Biallelic Variants in *NTHL1* and *MSH3* in Individuals Ascertained from a Multigene Panel Testing (MGPT) Cohort: a Descriptive Analysis

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BACKGROUND

- Biallelic pathogenic variants (BPVs) in *NTHL1* and *MSH3* have been implicated in polyposis and/or colorectal cancer.
- To date, approximately 20 families with *NTHL1*-related polyposis and 3 families with *MSH3*-related polyposis have been published[1,2,3]; there is limited data on the phenotypic spectrum in these families.
- We aim to contribute to the available data and describe features in individuals with *NTHL1* and *MSH3* BPVs identified via MGPT.

METHODS

- A retrospective data review of cases with *NTHL1* and *MSH3* BPVs detected by MGPT (32 to 81 genes) was conducted for cases received between January 2019 and December 2021.
  - Unless otherwise stated, individuals did not have co-occurring variants in other genes.
- Proband clinical histories were obtained via test requisition forms and clinical documents submitted to our laboratory.

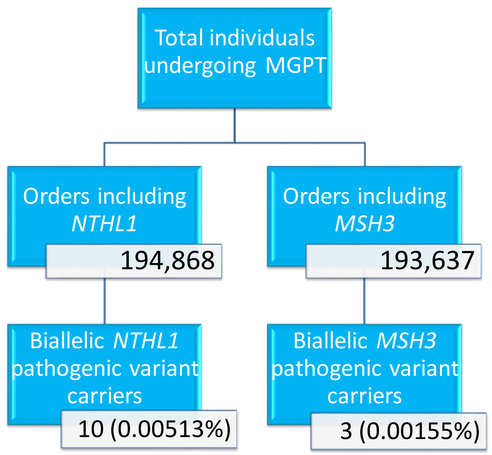
TAKE-HOME POINTS

Twelve of 13 individuals with biallelic *NTHL1* or *MSH3* mutations in our MGPT cohort had a polyposis and/or early-onset colorectal cancer phenotype.

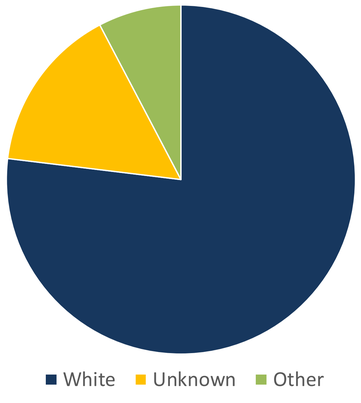
BPVs in *NTHL1* or *MSH3* are exceedingly rare but are likely associated with an autosomal recessive polyposis syndrome.

This data doubles the published literature on individuals with BPVs in *MSH3* and adds significantly to the published literature on individuals with BPVs in *NTHL1*.

NTHL1 and *MSH3* COHORT



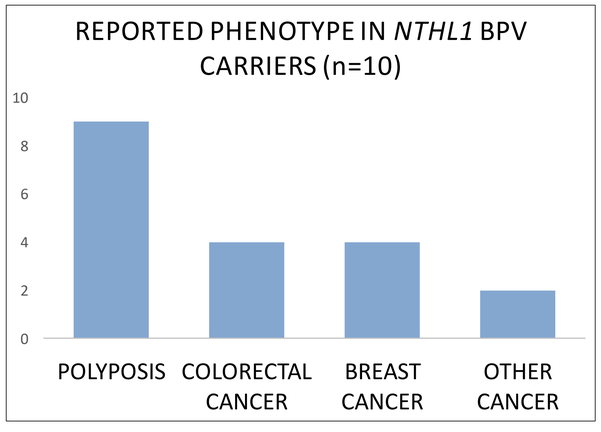
DEMOGRAPHICS

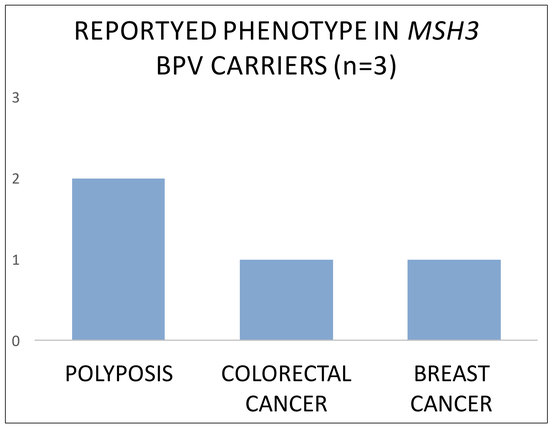


RESULTS

Case	Gene	Variants	Sex	Age at testing (in years)	Polyposis?/ # if known	CRC? (age at dx)	Other cancers
1	*NTHL1*	p.Y130* (c.390C>A) p.Q90* (c.268C>T)	F	59	Yes/unknown	No	melanoma, breast, head and neck cancer, SCC
2	*NTHL1*	p.Q90* (c.268C>T p.Q90* (c.268C>T)	F	44	Yes/9	No	bilateral breast, BCC
3	*NTHL1*	p.Q90* (c.268C>T) p.Q90* (c.268C>T)	F	50	Yes/10+	No	N/A
4	*NTHL1*	p.Q145* (c.433C>T) p.Q90* (c.268C>T)	F	51	Yes/unknown	Yes (45)	N/A
5	*NTHL1*	c.139+1G>A c.139+1G>A	M	73	Yes/40+	Yes (54)	N/A
6	*NTHL1*	p.Q90* (c.268C>T) p.Q90* (c.268C>T)	F	58	Yes/7+	Yes (56)	bilateral breast
7	*NTHL1*	p.Q90* (c.268C>T) p.Q90* (c.268C>T)	F	37	Not reported	No	breast
8	*NTHL1* *RAD51D*	p.Q90* (c.268C>T) p.Q90* (c.268C>T) p.R232* (c.694C>T)	M	41	Yes/20+	No	N/A
9	*NTHL1*	p.Q90* (c.268C>T) p.Q90* (c.268C>T)	M	77	Yes/17+	No	N/A
10	*NTHL1*	p.Q90* (c.268C>T) c.139+1G>A	M	44	Yes/30+	Yes (32)	N/A
11	*MSH3*	c.1660_1661delAT (p.M554Efs*14) c.1660_1661delAT (p.M554Efs*14)	F	50	Yes/unknown	No	breast
12	*MSH3*	c.2807delT (p.F936Sfs*21) c.2807delT (p.F936Sfs*21)	F	44	Not reported	Yes (44)	N/A
13	*MSH3*	c.978_984delTTCCCGG (p.F326Lfs*3) c.260_263delAGAA (p.K87Rfs*14)	M	66	Yes/19+	No	N/A

BCC = basal cell carcinoma; SCC = squamous cell carcinoma; s/p = status post; N/A = not applicable





REFERENCES

1. Kuiper R et al. In: GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993. 2020 Apr 2; 2. Adam R et al. *Am J Hum Genet*. 2016 Aug 4;99(2):337-51; 3. Aelvoet A et al. *Fam Cancer*. 2022 Jun 8.