity**: Disease results from *different variants in the same gene*
- **Locus Heterogeneity**: Disease results from *variants in different genes*
- **Phenotypic Heterogeneity**: Disease manifestations are *different in different people*
II. Genetic Terminology: Expressivity

**Disease Expression**
- What the *detectable disease manifestations* in an affected individual are
  - Phenotype
  - Molecular

**Variable Expressivity**
- Affected persons *show different features or different combinations of features*
- “Pleiotropy”

**Patterns**
- Within families ➔ unknown factors despite gene identity
- Among families ➔ genotype-phenotype correlations
II. Genetic Terminology: Penetration

**Complete Penetrance**

- Everyone with pathogenic genotype expresses the disease

**Incomplete Penetrance**

- Some, but not all, will express the disease
  - Lifelong
  - Age-related
  - Environment-dependent

“Because of evidence that the height range in hypochondroplasia may overlap that of the normal population, individuals with hypochondroplasia may not be recognized as having a skeletal dysplasia unless an astute physician recognizes their disproportionate short stature. However, there have been no reports of individuals with an FGFR3 mutation without demonstrable radiographic changes compatible with hypochondroplasia or one of the other phenotypes known to be associated with mutations in this gene (see Genetically Related Disorders).”

-- GeneReviews.org
III. Types of Genetic Alterations: Structure

- **Universal**
- **Three bases => 1 amino acid, or termination**
- **Degenerate**
  - some base changes don’t result in amino acid changes, they are ** synonymous**
- **Translation is reading-frame dependent**
  - Insert/delete can shift triplet frame → translated differently
III. Types of Genetic Alterations: Mutation

Micro

DNA

Mutagenic event

Deletion

Insertion

Substitution

Macro

Deletion

Duplication

Inversion

Substitution

Translocation
III. Types of Alterations: Variation

- Base Substitution – one base replaces another
- Copy Number
  - Deletion (copy loss)
  - Duplication, triplication, etc. (copy gain)
- Repeat Number
  - Location: Tandem, flanking
  - Orientation: Direct, inverted
  - Size: Large, Trinucleotide, mononucleotide
- Structural
  - Rearrangement (sections of DNA moved around)
  - Translocation (sections moved to a different chromosome)
- **Different lab technologies detect different types of variation!**
III. Types of Alternations: Variation

- Less function (*loss*)
- More function (*gain*)
- New function (*gain*)
- No change (*benign*)

Variation

Function

Environment
III. Types of Alterations: Variation

- Insufficient (loss)
- Excess (gain)
- Neomorph (new fxn)
- Enough (benign)

Function → Variation → Dose (dosage)
IV. Inheritance

- **Infer** from pedigree (family history)
- **Predict** from functional effect of pathogenic variant
- Correct for
  - Lethality
  - Germline vs. somatic
IV. Inheritance: Dominant

- **Affected**
  - both sexes
  - one of two alleles

- **Unaffected**
  - no disease allele
  - no transmission

- **Vertical pattern**
  - multiple generations
  - 50-50 chance of transmission
IV. Inheritance: Autosomal Recessive

- **Affected**
  - No normal copy

- **Unaffected**
  - At least one normal copy

- **“Carrier”**
  - Unaffected
  - Transmits 50-50

- **Both parents of an affected are carriers (or affected)**
  - An affected parent creates pseudo-dominant inheritance
IV. Inheritance: X-linked Recessive

- **Affected**
  - No normal copy
  - Males
  - All daughters are carriers
  - All sons are unaffected
  - Rare females

- **Unaffected**
  - At least one normal copy
  - Non-carrier males
  - Most females

- **“Carrier”**
  - Unaffected
  - Females (and XXY males)
  - Transmits 50-50

- **Mother of an affected is a carrier**
  - Always - for benign condition
  - 2 out of 3 - when affected males can’t reproduce
  - 1 out of 3 is de novo
IV. Inheritance: Y-linked
IV. Inheritance: Mitochondrial

Both sexes affected
- Variable expression

Vertical transmission
- Variable chance
- *Maternal lineage* only
- *No transmission* from males

Energy-intensive organs
- Brain
- Muscle
- Liver
- ...
IV. Inheritance: *De Novo* (New Mutation)

- No family history of (dominant) condition
- Not present in DNA of either parent
- Is evidence supporting variant pathogenicity
V. Case Study: Roger

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V. Case Study: Discussion Questions

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3. How can Roger’s diagnosis possibly help his father?

4. Only some persons with hypochondroplasia have intellectual disability. What two phenomena explain this?

5. The doctor could have ordered a complete radiographic survey including skull, pelvis, AP and lateral spine, legs, arms, and hands, instead of a genetic test, to diagnose hypochondroplasia. Give three reasons why she might have chosen the genetic test over the radiographic diagnostic approach. What did she risk by choosing the genetic test?
**Q.** Why do the cDNA variants c.1620C>A and c.1620C>G both result in protein variant p.Asn540Lys?

**A.** Degenerate Codons for Lysine amino acid

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Q. How many copies of the hypochondroplasia variant allele were found? Is this a dominant or recessive disorder?

A. One variant allele and one normal allele were identified in the ATP-binding segment of the FGFR3 tyrosine kinase domain.

The test result was heterozygous for the disease-associated variant (compared with a normal reference sequence).

Hypochondroplasia is a dominant disorder, both by inference from pedigrees, and by biologic basis, which is constitutive activation of the receptor tyrosine kinase, a “gain of function.”
Q. How can Roger’s diagnosis possibly help his father?

A. Father’s short stature and stocky build suggest Roger may have inherited Hypochondroplasia from him.

A significantly increased incidence of spinal stenosis and bony compression occurs in this disorder.

Roger’s diagnosis might lead to diagnosis in father, and detection of and surgery for spinal stenosis.

Roger’s father might recover from pain and disability.
V. Case Study: Answers

Q. Only some persons with hypochondroplasia have intellectual disability. What two phenomena explain this?

A. Variable expressivity.
   Genotype-phenotype correlation.
V. Case Study: Answers

Q. The doctor could have ordered a complete radiographic survey including skull, pelvis, AP and lateral spine, legs, arms, and hands, instead of a genetic test, to diagnose hypochondroplasia. Give three reasons why she might have chosen the genetic test over the radiographic diagnostic approach. What did she risk by choosing the genetic test?

A. The complete radiologic survey is necessary to diagnose hypochondroplasia, and radiation exposure is significant. Even then, radiologic diagnosis can be difficult and the criteria are controversial.

The gene test is less expensive ($200-300 for a single exon)

The tested-for variant is associated with higher incidence of intellectual disability. The positive test result will likely stop further etiologic testing for intellectual disability.

13% to 42% of Hypochondroplasia is due to other pathogenic variants in FGFR3 (allelic heterogeneity), or have no detectable FGFR3 mutation (locus heterogeneity). If the test result had been normal, she could have pursued whole gene sequencing, or radiologic survey for diagnosis, or for detection of other, clinically overlapping, skeletal dysplasias.
Thank you