Beyond the Colon: do biallelic variants in *NTHL1* predispose to breast cancer?

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Background

Biallelic pathogenic variants (BPVs) in *NTHL1* have been identified as a cause of hereditary colorectal polyposis and/or cancer. Extracolonic tumors have been observed in the approximately 20 families described in published literature; however, the full spectrum of the *NTHL1*-tumor syndrome (NTS) has yet to be fully characterized. We present 33 unrelated cases with BPVs in *NTHL1* ascertained from a multigene panel testing (MGPT) cohort.

Methods

A retrospective data review of cases was performed with *NTHL1* BPVs detected by MGPT (32- 81 genes) between April 2017-September 2022. Proband histories were obtained via test requisition forms and clinical documents submitted to our laboratory. Biallelic PVs include individuals with two PVs in *NTHL1.*

Results

Thirty-three individuals were found to have BPVs in *NTHL1*, 21 with reported polyps, 14 with breast cancer (BC), 13 with colorectal cancer, 10 with skin cancer (4 melanoma), 5 with brain tumors, and 3 with no cancer/polyps. Other tumors occurred in less than 10% of the cohort (n≤3). BC was the most common cancer, reportedly diagnosed in 14/22 females (63.6%). Of these, 4 females had more than one BC diagnosis. The average age of BC diagnosis was 47.15 years.

Conclusions

Individuals with BPVs in *NTHL1* in our cohort exhibit a multi-tumor predisposition. The high rate of breast cancer may be explained by the ascertainment bias inherent in MGPT, but when compared to the frequency of breast cancer in our MGPT cohort (45%), this tumor type is enriched in individuals with BPVs in *NTHL1*. Compared to the general population, individuals with BPV appear more likely to have multiple primary BCs (22% vs 1-11%) and are diagnosed at younger ages (47y vs 63y). This case series suggests that targeted study may be worthwhile to establish early-onset and/or multiple primary BC as a significant feature of NTS.