Germline Mosaicism Detection with Family-Centered Exome Sequencing: More common than previously recognized?

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BACKGROUND

- Since 2011, Family-Centered Exome Sequencing (FCE) has been instrumental in providing diagnoses for patients with a broad spectrum of genetic diseases.
- Previously, detection of germline mosaicism (GM) was elucidated through examining germline cells of parents of affected individuals. Rates of GM vary with genetic disease, are difficult to quantify, and incidence is largely unknown.
- Multiple similarly affected offspring without relevant family history is generally considered a strong indicator for autosomal and/or X-linked recessive Mendelian disorders.
- Although GM has significant implications for genetic counseling, statistics are limited and rates vary. Family-centered analysis is integral to the diagnostic yield of DES but also has important consequences in discovering cases of GM.

METHODS

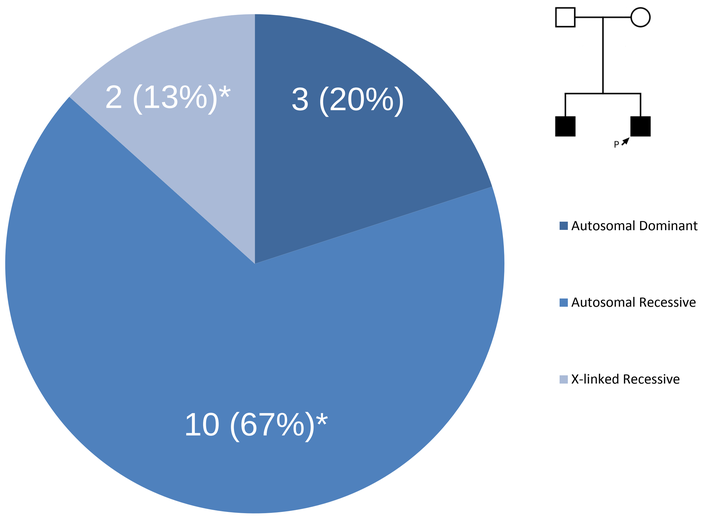
- **Patients/study population:** Genomic deoxyribonucleic acid (gDNA) was isolated from whole blood from probands and relatives referred to Ambry Genetics (Aliso Viejo, CA) for Family-Centered Exome Sequencing (FCE). Informed consent was obtained from all family members involved in the testing process. Diagnostic yield was calculated in the first 50 families with healthy parents but at least two affected offspring.
- **Exome library preparation**, sequencing, bioinformatics, and data analysis were performed as previously described (Farwell et al. 2014).
- **Statistical analyses** were computed by chi^2 goodness of fit tests and Fisher's Exact Probability.

AUTOSOMAL DOMINANT MUTATIONS FROM GERMLIME MOSAICISM IN THREE FAMILIES

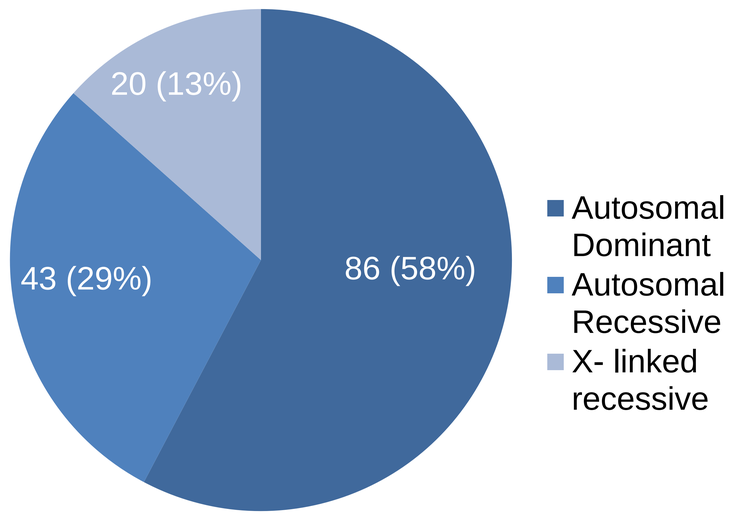
CONDITION	GENE	ALTERATION *
Familial Visceral Myopathy	*ACTG2*	c.770G>A (p.R257H)
Early infantile epileptic encephalopathy-17	*GNAO1*	*2*c.770G>A (p.R257H)
MTOR-related developmental brain disorder	*MTOR*	c.5395G>A (p.E1799K)

*Alterations were heterozygous in the proband and affected sibling, absent in unaffected parents; reported biological relationships were confirmed.

INHERITANCE OF CASES WITH HEALTHY PARENTS AND AT LEAST TWO AFFECTED OFFSPRING



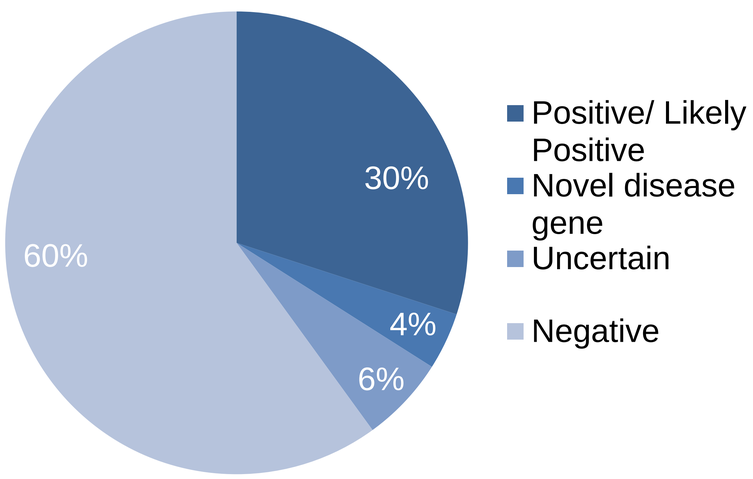
INHERITANCE OF CASES WITHOUT HEALTHY PARENTS AND AT LEAST TWO AFFECTED OFFSPRING



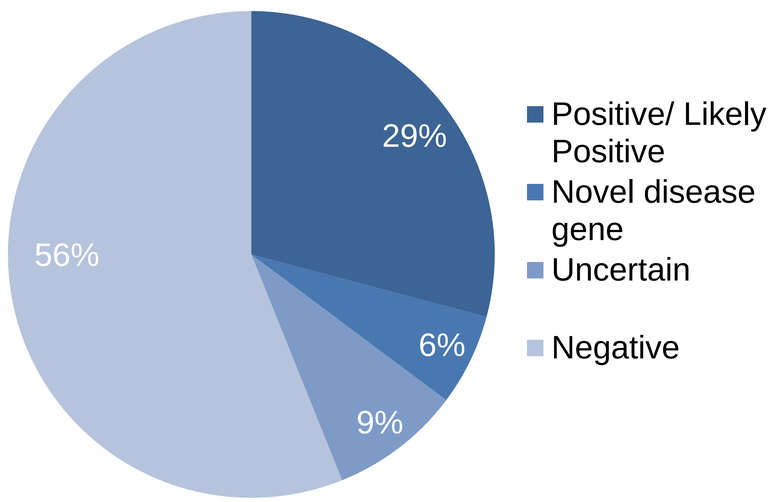
TAKE-HOME POINTS

- Germline Mosaicism is seen in 6% of FCE families and accounts for 20% of positive findings, more common than previously documented.
- Observation of multiple similarly affected offsprings is not a positive predictor for receiving a molecular diagnosis thought FCE.
- Discovering or ruling out GM has tremendous genetic counseling implications in regards to recurrence risk, family planning and testing options.

DETECTION RATE OF CASES WITH HEALTHY PARENTS AND AT LEAST TWO AFFECTED OFFSPRING



DETECTION RATE OF REMAINING 460 CASES



TERMINOLOGY

- **FCE**: Family-Centered Exome Sequencing and Analysis: The use of whole families to diagnose patients with Mendelian Diseases. FCE includes trio whole exome sequencing (generally parent-proband), co-segregation analysis of candidate alterations using all informative family members, and computational methods using family-history inheritance-based filtering.
- **Novel Mendelian disease gene*:*** A gene that is not currently known to underlie a Mendelian genetic condition.

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