***MSH2* variant causing atypical CMMRD and atypical LS**

Melyssa Aronson[1], Angela L. Jacobson[2], Brian H. Shirts[2], Andree MacMillan[3], Kathleen Buckley[4], Ashley P. L. Marsh[5], Lauren Currie[6], Allison Rusnak[7], Stephanie Wagler[8], Uri Tabori[9]

1. Zane Cohen Centre, Mount Sinai Hospital, Toronto, ON Canada
2. University of Washington, Seattle, WA, USA
3. Provincial Medical Genetics Program, St John's, NL, Canada
4. IWK Health, Halifax, NS, Canada
5. Ambry Genetics, Aliso Viejo, CA, USA
6. GeneDx, Seattle, WA, USA
7. Children's Hospital of Eastern Ontario, Ottawa, Canada
8. Grand River Hospital, Kitchener, ON Canada
9. Hospital for Sick Children, Toronto, ON Canada

Background and Aim

MSH2 heterozygous pathogenic variants causes Lynch syndrome (LS) with high-cancer risk, however, biallelic variants may be lethal and rare in CMMRD. In 2018, homozygous *MSH2* c.-82G>C was identified in an 18 year old with glioblastoma (GBM) and NF1 features. Her GBM (and her sister's at age 10) were MSH2/6 deficient, however, non-malignant tissue was MMR proficient, atypical for CMMRD. Family history revealed no other cancers, which is atypical for *MSH2*-related LS.

Methods

Information on individuals with *MSH2* c.-82G>C was collected from Ontario, Newfoundland, University of Washington, Ambry Genetics and GeneDx between 2018-2024.

Results

65 individuals (6 homozygous, 59 heterozygous) from 54 families were identified. Gender (n=57); 13 male, 44 females. Ancestry (n=50); 35 (70%) from Newfoundland (Canada), 1 Canadian (NOS), 1 Ashkenazi-Jewish, 13 White (NOS). 10% (10 of 40 families) reported 1+ kin with childhood/early-onset glioma; 5 affected kin had biallelic c.-82G>C variants, or MSH2/6 deficient glioma.

Of the 6 homozygous carriers, 1 child had no cancer history at age 6. 5 (83%) had childhood/early-onset high-grade glioma (HGG), age range: 8-18 years. 2 had NF1 features (café-au-lait-macules, axillary freckling). IHC showed MSH2/6 deficiency in 4 HGG, with proficient MMR in non-malignant tissue.

Medical information on 57 of 59 heterozygous carriers summarized (Table 1). Notably, 15 malignancies were MSH2/6 deficient and 5 tested showed secondary somatic loss or methylation in *MSH2*.

Conclusions

- *MSH2* c.-82G>C, a suspected Newfoundland founder variant, is associated with atypical CMMRD and atypical LS.
- Childhood/early-onset HGG seen in 83% of homozygous carriers, and in 10% of all families. Typical CMMRD features (e.g. MMR deficiency in non-malignant tissue, early-onset GI and hematological cancers) were not observed.

- IHC deficient LS-related cancers reported in heterozygous carriers, although cancer penetrance appears to be lower than typical *MSH2*-related LS.
- Further studies needed to assess risk and surveillance protocols

Table 1: Medical information for heterozygous *MSH2* c.-82G>C variants (n=57 individuals)

Cancer site	#	%	Age range	Median age	IHC done	MSH2 +/- MSH6	MSH6 def	Intact
Unaffected	17	30.5	20-65	51.5				
CRC^	9	15.2	25-85	52.5	8	7	0	1 (age 76)
Colon polyposis/TVA	3	5.1	65-68	66	0	0	0	0
Breast^	13	22.0	35-88	52.5	1	0	0	1 (age 79)
Endometrial*	4	6.8	45-65	56	4	3	1*	0
Gastric	1	1.7	75	75	1	0	0	1 (age 70s)
Melanoma	1	1.7	62	62	0	0	0	0
Ovarian~	3	5.1	70-84	70	3	0	0	1 (age 70)
Prostate	1	1.7	64	64	0	0	0	0
Sebaceous Neoplasm^	3	5.1	38-63	50.5	3	3	0	0
Urothelial	2	3.4	43-65	54	2	2	0	0
Lymphoma*	1	1.7	58	58	1	0	1*	0

^ One synchronous case reported

* One individual had metachronous endometrial and lymphoma cancer, and also had an *MSH6* PV

~ Two individuals also had *BRCA2* PV