

University of Groningen

## Analysis in the Prospective Lynch Syndrome Database identifies sarcoma as part of the Lynch syndrome tumor spectrum

PLSD Collaborators

*Published in:*  
International Journal of Cancer

*DOI:*  
[10.1002/ijc.33214](https://doi.org/10.1002/ijc.33214)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2021

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*  
PLSD Collaborators (2021). Analysis in the Prospective Lynch Syndrome Database identifies sarcoma as part of the Lynch syndrome tumor spectrum. *International Journal of Cancer*, 148(2), 512-513.  
<https://doi.org/10.1002/ijc.33214>

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

## LETTER TO THE EDITOR



# Analysis in the Prospective Lynch Syndrome Database identifies sarcoma as part of the Lynch syndrome tumor spectrum

Dear editor,

Lynch syndrome (LS) is the most common hereditary cancer syndrome. It results from heterozygous pathogenic germline variants in the mismatch repair (MMR) genes that are carried by over 1 in 200 individuals. Pathogenic variants in each of the MMR genes, *path\_MLH1*, *path\_MSH2*, *path\_MSH6* and *path\_PMS2*, result in different risks for cancers in organs including the colorectum, endometrium, ovaries, stomach, small bowel, bile duct, pancreas and upper urinary tract.<sup>1</sup> These cancers, but not sarcomas, are commonly cited as LS spectrum cancers. Sarcomas include osteosarcomas (OS) that have a worldwide incidence of 4.3 per million in males and 3.4 per million females per year,<sup>2</sup> and soft tissue sarcomas (STS) that are a heterogeneous group of cancers of mesenchymal origin with a population incidence of 3.5 per 100 000 people per year in the US.<sup>3</sup> In the most recent study from the Prospective Lynch Syndrome Database (PLSD) we reported 14 cases of sarcoma among 1808 prospectively observed tumors in 6350 carriers of *path\_MMR* variants with 51 646 follow-up years (FUY).<sup>1</sup>

The PLSD is an international multicenter prospective observational study without a control group, in which we record cancers diagnosed in genetically confirmed carriers of class 4 and 5 *path\_MMR* variants undergoing long-term surveillance. Data on previous cancers are collected at inclusion.

In the PLSD, the mean age at prospective diagnosis of OS ( $n = 10$ ) was 63 years (range, 32-74) and of STS ( $n = 4$ ) 62 years (range, 57-71). More than half of sarcomas (57%, 8/14) occurred in *path\_MSH2* carriers even though they comprised only 40% of PLSD patients, 21% were in *path\_MLH1* (3/14), 14% in *path\_PMS2* (2/14) and 7% (1/14) in *path\_MSH6* carriers. The type of *path\_MMR* variants identified in OS and STS patients were mainly predicted to cause missense changes (57%, 8/14), followed by deletions (4/14) and predicted splicing changes (2/14). Eight of 14 patients (57%) were male.

Comparing the prospectively observed incidence of OS in the PLSD (21 per 100 000 FUY) to the worldwide general population incidence reported by Mirabello et al showed a 50- to 63-fold relative incidence in LS.<sup>2</sup> This is particularly striking as OS is primarily a cancer of childhood and adolescence, while in the PLSD, prospective observation is limited to ages 25 to 80 years.<sup>1</sup> Cumulative incidence at 75 years (95% confidence interval) was 0.73% (0-1.56), 4.24% (0.54-7.93) 0 and 1.57% (0-4.63) in

*path\_MLH1*, *path\_MSH2*, *path\_MSH6* and *path\_PMS2* carriers, respectively, which for *path\_MSH2* carriers was significantly higher than the 0.1% population cumulative incidence at 75 years ( $P < .05$ ).<sup>3,4</sup> Lifetime risk of OS in *path\_MSH2* carriers based on this comparison would be 42.4-fold (5.4-79.3) that of the general population.

In addition to the 14 prospectively observed sarcomas in the PLSD, 16 further patients had been affected by sarcoma before or at their inclusion: 5 with OS and 11 with STS, with mean ages at diagnosis of 48.2 (range, 4-64) and 35.1 (range, 24-54) years, respectively. Again, *path\_MSH2* carriers were the most frequently affected (50%, 8/16), followed by *path\_MLH1* carriers (38%, 6/16). Regarding the type of *path\_MMR* variants identified in these patients, predicted missense changes were most common (7/16), followed by splicing (5/16) and deletion variants (4/16). Regarding gender, equal numbers of females (8) and males (8) were affected.

There is a paucity of studies linking OS and LS, even though MMR deficiency (dMMR) is seen very frequently in OS. In one previous study, loss of expression of MSH2/MSH6 was observed in 81% (54/67) of OS and was associated with better prognosis.<sup>5</sup> In contrast, in another retrospective study of 304 sarcomas that included only one case of OS, dMMR was confirmed in only 2.3% (7/304) and LS was diagnosed in one of these (14%).<sup>6</sup>

A more recent study found that 6% (45/785) of STS had a microsatellite instability-high (MSI-H) or intermediate (MSI-I) signature, and this was concordant with dMMR evaluated by immunohistochemistry. Two of the 45 cases (4.4%) had LS.<sup>7</sup> Most recently, *MSH2* was reported as one of a small number of genes that showed a significantly higher burden of pathogenic or likely pathogenic variants in European OS patients compared to controls (0.4%, 3 of 732 patients).<sup>8</sup>

We conclude that the incidence of OS in LS patients is significantly increased compared to the general population. We suggest that osteosarcoma is part of the LS spectrum in adults and seems to be associated particularly with the *path\_MSH2* genotype. The association of STS with *path\_MMR* variants is currently less clear, although there are case reports on young LS carriers with soft tissue sarcomas.<sup>9,10</sup>

## KEYWORDS

Lynch syndrome, *MSH2*, sarcoma

## ACKNOWLEDGEMENTS

The PLSD would not have been possible without its many contributors and without initial support from the core members of The European Hereditary Tumor Group (former Mallorca group) contributing all their follow-up data for the first PLSD version.

**Abbreviations:** dMMR, MMR deficiency; FUY, follow up years; LS, Lynch syndrome; MMR, mismatch repair; MSI-H, microsatellite instability high; MSI-I, microsatellite instability intermediate; OS, osteosarcoma; *path\_MLH1*, pathogenic (disease-causing) variants of the *MLH1* gene; *path\_MSH2*, pathogenic (disease-causing) variants of the *MSH2* gene; *path\_MSH6*, pathogenic (disease-causing) variants of the *MSH6* gene; *path\_PMS2*, pathogenic (disease-causing) variants of the *PMS2* gene; PLSD, Prospective Lynch Syndrome Database; SFT, soft tissue sarcoma.

## CONFLICT OF INTEREST



The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The cancer risk algorithm is available at the PLSD website ([www.plsd.eu](http://www.plsd.eu)) that is based upon the results presented in this report and enables interactive calculation of remaining lifetime risks for cancer in any LS patient by giving their age, gender, and gene variant.

## ETHICS STATEMENT

The study adhered to the principles set out in the Declaration of Helsinki. It was approved by the Oslo University Hospital ethical committee ref. S-02030 and its data governance rules by the Norwegian Data Inspectorate ref. 2001/2988-2. Genetic testing was performed with informed consent according to local and national requirements and all reporting centers exported only de-identified data to PLSD.

Mev Dominguez-Valentin<sup>1</sup>   
 Julian R. Sampson<sup>2</sup>  
 Pål Møller<sup>1</sup>  
 Toni T. Seppälä<sup>3</sup>   
 PLSD Collaborators<sup>†</sup>

<sup>1</sup>Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, part of Oslo University Hospital, Oslo, Norway

<sup>2</sup>Institute of Medical Genetics, Division of Cancer and Genetics, Cardiff University School of Medicine, Cardiff, UK

<sup>3</sup>Department of Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

### Correspondence

Mev Dominguez-Valentin, Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, part of Oslo University Hospital, Oslo, Norway.  
 Email: [mev.dominguez.valentin@rr-research.no](mailto:mev.dominguez.valentin@rr-research.no)

Toni T. Seppälä, Department of Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland.  
 Email: [toni.seppala@finnet.fi](mailto:toni.seppala@finnet.fi)

<sup>†</sup>PLSD collaborators: John-Paul Plazzer, BE; Sigve Nakken, PhD; Christoph Engel, MD; Stefan Aretz, MD; Mark A. Jenkins, PhD; Lone Sunde, MD, PhD; Inge Bernstein, MD, PhD; Gabriel Capella, MD; Francisc Balaguer, MD; Huw Thomas, PhD, FRCP; D. Gareth Evans, MD FRCP; John Burn, MD, FMedSci; Marc Greenblatt, MD; Eivind Hovig, PhD; Maartje Nielsen, MD, PhD; Wouter H. de Vos tot Nederveen Cappel, MD; Rolf H. Sijmons, MD; Lucio Bertario, MD; Maria Grazia Tibiletti, MD; Giulia Martina Cavestro, MD; Annika Lindblom, MD; Adriana Della Valle, MD; Francisco Lopez-Köstner, MD, PhD; Nathan Gluck, MD, PhD; Lior H. Katz, MD; Karl Heinemann, MD, PhD; Carlos A. Vaccaro, MD; Reinhard Büttner, MD; Heike Görgens, MD; Elke Holinski-Feder, MD; Monika Morak, PhD; Stefanie

Holzappel, MD; Robert Hüneburg, MD; Magnus von Knebel Doeberitz, MD; Markus Loeffler, MD; Nils Rahner, MD; Jürgen Weitz; Verena Steinke-Lange, MD; Sanne W. ten Broeke, PhD; Wolff Schmiegel, MD; Deepak Vangala, MD; Kirsi Pylvänäinen, MD; Laura Renkonen-Sinisalo, MD; John L. Hopper, PhD; Aung Ko Win, PhD; Robert W. Haile, PhD; Noralane M. Lindor, MD; Steven Gallinger, MD, PhD; Loïc Le Marchand, PhD; Polly A. Newcomb, PhD; Jane C. Figueiredo, PhD; Stephen N. Thibodeau, PhD; Lars Henrik Jensen, MD, PhD; Majbritt Busk Madsen, PhD; Lone Krøldrup, MD; Mef Nilbert, MD, PhD; Leticia Moreira, MD; Ariadna Sánchez, MD; Miquel Serra-Burriel, PhD; Marta Pineda, PhD; Matilde Navarro, MD; Joan Brunet Vidal; Ignacio Blanco, MD; Kate Green, MD; Fiona Laloo, MD, FRCP; Emma J. Crosbie, PhD, MRCOG; James Hill, MD; Oliver G. Denton, BSc; Einar Andreas Rødland, PhD; Hans Vasen, MD; Miriam Mints, MD; Florencia Neffa, MD; Patricia Esperon, PhD; Karin Alvarez, PhD; Revital Kariv, MD; Guy Rosner, MD; Tamara Alejandra Pinero, PhD; María Laura Gonzalez, MD; Pablo Kalfayan, MD; Douglas Tjandra, MD; Ingrid M. Winship, MD; Finlay Macrae, MD; Gabriela Möslin, MD; Jukka-Pekka Mecklin, MD.

## ORCID

Mev Dominguez-Valentin  <https://orcid.org/0000-0001-7856-0057>

Toni T. Seppälä  <https://orcid.org/0000-0002-4940-3498>

## REFERENCES

- Dominguez-Valentin M, Sampson JR, Seppala TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the prospective lynch syndrome database. *Genet Med*. 2019;22:15-25.
- Mirabello L, Troisi RJ, Savage SA. International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons. *Int J Cancer*. 2009;125(1):229-234.
- Surveillance Epidemiology, and End Results (SEER) Program. [www.seer.cancer.gov](http://www.seer.cancer.gov). 2020.
- Cancer Registry of Norway. *Cancer in Norway 2018—Cancer incidence, mortality, survival and prevalence in Norway*. Oslo: Cancer Registry of Norway; 2018.
- Jentzsch T, Robl B, Husmann M, Bode-Lesniewska B, Fuchs B. Expression of MSH2 and MSH6 on a tissue microarray in patients with osteosarcoma. *Anticancer Res*. 2014;34(12):6961-6972.
- Doyle LA, Nowak JA, Nathenson MJ, et al. Characteristics of mismatch repair deficiency in sarcomas. *Mod Pathol*. 2019;32(7):977-987.
- Latham A, Srinivasan P, Kemel Y, et al. Microsatellite instability is associated with the presence of lynch syndrome pan-cancer. *J Clin Oncol*. 2019;37(4):286-295.
- Mirabello L, Zhu B, Koster R, et al. Frequency of pathogenic Germline variants in cancer-susceptibility genes in patients with osteosarcoma. *JAMA Oncol*. 2020:e200197. [published online ahead of print]. <https://doi.org/10.1001/jamaoncol.2020.0197>
- Bjorkman P, Kantonen I, Blomqvist C, Venermo M, Alback A. En bloc resection of visceral aorta and right kidney due to aortic sarcoma using temporary extracorporeal bypass grafting. *J Vasc Surg Cases Innov Tech*. 2019;5(4):589-592.
- Tlemsani C, Leroy K, Gimenez-Roqueplo AP, et al. Chemoresistant pleomorphic rhabdomyosarcoma: whole exome sequencing reveals underlying cancer predisposition and therapeutic options. *J Med Genet*. 2020;57(2):104-108.