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Is Lynch syndrome a pediatric onset cancer predisposition syndrome: a systematic review

Chelsea Ash, PGY6 Pediatric Hematology-Oncology [1, 2]

Supervisors: Catherine Goudie [1], Prarthna Clare [2]

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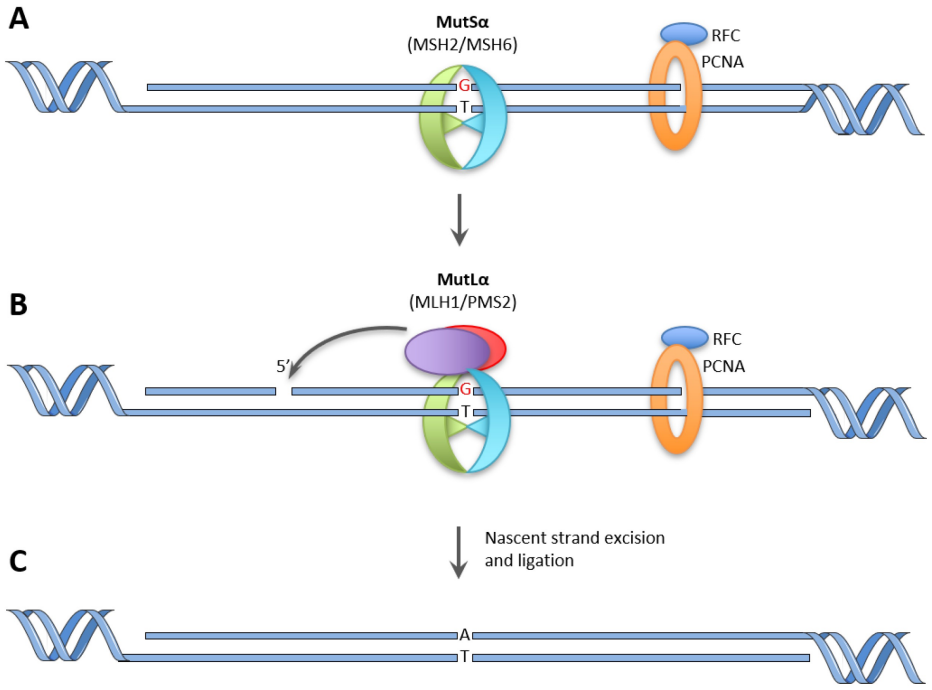
[1] McGill University

[2] University of Oxford

Background: Lynch syndrome

- Heterozygous, autosomal dominant variant in one of the DNA mismatch repair genes: [1]
  - *MLH1, MSH2, MSH6, PMS2*

- Failure to correct mismatching leads to hypermutation and subsequent errors in cell replication [1]



Frederiksen *et al.* 2021, *Int. J. Mol. Sci.*

Background: Lynch syndrome

- Cancers of the colon and rectum, stomach, small intestine, biliary tract, genitourinary tract, reproductive organs and brain [3]
  - Most commonly occur > age 40 years
  - Cancer risk is high: 66% of men develop colorectal cancer, 39% of women develop endometrial cancer

- Widened availability of genomic testing across the lifespan has revealed a growing collection of children with Lynch Syndrome but relevance is not well understood

Genomic sequencing in Quebec

- Since 2020 all pediatric cancer patients in Quebec are offered paired germline and tumour sequencing as part of research initiatives (Signature, Triceps & others [4])

- A unique opportunity to determine the prevalence and relevance of Lynch syndrome in unbiased children and adolescents with cancer

- To date, 599 patients have undergone successful germline analysis including WES/targeted cancer gene panel including MMR genes
  - 0.5% have been found to have a heterozygous, pathogenic germline variant in one of *PMS2*, *MSH6* and *MLH1*

Case example (MCH)

- Previously healthy 7-year-old boy newly diagnosed with SR B-ALL with favorable cytogenetics
- Family history:
  - Maternal grandmother - colorectal cancer (62)
  - Maternal great-grandmother - colorectal cancer (92)
  - Maternal great aunt – ovarian cancer (35)
  - Maternal great aunt – endometrial cancer (70s)
  - PGM breast cancer (61)
- Family consented to *Signature* study → found to have a pathogenic germline variant in *PMS2*
- Many questions arise from this case:
  1. **Are there other patients like him?**
  2. What does this finding mean for the patient?
  3. Is this finding relevant to his current cancer diagnosis and management?

Study aims

Primary objective:

What proportion of pediatric oncology patients who have undergone genetic sequencing have a pathogenic or likely pathogenic variant in a gene associated with Lynch Syndrome?

Secondary (future) objectives:

1. What proportion of pediatric oncology patients identified to have Lynch syndrome variants also have a second hit in tumour DNA?
2. How does this data compare with that of a control (non-oncology) cohort?

Methods

- Systematic review following the Principles of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement
  - Prospero ID: CRD42022359233
- Expert librarian recruited to develop search strategy (PubMed, Embase and Web of Science, grey search with Google Scholar)
- Article review by two independent reviewers → collection and organization via Rayyan software
- Inclusion criteria:

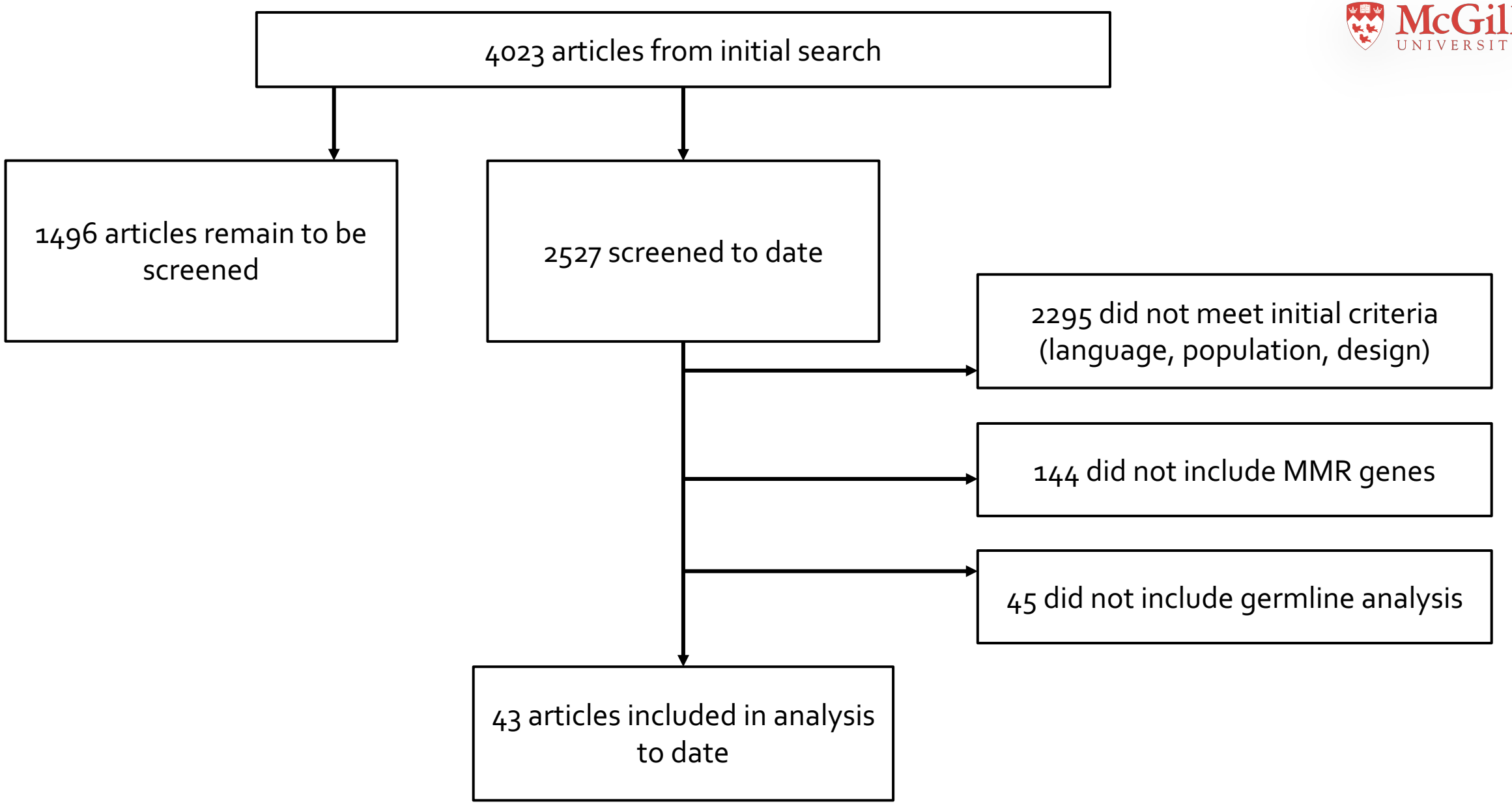
Observational studies (case reports, case series, and cohort) and intervention studies

Germline analysis of MMR genes (*MSH2*, *MSH6*, *PMS2*, *MLH1*) via targeted sequencing/WES/WGS

Pediatric (≤ 18 years) patients with a diagnosis of malignancy

Published from 2012 onwards

Published in English


4023 articles from initial search
1496 articles remain to be screened
2527 screened to date
2295 did not meet initial criteria (language, population, design)
144 did not include MMR genes
45 did not include germline analysis
43 articles included in analysis to date

Preliminary results

- 43 studies
- 3246 pediatric oncology patients who have undergone germline MMR gene testing
- 23 (0.7%) patients found to have pathogenic or likely pathogenic Lynch syndrome variants
- 8 females, 8 males, 7 not defined

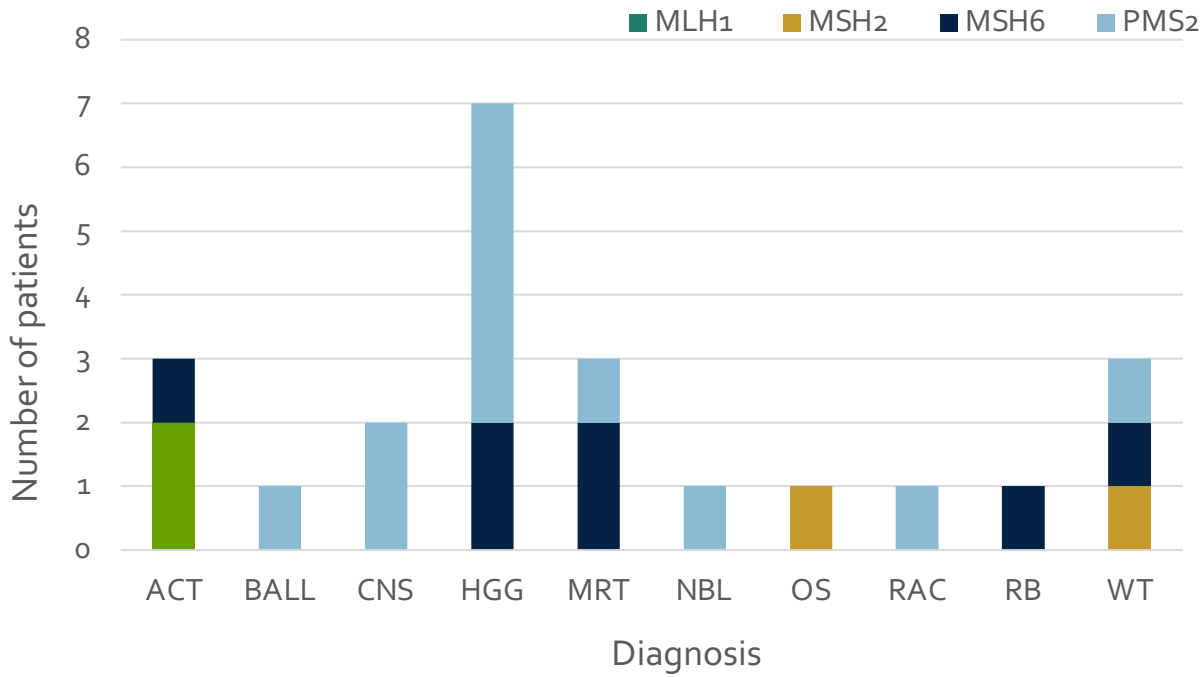


Figure 1. Lynch syndrome variants per pediatric oncologic diagnosis

ACT = adrenocortical tumour, **BALL** = B-cell acute lymphoblastic leukemia, **CNS** = central nervous system tumour, **HGG** = high-grade glioma, **MRT** = malignant rhabdoid tumour, **NBL** = neuroblastoma, **OS** = osteosarcoma, **RAC** = rectal adenocarcinoma, **RB** = retinoblastoma, **WT** = Wilms tumour

Conclusions

- Prevalence of Lynch syndrome in pediatric oncology patients in Quebec (0.5%) appears to be comparable to that of literature reports (0.7%)
- Findings may be relevant for families but evidence of causality is lacking

- Next steps:
  - Complete oncology cohort analysis & consideration of somatic second hits
  - Conduct genotype/phenotype correlation
  - Compare with a non-oncology cohort
  - Follow ongoing *Signature* data collection
  - Distribute findings beyond the oncology setting

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References

1. Idos, G., & Valle, L. (1993). Lynch Syndrome. In M. P. Adam, D. B. Everman, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. W. Gripp, & A. Amemiya (Eds.), GeneReviews((R)). Seattle (WA).

2. Frederiksen, J. H., Jensen, S. B., Tümer, Z., & Hansen, T. V. O. (2021). Classification of MSH6 Variants of Uncertain Significance Using Functional Assays. International journal of molecular sciences, 22(16), 8627. https://doi-org.proxy3.library.mcgill.ca/10.3390/ijms22168627

3. Stoffel, E., Mukherjee, B., Raymond, V. M., Tayob, N., Kastrinos, F., Sparr, J., . . . Gruber, S. B. (2009). Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. Gastroenterology, 137(5), 1621-1627. doi:10.1053/j.gastro.2009.07.039

4. Khater, F., Vairy, S., Langlois, S., Dumoucel, S., Sontag, T., St-Onge, P., Bittencourt, H., Dal Soglio, D., Champagne, J., Duval, M., Leclerc, J. M., Laverdiere, C., Tran, T. H., Patey, N., Ellezam, B., Perreault, S., Piché, N., Samson, Y., Teira, P., Jabado, N., … Sinnett, D. (2019). Molecular Profiling of Hard-to-Treat Childhood and Adolescent Cancers. JAMA network open, 2(4), e192906. https://doi-org.proxy3.library.mcgill.ca/10.1001/jamanetworkopen.2019.2906