Variant of Unknown Significance Rates Vary by Ethnicity and Genes Analyzed

L. Panos, J. Thompson, V. Speare, J. S. Dolinsky, K. Panchani, H. LaDuca
[1]Ambry Genetics, Aliso Viejo, CA

BACKGROUND

- Variants of unknown significance (VUS) are a concern with multi-gene panel testing (MGPT).
- VUS rates tend to be higher in:
  - More recently described genes
  - Larger, more complex genes
  - People of ethnic groups studied less extensively with less control data available.

METHODS

- Retrospective review of >55,000 consecutive patients undergoing MGPT for hereditary cancer
- Ethnicity was obtained for >48,000 patients; self-reported or provider-indicated on requisition.
  - 5 groups analyzed: African American, Ashkenazi Jewish, Asian, Caucasian, and Hispanic
- Ambry's variant classification protocol, using IARC[1] and ACMG[2] guidelines, was applied:
  - Pathogenic, Likely Pathogenic, VUS, Likely Benign, Benign
- Individuals with one or more VUS, regardless of pathogenic mutation status, were included.
- VUS rates from 10 different MGPTs ranging in size from 5-41 genes were calculated.
- VUSs were scanned in Exome Aggregation Consortium (ExAC) for frequency >1%.
- Gene size and patient ethnicity were considered in VUS likelihood analyses.
- *EPCAM* analysis includes only deletion/duplication testing and *MITF* analysis is only a specific site analysis – both were excluded from this data set.

TABLE 1: VUS Rates (%) by Ethnicity and MGPT

MGPT	Caucasian (n=37,151)	African American (n=3,079)	Ashkenazi Jewish (n=3,281)	Asian (n=1,873)	Hispanic (n=2,722)	OVERALL (N=48,106)
BRCAplus	4.4	8.9	2.6	13.7	8.0	5.20
GYNplus	10.8	17.0	15.6	24.5	15.2	11.46
PGLNext	10.9	33.3	0.0	28.6	16.0	11.55
PancNext	18.0	39.4	17.1	27.8	29.4	18.06
BreastNext	22	37.1	24.7	42	29	21.92
ColoNext	16.1	21.6	16.6	35.7	29.6	16.31
RenalNext	18.0	30.0	16.7	47.6	27.3	19.37
OvaNext	27.4	43.0	27.6	54.3	37.2	26.21
CancerNext	29.9	48.3	33.1	59.1	36.8	28.08
CancerNext-*Exp* (CNE)	39.4	57.1	41.7	74.4	52.7	37.8

- VUS rates were lowest for Caucasian and Ashkenazi Jewish individuals across all panels.
- Asians showed the highest MGPT VUS rates on all panels except PancNext.

TABLE 2: VUSs in Cohort with ExAC[3] Population Frequency >1%

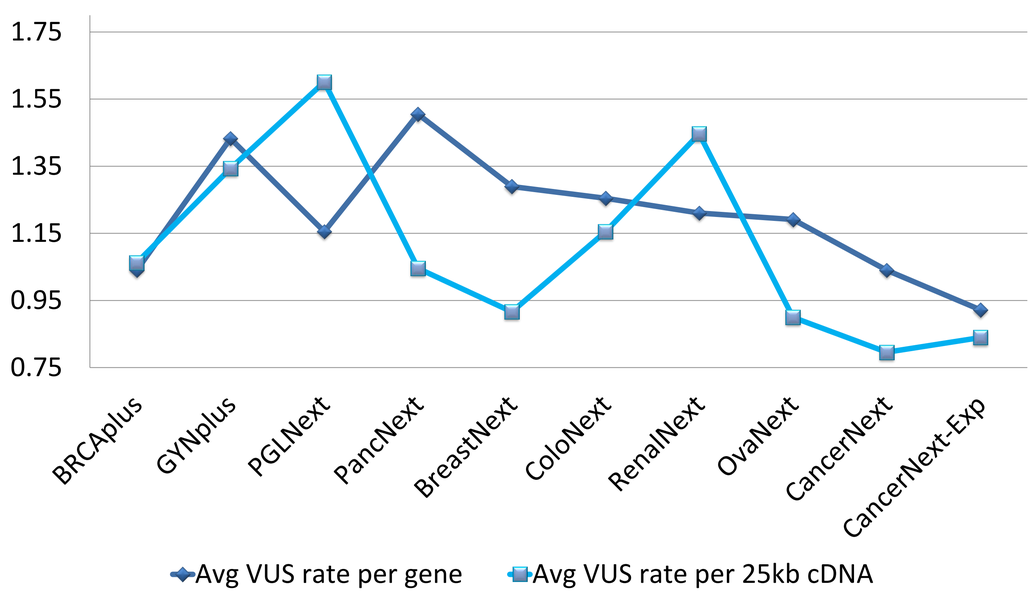
Gene	Nucleotide Change	Population	Allele Frequency (%)
FH	c.77C>T	East Asian	2.61
TMEM127	c.53C>T	East Asian	2.08
SDHA	c.163T>C	East Asian	2.12
CDKN2A	c.-2G>A	African American	2.86
CDKN2A	c.151-4G>C	South Asian	1.64
BMPR1A	c.676-5T>C	South Asian	1.86
RET	c.341G>A	East Asian	1.17
TSC2	c.2032G>A	East Asian	2.32
BRIP1	c.1433A>G	South Asian	1.93
NF1	c.*4T>C	South Asian	2.07

- A total of 5,580 VUSs identified
- 10 VUSs had frequency >1% in ExAC
- 9/10 were in ExAC Asian population

TABLE 3: Gene and cDNA Content per Panel

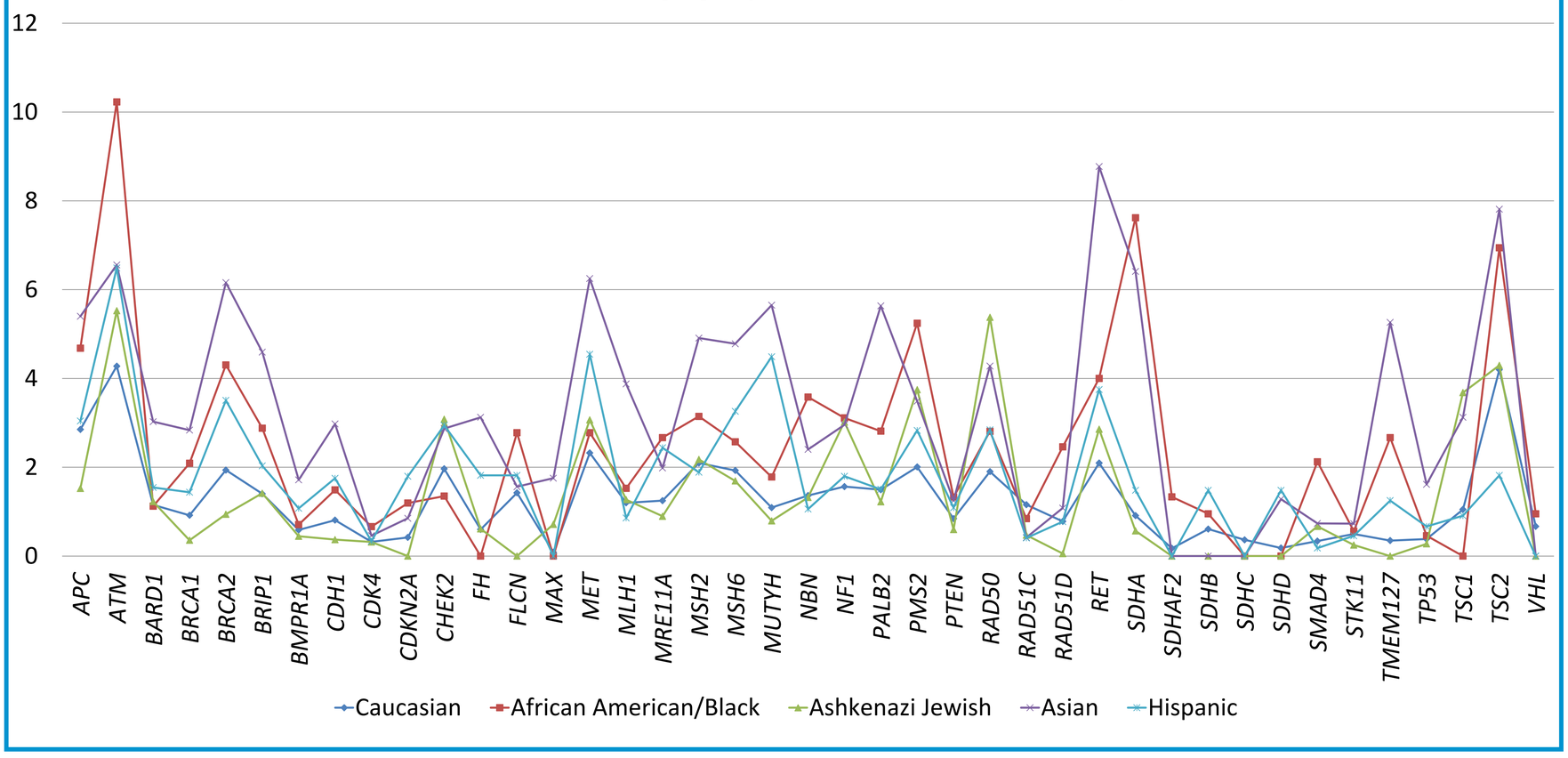
MGPT	Number of Genes Analyzed	Total cDNA Content
BRCAplus	5	12,234
GYNplus	8	21,324
PGLNext	10	18,032
PancNext	12	35,305
BreastNext	17	43,177
ColoNext	13	33,481
RenalNext	16	59,804
OvaNext	22	72,845
CancerNext	27	88,197
CancerNext-Exp (CNE)	41	112,587

FIGURE 1: VUS Rates (%) by Panel, Proportionate to Size



Fun Fact: Considering gene size by total nucleotides sequenced, VUSs were most frequently reported in *CHEK2, TSC2, CDKN2A, PMS2,* and *MUTYH*, respectively and least frequently reported in *BRIP1, BMPR1A, NF1, SMAD4*, and *STK11,* respectively.

FIGURE 2: VUS (%) by Genes and Ethnicity



TAKE-HOME POINTS

- VUS rates for MGPT vary based on ethnic background and the total gene size/panel size analyzed.
- Panel content analyzed also play a role, as genes differ in size and some tolerate more variability than others.
- Population frequency data contributes to VUS rate variation by ethnicity. Gaps will continue to decrease as more data on additional ethnic groups emerges; *e.g.* recent availability of more Asian alleles in ExAC.
- The moderate penetrance genes *BARD1, CHEK2, MRE11A,* and *RAD51C* exhibited lower-than-expected variation in VUS rates across ethnicities based on their relatively recent description, while some well-described genes (Lynch syndrome and *BRCA1/2*) showed higher variances in VUS rates. This potentially results from a bias due to extensive study of well-described genes in select ethnicities.

REFERENCES

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