Frequency of mutations in moderate penetrance breast cancer: Genes *NBN* and *ATM* identified through expanded carrier screening

Counsyl

South San Francisco, California

Kristin Price, MS, CGC; Kenny Wong, MS, CGC; Leslie Bucheit MS, CGC; Carlo Artieri, PhD; Eerik Kaseniit MEng; Imran S. Haque, PhD

Background

- *ATM* and *NBN* have been described as moderate risk breast cancer genes. There is limited published data on the frequency of pathogenic mutations in these genes in the general population.
- *ATM* and *NBN* are often included in expanded carrier screening (ECS) due to their association with recessive disease.
- We analyzed Counsyl's laboratory experience from over 100,000 patients who underwent ECS using next generation sequencing (NGS) to examine the frequency of pathogenic mutations in *ATM* and *NBN* in a population unselected for personal or family history of cancer.

Table 1: Clinical Characteristics Associated with Mutations in *ATM* and *NBN*

Gene	Homozygous State	Heterozygous State
ATM	***Ataxia telangiectasia***	***ATM-associated hereditary cancer***
Cancer risk	Estimated 25% lifetime risk to develop cancer Leukemia and lymphoma are the most common cancer types[1]	Estimated 2.8 fold increased risk for breast cancer Potential increased risk for other cancer types including pancreatic cancer[2] 7271T>G mutation associated with the highest risk for breast cancer
Other clinical findings	Ataxia Slurred speech Choreoathetosis Telangiectasias Frequent infection Hypersensitivity to radiation[3]	No known clinical findings beyond cancer risk
NBN	***Nijmegen breakage syndrome***	***NBN-associated hereditary cancer***
Cancer risk	Estimated 40% risk to develop cancer before age 20y Lymphoma is the most common cancer type[4]	Estimated 2.7 fold increased risk for breast cancer[2] Cancer risk estimates based on founder mutation c.657_661del5
Other clinical findings	Microcephaly Growth delay Craniofacial features Frequent infection Premature ovarian insufficency[4]	No known clinical findings beyond cancer risk

Methods

- Individuals were tested for carrier status in up to 108 genes by NGS.
- Variants identified by NGS were curated for recessive disease based on ACMG guidelines. Pathogenic and likely pathogenic variants were included in this analysis.
- Carrier frequencies for the *ATM* and *NBN* genes were computed from de-identified aggregate data, tabulated by ethnic group, weighted by US Census Data 2010, and summated to represent the ethnic distribution in the USA.

Results

Carrier frequencies are derived from 100,434 patients who underwent ECS with an indicated purpose of "routine carrier screening". Individual carrier frequencies by ethnicity are detailed below.

Table 2: Carrier Frequencies of *ATM* and *NBN* Across All Ethnicities

Gene	Carrier Frequency weighted by US Census Data 2010
ATM	1/270 (0.37%)
NBN	1/508 (0.20%)

We report below on ethnicities where N tested exceeds 2,000. Other individual ethnicities were too small to report at this time.

Figure 1: Carrier Frequency for *ATM* by Ethnicity

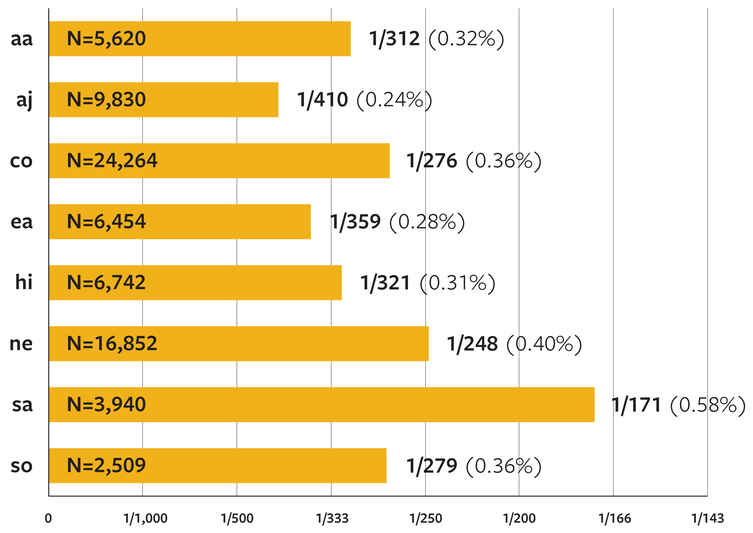
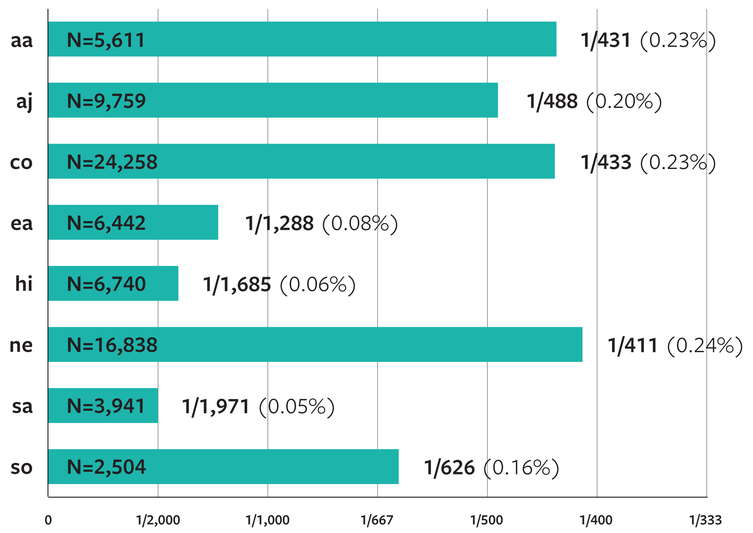


Figure 2: Carrier Frequency for *NBN* by Ethnicity

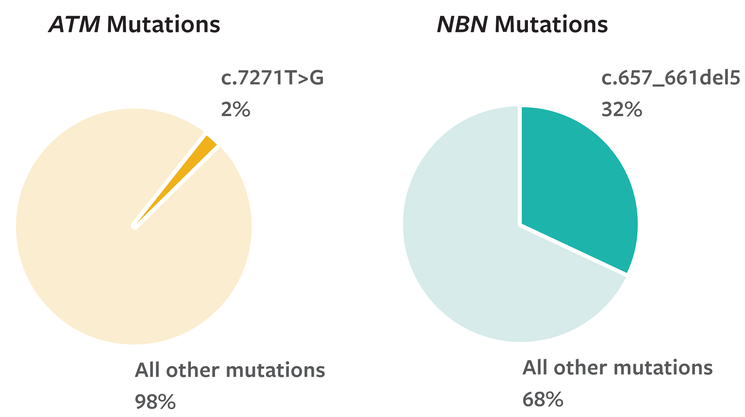


Test requisition forms required individuals to self-report their racial/ethnic background in 1 of 14 categories: African/African American (af); Ashkenazi Jewish (aj); Mixed or Other Caucasian (co); French Canadian or Cajun (cj); East Asian (ea); Finnish (fi); Hispanic (hi); Middle Eastern (me); Native American (na); Northern European (ne); Pacific Islander (pi); South Asian (sa); Southeast Asian (se); Southern European (so); and Unknown (uk).

Cancer screening management guidelines for *NBN* are based on the well-described Slavic founder mutation c.657_661del5; however, we observe that this mutation accounts for only 31.8% of *NBN* positives in this population.[5]

The c.7271T>G (V2424G) dominant-negative missense mutation, which has been reported to cause the highest cancer risk in *ATM* carriers, was found to account for 2.4% of all pathogenic mutations in *ATM*.[5]

Figure 3: Mutation Distribution of *ATM* and *NBN* Across All Ethnicities



Conclusions

- We estimate pathogenic mutations in *ATM* occur in approximately 1/270 individuals in the US population. A well-described missense mutation causing the highest reported risk for cancer made up only a small percentage of all pathogenic *ATM* mutations, while the majority of positive results were due to a wide range of mutations that may cause varied, more moderate, risks for cancer.
- We estimate pathogenic mutations in *NBN* occur in approximately 1/508 individuals in the US population. Although breast cancer screening and prevention guidelines for *NBN* are based on data pertaining to a specific Slavic founder mutation, the majority of carriers in this cohort were found to have other mutations in *NBN*; management recommendations may need to be adjusted for such individuals.
- More research is needed to better understand the wide variety of pathogenic mutation types in *ATM* and *NBN* across diverse populations and their contribution to cancer risk.

REFERENCES: 1. Suarez, F. et al. Incidence, Presentation, and Prognosis of Malignancies in Ataxia-Telangiectasia: A Report From the French National Registry of Primary Immune Deficiencies. J Clin Oncol. 2015;33(2):202-8. | **2.** Easton, D. F. et al. Gene-panel sequencing and the prediction of breast-cancer risk. N. Engl. J. Med. 2015; 372: 2243-2257. | **3.** Rothblum-Oviatt, C. et al. Ataxia telangiectasia: a review. Orphanet Journal of Rare Disease. 2016; 11:159. | **4.** Chrzanowska, K. H. et al. Nijmegen breakage syndrome (NBS). Orphanet J Rare Dis. 2012;7:13. | **5.** National Comprehensive Cancer Network. NCCN Guidelines Version 2.2017: Genetic/Familial High-Risk Assessment: Breast and Ovarian. URL: nccn.org.