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By the Way: The Incidental Benefit of Exome Sequencing to Enable Life-Saving Intervention via Secondary Findings

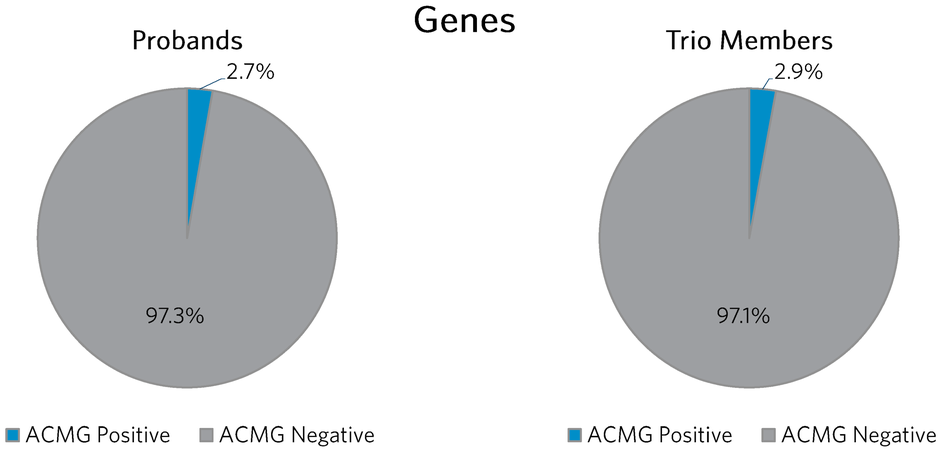
Jennifer Huang, PhD; Christina Alamillo, MS, CGC; Zöe Powis, MS, CGC; Sha Tang, PhD, DABMG; Kelly Farwell Hagman, MS, CGC

Jennifer Huang jhuang@ambrygen.com

BACKGROUND

- In 2013, the American College of Medical Genetics (ACMG) issued recommendations for the reporting of disease-causing mutations within 56 genes identified incidentally during exome analysis (Green, 2013).
- In 2016, the ACMG published an updated list of 59 genes (Kalia, 2017).
- Our laboratory reported patients' decisions to receive secondary findings (SF) results from the first 200 patients sent to our laboratory for DES; the current study expands our analysis of patients' decisions and SF results to a significantly larger cohort (Shahmirzadi, 2014).

Rates of Positive Secondary Findings in the ACMG Recommended Genes



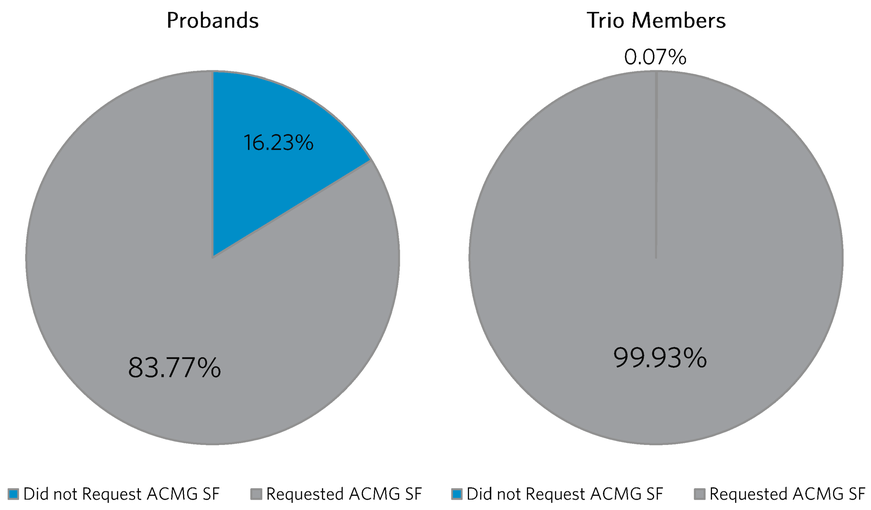
METHODS

- Retrospective analysis of positive SF rates among the first 8270 probands who underwent diagnostic exome sequencing (DES) who had the option of requesting SF results and 8145 trio members.

RESULTS

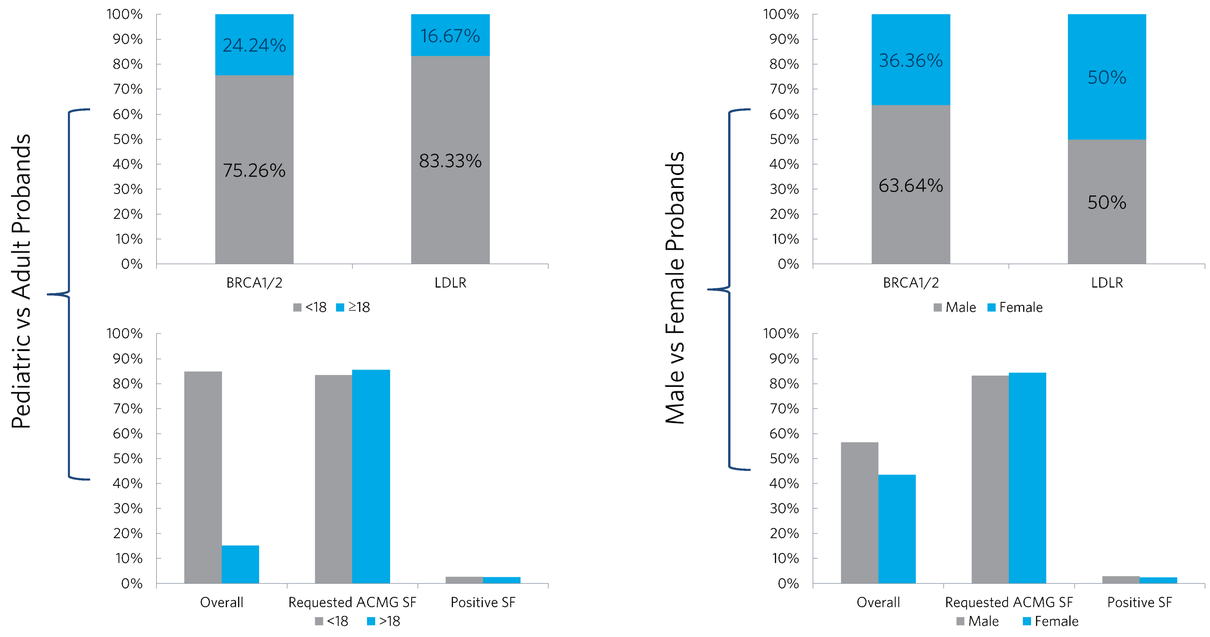
- 6928/8270 (83.8%) DES patients and 8139/8145 (99.9%) of the trio members who requested SF chose to receive results from the ACMG panel
- 424/15067 of the tested individuals had a positive SF within the ACMG recommended list of genes, including 190/6928 probands (2.7%)
- The genes with the most commonly ascertained SFs were BRCA2 (50 families), LDLR (26 families), and BRCA1 (20 families).

Uptake of ACMG Secondary Findings Testing

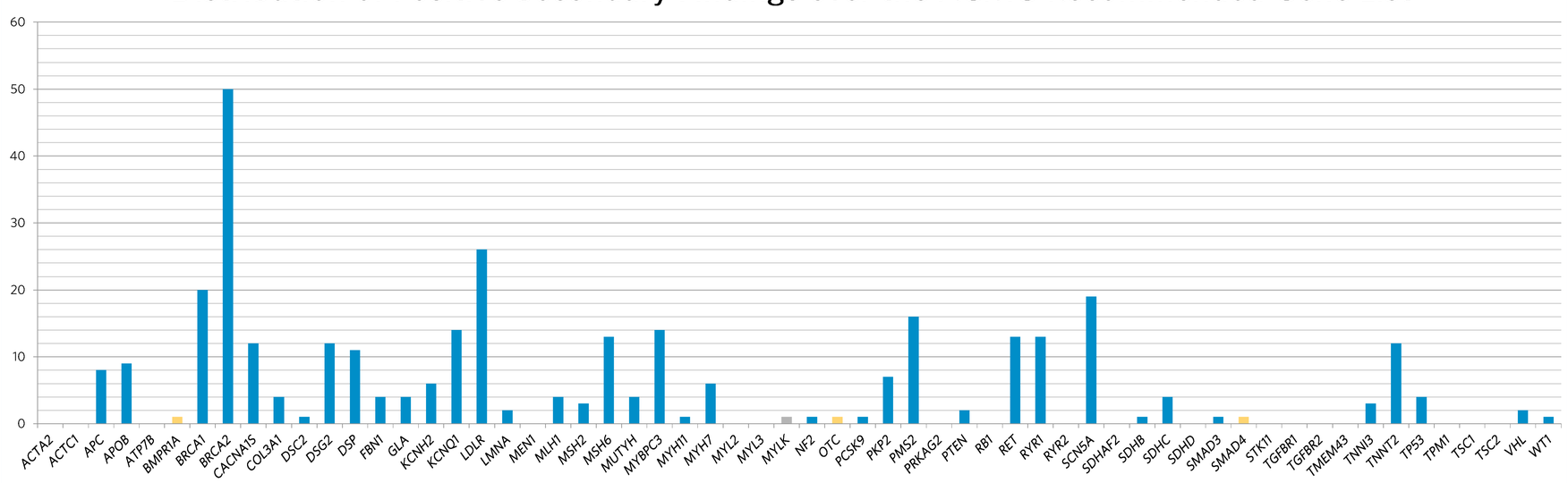


*Probands or trio members who requested secondary findings and chose to receive results from the ACMG panel

Demographic Characteristics of Probands who Requested Secondary Findings



Distribution of Positive Secondary Findings over the ACMG Recommended Gene List



The ACMG guidelines v.2.0 removed the MYLK gene (grey) and added the ATP7B, BMPR1A, SMAD4, and OTC genes (orange), for a total of 59 recommended genes (Kalia, 2016).

TAKE-HOME POINTS

- This poster describes a cohort of 8270 probands who underwent diagnostic exome sequencing (DES) and 8145 trio members.
- Approximately 2.8% of patients who chose to receive secondary findings results had a positive finding.
- Secondary findings in BRCA1 and BRCA2 made up a large proportion of the positive findings, and the majority of BRCA1/2 findings were identified in males under the age of 18.
- The changes in the ACMG recommended secondary findings genes did not significantly impact the overall rate of positive secondary findings in this population.

REFERENCES

1. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15(7):565-574.
2. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond KE, Richards CS, Vlangos CN, Watson M, Martin CL, Miller DT. *Genet Med.* 2017 Feb;19(2):249-255.
3. Shahmirzadi L, Chao EC, Palmaer E, Parra MC, Tang S, Gonzalez KD. Patient decisions for disclosure of secondary findings among the first 200 individuals undergoing clinical diagnostic exome sequencing. Genet Med. 2014;16(5):395-399.

15 Argonaut, Aliso Viejo, CA 92656 Toll Free 866 262 7943 Fax 949 900 5501 ambrygen.com