Revision af polyposeguideline

Charlotte Lautrup, on behalf of the guideline working group

”Udredning og opfølgning for arvelige polyposesyndromer” (fra 2020)

og

”Udredning for FAP, A-FAP og GAPPS” (fra 2020)

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Dansk Selskab for Medicinsk Genetik (DSMG)
Dansk Kirurgisk Selskab (DKS)

Working group

- Anne Marie Jelsig, overlæge, Afdeling for Genetik, Rigshospitalet (tovholder)
- Charlotte Lautrup, overlæge, Klinisk Genetisk Afdeling, Aarhus Universitetshospital
- Karina Rønlund, overlæge, Klinisk Genetisk Afdeling, Vejle, Sygehus Lillebælt
- Lone Sunde, overlæge, professor, Klinisk Genetisk Afdeling, Aalborg Universitetshospital
-
- DKS: John Gásdal Karstensen, overlæge, Professor, Gastroenheden, Hvidovre Hospital
- Niels Jespersen, overlæge, Gastroenheden, Hvidovre Hospital
- Niels Qvist, overlæge, professor, Kirurgisk Afdeling A, Odense Universitetshospital
- Ole Thorlascius-Ussing, overlæge, professor, Kirurgisk afdeling, Aalborg Universitetshospital
-
- **Udpeget fra Dansk Selskab for Gynækologi og Obstetrik**
- Zohreh Ketabi, overlæge, Gynækologisk Klinik, Rigshospitalet

Major changes

- Serrat polyposis syndrome
- MUTYH Heterozygotic carriers
- Polyposis of unknown etiologi – definition and surveillance

Ændringer i den genetiske udredning:

APC

AXIN2

BMPR1A

GREM1 (duplikationer)

MLH1

MLH3

MSH2

MSH3

MSH6

NTHL1

PMS2

POLD1

POLE

PTEN

SMAD4

STK11

Gener, der kan overvejes

MBD4

RNF43

Colorectal polyps are common

- Most of these won't evolve into cancer
- 30-50% >50y have colonic polyps

Risk factors

- Male sex
- Red meat, smoking, high BMI
- Teraphy-induced (Chemo/radiation at young age)
- Colibactin-producing pks+Escherichia coli

- **More and more adenomas are detected:**

- 1) Population screening
- 2) The quality of endoscopes has improved

When to suspect inherited polyposis syndrome

2c: Serrate polypper

En patient med ≥5 serrate læsioner/polypper proksimalt for rectum (hvor alle er på 5 mm eller større, og hvor to eller flere er minimum 10 mm)

En patient med >20 serrate læsioner/polypper uanset lokalisation, men hvor fem eller flere er lokaliseret proksimalt for rektum.

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ORIGINAL ARTICLE

Germline pathogenic variants in *RNF43* in patients with and without serrated polyposis syndrome

Heidi Hesselø Brinch[1] · Anna Byrjalsen[1] · Zuzana Lohse[2] · Andreas Ørslev Rasmussen[3] · John Gásdal Karstensen[4] · Britta Schlott Kristiansen[5] · Anne Marie Jelsig[1]

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literature. The patients were referred to genetic counseling due to suspicion of hereditary cancer. They underwent genetic testing with custom NGS gene panels including *RNF43* as part of a routine genetic work-up. Three LPVs, one multi-exon deletion and two nonsense variants, were detected in four families. Family I had a history of CRC and serrated polyps, but in the three other families (II–IV) there was no history of CRC or serrated polyps. Colonoscopies in the probands of these families did not reveal any serrated polyps and/or CRC despite some of them being relatively old. Our findings suggest that the penetrance of *RNF43*-related disease is much lower than previously thought, and raise questions about the connection between *RNF43* and disease. The results highlight the complexity of genetic counseling in *RNF43* positive families– particularly in families without polyposis. Further research is needed to elucidate the role of *RNF43* in the risk of SPS and CRC.

Serrat polyposis syndrome

- "There is no clear evidence to support genetic testing in patients who meet the clinical criteria for SPS. In a few families, a pathogenic variant in RNF43 has been identified, which appears to segregate with SPS in the family.“

- "It is currently known that many (over 1,000) in Denmark meet the clinical criteria, and studies have shown that the risk of advanced disease does not increase if the intervals between endoscopies are extended, which is why the surveillance intervals can safely be prolonged."

Surveillance Serrat polyposesyndrom

- Every 3rd year for the patient – depending on findings on colonoscopy
- FDRs: similar to CRC – let øget risiko

2b: Adenomer

En patient der i alt har haft >25 adenomer

En patient der i alt har haft >10 adenomer før 50-årsalderen

En patient der i alt har haft ≥3 adenomer før 30-årsalderen

Familieanamnese med et af de adenomatøse polyposesyndromer

En patient, der har haft adenomer og/eller ekstraintestinale manifestationer, som indikerer et arveligt polyposesyndrom, f.eks. desmoide tumores, papillær thyoideacancer, epidermale cyster, osteomer, *café-au-lait*-pletter eller tandanomalier

MUTYH heterozygote

- No longer surveillance recommendation to heterozygotic carriers
- Previously: Colonoscopy every 5th year 50-70y, if FDR with CRC

Justified by:

- Larger studies60,000 CRC patients and approximately 70,000 controls, which showed no increased incidence of CRC in patients with MUTYH, p.Gly39 and p.Tyr179Cys. (Mahmood et al. 2024)
- +MUTYH vs. controls: no increased risk of CRC/endometrial/breast cancer (Thompsen et al. 2022)

Polyposis of unknown etiology

- Individuals with **30** to 99 colorectal adenomas, with no identified hereditary cause:Surveillance every 3 years.
- However, the starting age and frequency of surveillance should be assessed based on clinical presentation, family history, age, and the total number of adenomas.

- First-degree relatives:Surveillance every 3 years from age 40 to 75.Surveillance may be omitted based on individual clinical judgment, and both initiation and frequency should be assessed based on clinical presentation, family history, age, and the total number of polyps.