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

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Background
Autosomal recessive familial polyposis has been reported in association with biallelic pathogenic variants (BPVs) in *NTHL1* and *MSH3*. Current publications for these genes describe a small number of families ascertained from colorectal cancer (CRC) and/or polyposis cohorts. We aim to contribute to the available data and describe features in individuals with *NTHL1* and *MSH3* BPVs identified via multi-gene panel testing (MGPT).

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

Results
Ten individuals (6 females, 4 males) were found to have BPVs in *NTHL1*, 9 with a history of polyposis and 4 with a diagnosis of CRC (mean age of diagnosis: 46.75 years). Of the females, 4 had breast cancer (mean age of diagnosis: 50.4 years), 2 of which were bilateral. Three individuals were found to have BPVs in *MSH3*, 2 with a history of polyposis and 1 with a diagnosis of CRC at 44 years. The positive rate for *NTHL1* and *MSH3* BPVs was 0.00513% and 0.00155%, respectively.

Conclusions
This descriptive analysis adds to the limited literature on individuals with BPVs in *NTHL1* and *MSH3* and supports the hypothesis that BPVs in *NTHL1* and *MSH3* predispose to familial polyposis. In our cohort, 12 of 13 individuals reported a personal history of CRC or polyposis. Our results indicate that BPVs in *NTHL1* and *MSH3* are exceedingly rare and continued study is necessary to determine the full phenotypic spectrum and penetrance of tumors in individuals with BPVs - particularly for the observed breast cancer, which could be a product of a MGPT cancer predisposition cohort.

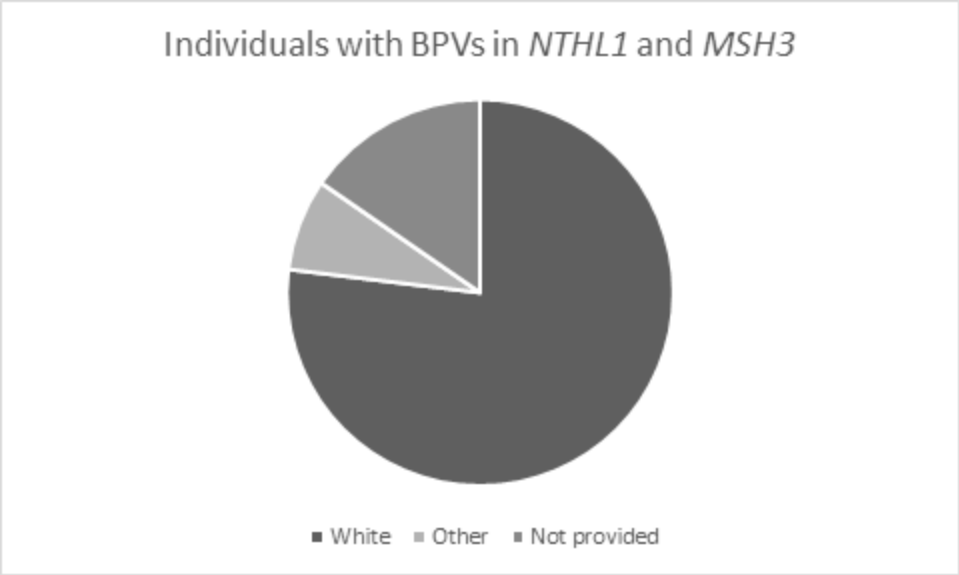
Table 1

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

Figure 1


Individuals with BPVs in *NTHL1* and *MSH3*
White
Other
Not provided