CSER and Beyond Challenges and Opportunities in Interpreting Variants: CAP Response

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Consistent Annotation

- Bake off results encouraging, yet improvements needed
  - ≤1 degree of separation
    - What is the target performance?
  - > 1 degree of separation
    - Follow up
      - Identify problematic or misunderstood ACMG/AMP evidences?
      - Sharing of evidences - do some laboratories have internal information not widely available?

Clinical Significance (Last evaluated)	Review status (Assertion method)
Uncertain significance (Jan 16, 2015)	Criteria provided, single submitter (EGL Classification Definitions)
Likely benign (Jun 25, 2014	Criteria provided, single submitter (GeneDx Variant Classification [06012015])
Pathogenic (Dec 4, 2012	No assertion criteria provided

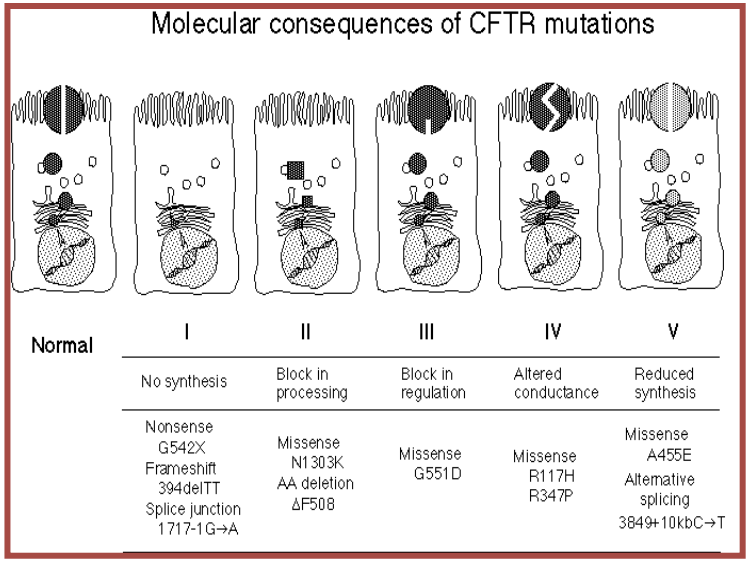
Clinical Scenario

- Problem:
  - Requested for familial targeted variant, but disagree with classification from other lab
  - How to interpret/report presence or absence of familial variant

- Solution:
  - Consistency in variant classification
  - Transparency in Evidences used

Additional Guidance

- Low penetrance or mild variants
  - Combinations of mutations
  - Terminology: Mild, low penetrance variant, mild disease, atypical disease
  - Risk alleles
- Somatic variants
  - Efforts for Somatic Interpretation of Sequence Variants
  - Differences between somatic and germline



"Cystic Fibrosis: Genotypic and Phenotypic Variations" by J. Zielenski and L.-C. Tsui in Annual Rev. of Genet. (29: 777-807, 1995).

http://www.cftr2.org/mutation.php?view=scientific&mutation_id=220

ANNOTATION JUSTIFICATION

Sharing evidences - Submit to ClinVar

Clinical Assertions - Germline

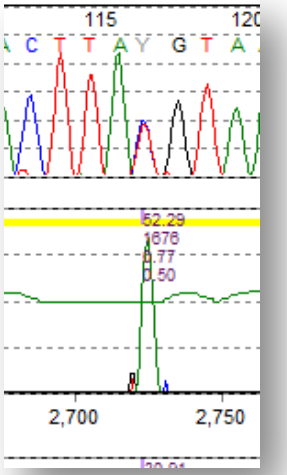
Clinical Significance (Las evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter – Study name (Last submitted)	Submission accession
Pathogenic (Oct 16, 2012)	Criteria provided, single submitter (LMM Criteria)	Clinical testing	Deafness, autosomal recessive 1A (Autosomal recessive inheritance) [MedGen | OMIM]	Germline	PubMed (12) [See all records that cite these PMIDs]	Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine (Jan 29, 2015)	SCV000061530
Pathogenic (Feb 8, 2013)	Criteria provided, Single submitter (ACMG Guidelines,	Clinical testing	Hearing impairment (Autosomal recessive inheritance) [MedGen | Human Phenotype Ontology]	Germline	PubMed (1) [See all records that cite these PMIDs]	Genetics Services Laboratory, University of Chicago (Sep 11, 2014)	SCV000193179

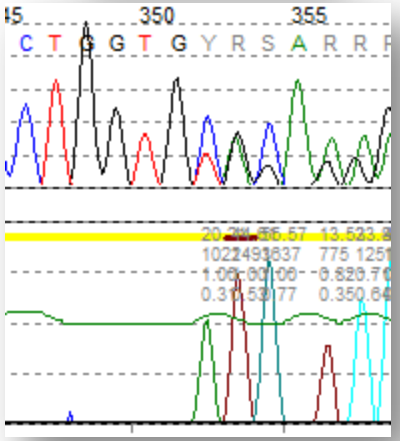
FULL DESCRIPTION FOR LABORATORY FOR MOLECULAR MEDICINE, PARTNERS HEALTHCARE PERSONALIZED MEDICINE

The Asn206Ser variant in GJB2 has been reported in many individuals with hearing loss (Kenna 2001, Cryns 2004, Marlin 2005, Me_e 2004, Me_e 2008, Pandya 2003, Putcha 2007, Rodriguez-Paris 2008, Roux 2004, Snoeckx 2005, Wu 2002). Several of these individuals were homozygous or compound heterozygous. In summary, this variant meets our criteria to be classified as pathogenic (http://pcpgm.partners.org/LMM)

Case Level Data

- Example: MSH6 p.R1076C
  - Previously classified as pathogenic
    - Described in literature
    - In 11/121330 total alleles ExAC browser. R is conserved, both PolyPhen and SIFT predict damaging/deleterious.
  - InSIGHT re-classified to VUS
    - Reported in 3 patients: suspected Constitutional (bi-allelic) Mismatch Repair Deficiency (CMMRD)
      - MSI-H
      - MSH6 immunoloss
      - Cancer in their 20's
    - Not well-described alone
    - Internal
      - One case consistent with C-MMRD with second truncating variant
      - One p.R1076C alone, no cancer (>60 years) moderate family history of cancer, identified in one sibling with cancer >50 years
    - Per author "its an enigma"





Re-analysis/Re-interpretation

- Re-analyze vs re-test
  - Instruments/chemistry continue to improve
  - More complete data
- Re-interpret
  - Change classification
  - Duty to re-contact?

Clinical Validity/Utility

- Gene lists?
- From specialty practices to primary care
  - Clinicians understanding of results
    - Prior probability?
- From affected to healthy populations
  - How to do it 'right'
    - Limit unnecessary procedures
    - Ensure appropriate procedures

And Beyond

Need careful scientific evaluation, one gene, one variant a time