The Post Mortem Genetics Clinic Visit

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Initial Discussion

- Family goals and questions
- Intake:
  - Circumstances of death
  - Premorbid medical history
    - Known cardiac history
    - Fainting/syncope
    - Illnesses
    - Medical records

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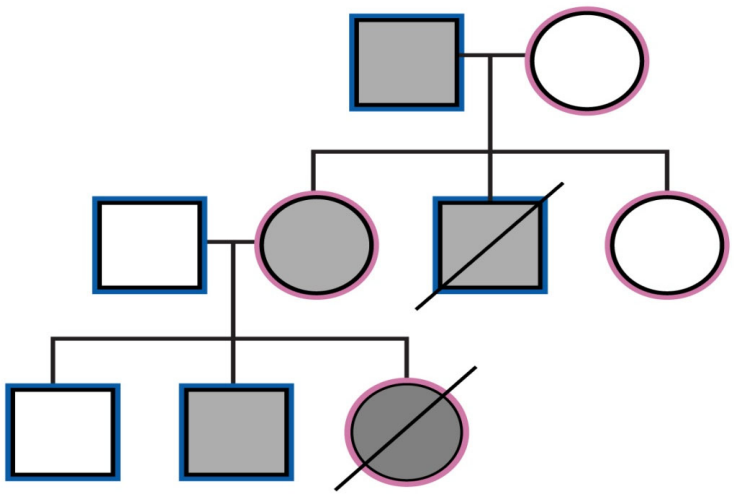
Pedigree



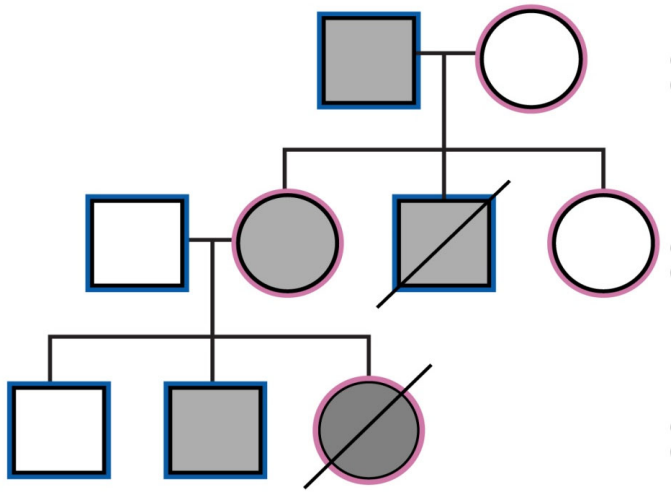
- Sudden death
- Cardiac arrest
- Heart attack
- Cardiology care
- Fainting
- Seizures
- Other features of associated conditions: hearing loss, lens dislocation, connective tissue complaints (organ rupture, hypermobility, etc)

Pedigree Considerations

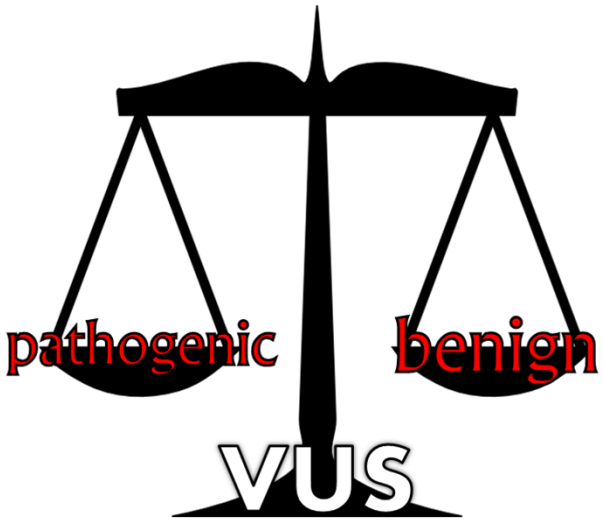
- Lack of information
- Omitted relatives
  - SIDS, young deaths
- Additional information regarding “accic
  - Drowning, single motor vehicle accidents, drug abuse
- Unaffected relatives

Testing Strategy

- Integrate information regarding decedent, autopsy results, family history
- Testing candidates
  - Proband
  - Other affected relative
- Breadth of testing
  - Targeted tested for genes of interest based on phenotype
  - Whole exome sequencing



Genetic Testing Limitations



- Negative ≠ “not genetic”
  - Yield of testing varies 15-30% yield. Improves over time
    - Undiscovered genes
    - Polygenic inheritance
    - Types of gene changes
    - Limitations of technology
- Variants of uncertain significance

Classifying variants

Benign | Likely Benign | Uncertain | Likely pathogenic | Pathogenic

Table 5 Rules for combining criteria to classify sequence variants

Pathogenic	(i) 1 Very strong (PVS1) *AND* (a) ≥1 Strong (PS1–PS4) *OR* (b) ≥2 Moderate (PM1–PM6) *OR* (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR* (d) ≥2 Supporting (PP1–PP5) (ii) ≥2 Strong (PS1–PS4) *OR* (iii) 1 Strong (PS1–PS4) *AND* (a)≥3 Moderate (PM1–PM6) *OR* (b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR* (c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Likely pathogenic	(i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR* (ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR* (iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR* (iv) ≥3 Moderate (PM1–PM6) *OR* (v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR* (vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Benign	(i) 1 Stand-alone (BA1) *OR* (ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR* (ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory

Criteria revised in 2015 by ACMG

- presence or absence of variant does not change screening
- : molecular evidence, molecular modeling, conservation data, biochemical difference, segregation with disease in families, presence/absence in population controls

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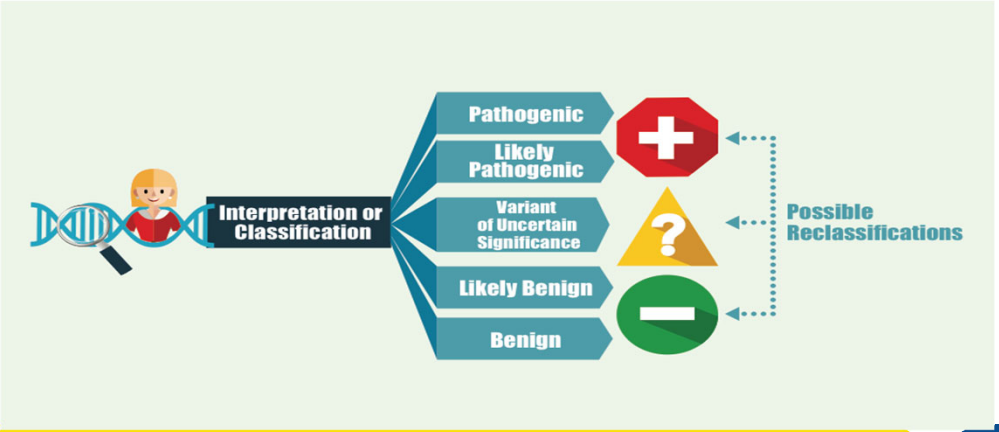
Variants of uncertain significance

- Unclear whether benign or harmful
- Typically ACMG recommends not changing care based on variant of uncertain significance
- Reclassified over time based on multiple factors
- Test relatives for segregation with phenotype, NOT for screening guidance



Genetics Visit Summary

- Information gathering: decedent's history, circumstances of death, autopsy results, pedigree
- Discussion of testing: testing candidate, practical considerations, type of test, limitations of testing, follow up plan
- Discussion of inheritance: who else is at risk
- Importance of follow up over time

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