Prevalence of Monoallelic *MUTYH* Carrier Status in Patients of Varied Ancestries Ascertained for Clinical Hereditary Cancer Risk Testing

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BACKGROUND

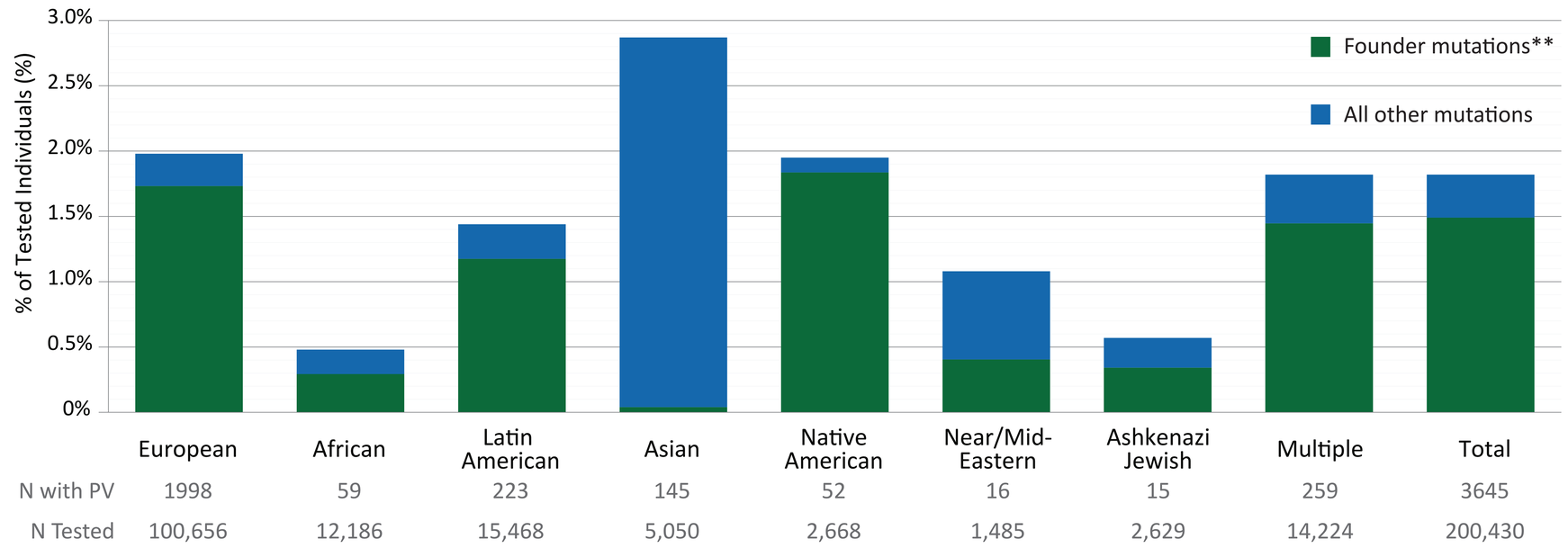
- Individuals with biallelic pathogenic variants (PVs) in the *MUTYH* gene have a 43–100% lifetime risk for colorectal cancer (CRC) due to the recessive condition *MUTYH*-Associated Polyposis (MAP).
- Carriers of a single *MUTYH* PV (monoallelic) may have up to a 2-fold increased risk for CRC.
- The prevalence of monoallelic *MUTYH* PVs in Northern Europeans is estimated to be 1-2%, due primarily to two common founder mutations [c.536A>G (p.Tyr179Cys) and c.1187G>A (p.Gly396Asp)].
- Here we determined the prevalence of monoallelic MUTYH PVs by ancestry to:
  - Compare the risk for MAP
  - Establish the proportion of tested individuals identified as candidates for modified colonoscopy screening according to recent NCCN recommendations

METHODS

- 200,430 individuals were tested with a 25-gene hereditary cancer panel that included *MUTYH*.
- All were ascertained for clinical testing based on suspicion of hereditary cancer risk.
- Individuals who underwent genetic testing prior to panel testing were excluded.
- 131 individuals with biallelic *MUTYH* PVs were also excluded.
- PVs are variants that receive a laboratory classification of Deleterious or Suspected Deleterious.
- All clinical data was obtained by health care provider report on the test request forms.
- The prevalence of the most common monoallelic *MUTYH* PVs identified among individuals of the 4 most frequently reported ancestries (European, Asian, African, Latin American) were also assessed.

RESULTS

Figure 1. Prevalence of Monoallelic MUTYH According to Ancestry*



* Individuals who did not specify an ancestry are not included

**c.1187G>A (p.Gly396Asp) and c.536A>G (p.Tyr179Cys)

Table 1. Possible Founder Monoallelic MUTYH PVs

MUTYH PV	N	Prevalence	N	Prevalence	N	Prevalence
	Full European		Partial European		No European	
c.1187G>A (p.Gly396Asp)	1242	1.23%	140	1.17%	243	0.58%
c.536A>G (p.Tyr179Cys)	506	0.50%	50	0.42%	57	0.14%
c.933+3A>C	34	0.03%	4	0.03%	1	0.00%
c.1147del (p.Ala385Profs*23)	26	0.03%	1	0.01%	6	0.01%
c.1437_1439del (p.Glu480del)	25	0.02%	4	0.03%	4	0.01%
	Full Asian		Partial Asian		No Asian	
c.934-2A>G	129	2.55%	21	1.83%	8	0.01%
c.1438G>T (p.Glu480*)	6	0.12%	0	0.00%	1	0.00%
	Full African		Partial African		No African	
c.1435G>T (p.Glu479*)	5	0.04%	2	0.07%	1	0.00%
	Full Latin Am		Partial Latin Am		No Latin Am	
c.1227_1228dupGG (p.Glu410Glyfs*43)	10	0.06%	2	0.06%	16	0.01%
c.1012C>T (p.Gln338*)	7	0.05%	0	0.00%	4	0.00%

Partial ancestry corresponds to individuals who listed multiple ancestries, one of which is the indicated ancestry; Individuals who did not specify an ancestry are not included.

- 3,645 (1.8%) individuals were found to carry a monoallelic *MUTYH* PV, with ancestry-specific positive rates ranging from 0.5–2.9% (Fig. 1).
  - The highest positive rate was observed among individuals of Asian ancestry (2.9%).
  - The positive rate among individuals of European ancestry (2.0%) is consistent with previous estimates of the monoallelic *MUTYH* prevalence in the general population.
  - The European founder mutations account for >50% of the monoallelic *MUTYH* PVs identified in all ancestries, except Asian and Near/Middle Eastern.
- There was no difference in the incidence of monoallelic *MUTYH* PVs among individuals ascertained for colorectal cancer versus other hereditary cancer risks.
- c.934-2A>G accounts for the majority of monoallelic *MUTYH* PVs among individuals of full Asian ancestry, with a prevalence of 2.55% (Table 1).
- There is evidence of possible founder mutations among individuals of African and Latin American ancestry (Table 1).

CONCLUSIONS

- This is the largest study to date of the prevalence of monoallelic *MUTYH* PVs among individuals of different ancestries through clinical panel testing for inherited cancer risk.
- The overall monoallelic *MUTYH* carrier rate was 1.8%, and may represent a reasonable approximation of the carrier frequency of monoallelic *MUTYH* PVs in the general population.
- The monoallelic *MUTYH* carrier rate was substantially higher in Asians compared to other populations, due primarily to a high frequency of a single PV, c.934-2A>G, previously reported in other studies.
- The well-studied European founder mutations are responsible for a majority of PVs in the European, Native American, Latin American, and African populations.
- We also found evidence of possible founder mutations among individuals of African and Latin American ancestry. Additional research is required to confirm these findings.
- These findings have important implications for the choice of testing strategies for the relatives of individuals with MAP and the implementation of new NCCN guidelines for earlier and more frequent colonoscopies than what is recommended for average risk individuals.

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