Combining clinical and genome information to improve diagnosis

How diagnosis is getting easier

Update on the lidocaine-insensitive type of periodic paralysis

Why some diagnosis is still difficult

Michael Segal MD PhD, Founder and Chief Scientist, SimulConsult

Supported in part by the NIH (National Library of Medicine and National Human Genome Research Institute)
Why diagnosis is not simple

Finding-based diagnosis

- ✓ Finding
- @6m Finding
- X Finding

→

Disease

Narratives

Disease

→

Finding: onset, frequency
Finding: onset, frequency
Finding: onset, frequency
New technology: genome analysis

The hope:
Knowledge about the genome will make diagnosis more effective

The problem:
“We are close to having a $1,000 genome sequence, but this may be accompanied by a $1 million interpretation”

- Bruce Korf MD PhD
**Fragmented approaches**

**Lab (Genome)**
- Filter based on genetic abnormalities
- Apply stringent criteria
- Apply looser criteria
- Miss diagnosis or 2nd diagnosis
- Miss non-genetic diagnosis
- Manual review too costly
- Miss non-genetic diagnosis

**Clinic (Phenome)**
- Filter based on clinical abnormalities
- Order single gene
- Order panel
- Miss unusual diagnosis
- Miss 2nd diagnosis

**Integrated approach**

**Genome-Phenome**
- Don’t filter. Rate & correlate
- Good fits bubble to the top

Launch demo (local)
Patient: 25 year old man

Pertinent positive findings
- Recurrent exacerbations
- Weakness, significant

Pertinent negative findings
- Early death if undiagnosed

Tip: Hypokalemic periodic paralysis - an owner's manual
Tip: GeneReviews: Hypokalemic Periodic Paralysis
Update on the lidocaine-insensitive type of periodic paralysis

*Why some diagnosis is still difficult*
Molecular diagnosis for Hypokalemic Periodic Paralysis

- **CACNA1S ~60%**
- **SCN4A ~10%**
- **Third gene (lidocaine insensitive type of hypokalemic periodic paralysis)**
- **Other hypokalemic periodic paralysis genes?**
- **Other diagnoses**
  - Normokalemic & hyperkalemic periodic paralysis, and potassium-aggravated myotonia
  - Paramyotonia congenita
  - Andersen-Tawil syndrome
  - Thyrotoxic periodic paralysis
  - Autoimmune reactions to potassium channels
  - Diseases of oxidative metabolism such as mitochondrial diseases
  - Porphyria
  - Narcolepsy-cataplexy if there are hallucinations, sudden episodes of sleepiness, or trigger by laughing
  - Low potassium caused by foods and drugs: licorice, barium exposure, diuretics, steroids and others
  - Diseases in which potassium is chronically low because of kidney problems:
    - Renal Tubular Acidosis
    - Bartter syndromes and Gitelman hypomagnesemia-hypokalemia
    - Sjögren syndrome
    - Conn’s syndrome (hyperaldosteronism)
Lidocaine-insensitive type of hypokalemic periodic paralysis

- Hypokalemic periodic paralysis:
  - Episodic weakness
  - Triggered by:
    - high glucose
    - low potassium
    - high sodium
  - Potassium goes even lower during episodes
- Lidocaine hardly works as a local anesthetic
- ADHD or Asperger syndrome (primarily in males)
- Severe premenstrual symptoms (PMS) in females
- No known mutations in *CACNA1S* or *SCN4A* genes

Inheritance is autosomal dominant in all families studied
Dr. Lehmann-Horn’s lab is working on finding the gene

- Studying large families with distant cousins affected
- DNA studies allow “painting” of chromosome maps to show which parts of chromosomes came from which ancestors
- This approach finds the small chromosomal region that contains the gene responsible for this third form of hypokalemic periodic paralysis
Not always easy to find the gene

- Gene is in this region but not previously recognized as part of the 1% of DNA that is genes
- Gene is a one already known to be in this region but:
  - Part of the gene is not reliably sequenced in “whole exome sequencing”
  - Abnormality is in an “intron” of a gene
  - Abnormality is in a regulatory DNA outside a gene