Mismatch repair deficiency and MUTYH variants in small intestine-neuroendocrine tumors

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Original contribution

Mismatch repair deficiency and *MUTYH* variants in small intestine-neuroendocrine tumors☆,☆☆

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Summary Small intestine-neuroendocrine tumors (SI-NETs) are one of the most common tumors of the small bowel. Despite an increasing incidence, the exact mechanisms driving underlying pathology remain to be determined. Interestingly, recent studies linked the development of (SI-)NETs to both Lynch syndrome (LS) and *MUTYH* variants. If confirmed, these associations would have important consequences for treatment. In this study we therefore investigated the prevalence of mismatch repair (MMR) deficiency and *MUTYH* variants in 64 primary resected SI-NETs. Immunohistochemistry was used to assess the expression of the MMR genes, and competitive allele-specific PCR (KASPar) targeting two hotspot *MUTYH* variants [p.(Tyr179Cys), p.(Gly396Asp)] was performed to determine their prevalence in SI-NETs. Strikingly, all 64 SI-NETs stained positive for MSH6 and PMS2, indicating

Abbreviations: CRC, Colorectal cancer; LS, Lynch syndrome; MAP, *MUTYH*-associated adenomatous polyposis; MMR, Mismatch repair; *MUTYH*, MutY DNA glycosylase; NEC, Neuroendocrine carcinoma; (SI-)NET, (Small intestine-)neuroendocrine tumor; VAF, Variant allele frequency.

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MMR proficiency. In addition, no *MUTYH* hotspot variant was found in any of the 64 SI-NETs. As such, these results do not support an association between SI-NET development and LS or *MUTYH* variants. In order to gain insight into SI-NET pathogenesis and optimally manage patients, future research should therefore focus on other candidate genes.

1. Introduction

Small intestine-neuroendocrine tumors (SI-NETs) represent one of the most common tumor subtypes in the small bowel [1,2]. In contrast to small bowel adenocarcinomas, which are predominantly located in the duodenum and proximal jejunum, SI-NETs more often occur in the ileum and jejunum [3]. Several environmental factors, including alcohol consumption and smoking, have been linked to the development of SI-NETs, though data are mixed and a strong correlation between risk factors and disease has not been reported [4,5]. Symptoms range from abdominal pain to the manifestations of carcinoid syndrome, including episodic facial flushing, dyspnea and diarrhea [2,6].

SI-NET incidence has risen in recent decades, partly as a result of increased incidental discovery and improved pathological classification. According to the most recent estimates from the SEER database, SI-NET incidence is approximately 1.2 per 100,000 persons per year, having risen from around 0.02 per year in the 1970's [1,7] Despite this increasing incidence, little research has been conducted regarding possible genetic mechanisms. SI-NETs were long considered sporadic but clustering of SI-NETs in certain families suggests a genetic element and a recent study argued that at least a subset of SI-NETs has a familial origin [8]. Interestingly, NETs at several locations outside the small bowel are linked to genetic cancer predisposition syndromes such as multiple endocrine neoplasia type 1 and von Hippel-Lindau syndrome [9−11]. In addition, there have been numerous reports of patients with Lynch syndrome (LS) who developed either a mismatch repair-deficient (MMR) NET, or a more advanced, poorly differentiated MMR-deficient neuroendocrine carcinoma (NEC) [12−18]. LS is caused by a pathogenic germline variant in one of the MMR genes (*MLH1*, *MSH2* (*EPCAM*), *MSH6* and *PMS2*), which encode proteins involved in the recognition and repair of nucleotide mismatches in DNA [19−21]. Carriers of pathogenic MMR variants are at high risk for colorectal cancer (CRC) and endometrial cancer, but also have a relative risk>100 (1−4% lifetime risk) for small bowel cancer [22,23]. As there are case reports of patients with LS who also had a NET, it is conceivable that LS contributes to the development of SI-NETs. However, several studies have failed to detect the presence of MMR deficiency/microsatellite instability in SI-NETs so far [16,24−28]. As such, a large-scale, unbiased screen of SI-NETs for the presence of MMR deficiency is needed in order to validate the previous findings and in this way confirm whether or not SI-NETs belong to the cancer spectrum of LS.

In addition to LS, numerous candidate genes and genomic alterations may be involved in the development of SI-NETs. The most compelling finding is loss of heterozygosity at chromosome 18, with a reported prevalence in SI-NETs of 55−78% [29−34]. Variants in *MEN1* [35−38], *CDKN1B* [39−41], *NF1* [42,43] and *IMPK* [44,45] have all been found as somatic and/or germline variants in SI-NETs, although the level of supporting evidence varies strongly per gene. Recently, mutY DNA glycosylase (*MUTYH*) was proposed as a new candidate gene by Dumanski et al. [46]. These authors reported that a monoallelic variant of *MUTYH*, p.(Gly396Asp), was enriched in SI-NET patients compared to several population control cohorts. Interestingly, the same variant, along with other pathogenic variants in this gene, was described by Scarpa et al. [15], who studied the molecular profile of pancreatic NETs, as well as by Weidner et al. [47], who reported a SI-NET in a *MUTYH*-associated adenomatous polyposis (MAP) patient. *MUTYH,* best known for its involvement in the cancer predisposition syndrome MAP, encodes a DNA glycosylase involved in the repair of oxidative DNA damage [21,48]. When defective, increases in oxidative stress may promote the development of cancer [21,48]. Interestingly, the presence of heterozygous *MUTYH* variants already increases CRC risk [49] and as such may be a driver of SI-NET tumorigenesis.

As the suggested associations of LS and *MUTYH* variants with SI-NET are currently supported by only a limited number of studies, implications for the management and follow-up of SI-NETs remain theoretical. If confirmed, they may have important implications for daily clinical practice, including testing for LS and/or *MUTYH* variants in families with clustered SI-NETs. With this in mind, as well as gaining a better understanding of SI-NET pathogenesis, we determined the prevalence of both MMR deficiency and *MUTYH* variants in a Dutch nationwide cohort of 64 primary resected SI-NETs.

2. Materials and methods

2.1. Cohort

Formalin-fixed, paraffin-embedded tissue from 64 primary resected SI-NETs, registered during a 5-year period (2012−2016), were obtained via the Dutch Pathology Registry (PALGA) (Supplementary Table 1).[50] Clinical data were retrieved from pathology reports. Since all data were anonymized, patient consent was not required.

2.2. Study procedure

For a detailed description of the study procedure and protocols used for MMR analysis, see Suerink et al. [51], as well as the Supplementary Methods. Briefly, 4 μm sections taken from formalin-fixed paraffin-embedded tissue blocks were stained for PMS2 and MSH6 using standard immunohistochemical procedures. Positive expression was defined as the presence of nuclear staining within both the neoplastic and adjacent non-neoplastic cells, while loss of expression was defined as the absence of nuclear staining in neoplastic cells in combination with the presence of nuclear staining in non-neoplastic cells (Supplementary Fig. 1). If loss of expression of PMS2 or MSH6 was detected, the SI-NET was additionally stained for MLH1 or MSH2, respectively. This approach shows good sensitivity and is based on the well-known MLH1-PMS2 functional heterodimer (MutLα) that prevents PMS2 degradation, while MSH2 partners with MSH6 (MutSα) to prevent MSH6 degradation. While MSH6 or PMS2 protein expression indicates intact MutS or MutL DNA repair, loss of expression of one of these proteins has several possible explanations and therefore requires further analysis of other MMR proteins. This two-antibody approach is validated for clinical decision making and has been shown to be cost-effective [52,53]. Competitive allele-specific PCR (KASPar), as described previously [54−56], was used to identify the two common *MUTYH* variants in all SI-NETs, p.(Tyr179Cys) and p.(Gly396Asp), which together account for the majority of all *MUTYH* variants. One sample known to be heterozygous for p.(Gly396Asp) and two samples known to be heterozygous for p.(Tyr179Cys) were used as controls.

3. Results

3.1. Cohort description

A total of 64 SI-NETs from 64 patients were included in the study (Supplementary Table 1). The mean age of SI-NET diagnosis was 65.9 (±10.2) years (Table 1). At the time of diagnosis the majority of SI-NETs were advanced, with 73% classified as stage III and 14% as stage IV according to the staging system of American Joint Committee on Cancer [57]. Histologically, all SI-

Table 1 Cohort description.

Description	Patients (n = 64)
Sex (%)	
Male	35/64 (55)
Female	29/64 (45)
Age of diagnosis (years)	
Mean (SD)	65.9 (10.2)
Median (IQR)	66.5 (58.3−74)
Range	46−84
Histological grade (%)	
G1-2	64/64 (100)
Tumor status (%)	
T1	1/44 (2)
T2	10/44 (23)
T3	19/44 (43)
T4	14/44 (32)
Missing	20/64 (32)
Nodal status (%)	
N0	5/44 (11)
N1	37/44 (84)
N2	0/44 (0)
NX[a]	2/44 (5)
Missing	20/64 (31)
Metastases status (%)	
M0	1/44 (2)
M1	6/44 (14)
MX[a]	37/44 (84)
Missing	20/64 (31)
Stage according to AJCC (%)	
1	2/44 (5)
2	4/44 (9)
3	32/44 (73)
4	6/44 (14)
Missing	20/64 (31)
Location (%)	
Duodenum	7/64 (11)
Ampulla of Vater	0/64 (0)
Jejunum	2/64 (3)
Ileum	29/64 (45)
Small bowel not otherwise specified	26/64 (40)
History of other cancer (%)[b]	13/64 (20)
Breast	1/6 (17)
Carcinoma in situ (bladder)[c]	1/7 (14)
Colon[c]	2/7 (29)
Liver	2/6 (33)
Prostate	2/6 (33)
Sigmoid/rectum[c]	1/7 (14)
Skin (melanoma)	1/6 (17)
Stomach[c]	1/7 (14)
Urinary tract[c]	2/7 (29)
MMR-proficient (%)	64/64 (100)
MUTYH variants (%)	
p.(Tyr179Cys)	0/64 (0)
p.(Gly396Asp)	0/64 (0)

Abbreviations: AJCC, American Joint Committee on Cancer; MMR, mismatch repair; MUTYH, mutY DNA glycosylase; SD, standard deviation; IQR, interquartile range(25−75%).

[a] A stage could not be assigned with certainty.

[b] Basal cell carcinomas were excluded.

[c] Fit the cancer spectrum of Lynch Syndrome.

NETs were classified as NET grade 1/2 according to the latest version of the WHO classification (2019) [58]. In line with literature, most SI-NETs were found in the ileum (45%), although the duodenum was also commonly affected (11%). Thirteen of 64 (20%) SI-NETs originated in patients with a previously diagnosed other type of cancer, of which seven (11%) fit the cancer spectrum of LS.

3.2. Lack of MMR deficiency in SI-NETs

All 64 SI-NETs showed a normal staining pattern for MSH6 and PMS2 (Table 1). One SI-NET (ID = 39) showed weak staining for the PMS2 protein, although sufficient to allow both pathologists to classify the tumor as PMS2 proficient.

3.3. Lack of MUTYH variants in SI-NETs

None of the 64 SI-NETs were found to carry either the p.(Tyr179Cys) or the p.(Gly396Asp) *MUTYH* variant (Table 1).

4. Discussion

Despite the increasing incidence of SI-NETs, little is known about pathogenesis. It was recently suggested that the development of at least a subset of SI-NETs depends on a familial predisposition. In line with this, associations between LS and NETs and between *MUTYH* variants and SI-NETs have been suggested [12−15,46,47]. However, in this study of 64 primary resected SI-NETs neither MMR deficiency nor *MUTYH* variants were identified. Therefore, our results do not support LS or *MUTYH* carriership as genetic risk factors for the development of SI-NETs.

These results highlight the differences between SI-NETs and other types of small bowel cancer in which MMR deficiency is commonly found. For example, Suerink et al. [51] recently showed that the contribution of MMR and LS to the development of small bowel adenocarcinoma, which together with SI-NETs constitute the majority of small bowel tumors, is at least comparable to that of CRCs. Regarding earlier studies that linked LS to NET development, the complete absence of MMR deficiency in our cohort may have been a consequence of the inclusion of only grade 1/2 SI-NETs, whereas the majority of previous studies that linked LS to neuroendocrine malignancies focused on NECs and NETs located outside the small bowel [12−18]. As NECs are known to more resemble adenocarcinomas, in which MMR deficiency is commonly found, this may in part explain observed differences with our cohort. Nonetheless, our results are in line with previous studies which failed to detect microsatellite instability in SI-NETs [16,24−28], as well as with the literature describing the genetic landscape of SI-NETs, which is characterized by relatively few variants that affect only a small number of genes compared to other tumor types [9]. Although the mechanism behind this mutagenically mild phenotype in (low-grade) SI-NETs has yet to be elucidated, our results may have immediate clinical implications in that the complete absence of MMR deficiency suggests that universal screening of SI-NETs for LS/MMR deficiency cannot be recommended. Additionally, as tumors displaying MMR deficiency show improved responses to immunotherapies as compared to tumors with an MMR proficient status, our results implicate that SI-NET patients may not be good candidates for immunotherapies [59]. To what extent these findings can be applied to grade 1/2 NETs at other locations (e.g. pancreas, thyroid gland, adrenal glands) remains to be elucidated. Several case reports have already described MMR deficiency in NETs outside the small intestines, so although a high prevalence of mismatch repair deficiency and/or Lynch syndrome is not expected, similar studies within large cohorts of these tumors would be required [12,13,15,60,61].

Regarding the recent proposal by Dumanski et al. [46] of *MUTYH* as a candidate gene for SI-NETs, we could not confirm the enrichment of the monoallelic p.(Gly396Asp) variant in the SI-NETs in our cohort. However, the conclusion by Dumanski et al. [46] that there is a statistically significant enrichment for the p.(Gly396Val) *MUTYH* variant in their cohort may be an overinterpretation of the data. Dumanski et al. [46] reported a VAF of 0.013 for SI-NETs and compared this to a VAF of 0.003 in the control group. However, the overall carrier frequency for (likely) pathogenic *MUTYH* variants in the general population is estimated to be 0.010 [62]. Considering that the p.(Glu396Val) variant is one of the most common *MUTYH* variants, the overrepresentation of this specific variant in the cohort could be coincidental although a variant specific NET risk cannot be excluded. Furthermore, no statistical correction was applied for multiple testing.

This study has a number of strengths as well as weaknesses. To the best of our knowledge, this is one of the largest, unbiased screen of SI-NETs for the presence of MMR deficiency. Nevertheless, the sample size may have been too small to detect a possible correlation between SI-NETs and *MUTYH* variants. Furthermore, our analysis of *MUTYH* was limited to two well-known hotspot variants and the possible presence of other variants in *MUTYH* was not analyzed. As tissue and data were provided anonymously, no data on family history or alternative genetic diagnoses were available.

In conclusion, we found no association between LS or *MUTYH* variants and the development of SI-NETs. Further research focusing on current and new candidate genes is therefore of vital importance regarding a possible genetic contribution to the pathogenesis of SI-NETs. Only then will we reach our goal of optimizing the management of patients with SI-NETs.

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Patient consent for publication: Patient consent was waived since this study had a national, non-interventional retrospective design and all data were analyzed anonymously. All data were handled according to the General Data Protection Regulation.

Data availability statement: The data that support the findings of this study are available from PALGA but restrictions apply to the availability of these data, which were used under license for the current study and are therefore not publicly available. Data are available from the authors upon reasonable request and with the permission of PALGA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2022.04.003.

References

[1] Pan SY, Morrison H. Epidemiology of cancer of the small intestine. World J Gastrointest Oncol 2011;3:33−42. https://doi.org/10.4251/wjgo.v3.i3.33.

[2] Scott AT, Howe JR. Management of small bowel neuroendocrine tumors. J Oncol Pract 2018;14:471−82. https://doi.org/10.1200/JOP.18.00135.

[3] DiSario JA, Burt RW, Vargas H, McWhorter WP. Small bowel cancer: epidemiological and clinical characteristics from a population-based registry. Am J Gastroenterol 1994;89:699−701.

[4] Haugvik SP, Basim Ibrahim I, Hedenstrom P, Valente R, Hayes AJ, Siuka D, et al. Smoking, alcohol and family history of cancer as risk factors for small intestinal neuroendocrine tumors: a systematic review and meta-analysis. Scand J Gastroenterol 2017;52:797−802. https://doi.org/10.1080/00365521.2017.1310290.

[5] Leoncini E, Carioli G, La Vecchia C, Boccia S, Rindi G. Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. Ann Oncol 2016;27:68−81. https://doi.org/10.1093/annonc/mdv505.

[6] Rubin de Celis Ferrari AC, Glasberg J, Riechelmann RP. Carcinoid syndrome: update on the pathophysiology and treatment. Clinics (Sao Paulo). 2018;73:e490s. https://doi.org/10.6061/clinics/2018/e490s.

[7] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3:1335−42. https://doi.org/10.1001/jamaoncol.2017.0589.

[8] Neklason DW, VanDerslice J, Curtin K, Cannon-Albright LA. Evidence for a heritable contribution to neuroendocrine tumors of the small intestine. Endocr Relat Cancer 2016;23:93−100. https://doi.org/10.1530/ERC-15-0442.

[9] Crona J, Skogseid B. GEP- NETS UPDATE: genetics of neuroendocrine tumors. Eur J Endocrinol 2016;174:R275−90. https://doi.org/10.1530/EJE-15-0972.

[10] Kim JY, Hong SM. Recent updates on neuroendocrine tumors from the gastrointestinal and pancreatobiliary tracts. Arch Pathol Lab Med 2016;140:437−48. https://doi.org/10.5858/arpa.2015-0314-RA.

[11] Taal BG, Visser O. Epidemiology of neuroendocrine tumours. Neuroendocrinology 2004;80:3−7. https://doi.org/10.1159/000080731.

[12] Sorscher S, Saroya B. A molecularly confirmed neuroendocrine tumor resulting from Lynch Syndrome. J Gastrointest Oncol 2013;4:95−6. https://doi.org/10.3978/j.issn.2078-6891.2012.040.

[13] Serracant Barrera A, Serra Pla S, Blazquez Mana CM, Salas RC, Garcia Monforte N, Bejarano Gonzalez N, et al. Pancreatic non-functioning neuroendocrine tumor: a new entity genetically related to Lynch syndrome. J Gastrointest Oncol 2017;8:E73−e79. https://doi.org/10.21037/jgo.2017.07.02.

[14] Farha N, Hrabe J, Sleiman J, Beard J, Lyu R, Bhatt A, et al. Clinically actionable findings on surveillance EGD in asymptomatic patients with Lynch syndrome. Gastrointest Endosc 2022;95:105−14. https://doi.org/10.1016/j.gie.2021.07.004.

[15] Scarpa A, Chang DK, Nones K, Corbo V, Patch AM, Bailey P, et al. Corrigendum: whole-genome landscape of pancreatic neuroendocrine tumours. Nature 2017;550:548. https://doi.org/10.1038/nature24026.

[16] Fraune C, Simon R, Hube-Magg C, Makrypidi-Fraune G, Kluth M, Buscheck F, et al. Homogeneous MMR deficiency throughout the entire tumor mass occurs in a subset of colorectal neuroendocrine carcinomas. Endocr Pathol 2020;31:182−9. https://doi.org/10.1007/s12022-020-09612-7.

[17] Lou L, Lv F, Wu X, Li Y, Zhang X. Clinical implications of mismatch repair deficiency screening in patients with mixed

neuroendocrine non-neuroendocrine neoplasms (MiNEN). Eur J Surg Oncol 2021;47:323−30. https://doi.org/10.1016/j.ejso.2020.08.022.
[18] Sahnane N, Furlan D, Monti M, Romualdi C, Vanoli A, Vicari E, et al. Microsatellite unstable gastrointestinal neuroendocrine carcinomas: a new clinicopathologic entity. Endocr Relat Cancer 2015;22:35−45. https://doi.org/10.1530/ERC-14-0410.
[19] Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895-2015. Nat Rev Cancer 2015;15:181−94. https://doi.org/10.1038/nrc3878.
[20] Tamura K, Kaneda M, Futagawa M, Takeshita M, Kim S, Nakama M, et al. Genetic and genomic basis of the mismatch repair system involved in Lynch syndrome. Int J Clin Oncol 2019;24:999−1011. https://doi.org/10.1007/s10147-019-01494-y.
[21] Weinberg RA. The biology of cancer. 2nd ed. ed. Garland Science; 2014.
[22] Rodriguez-Bigas MA, Vasen HF, Lynch HT, Watson P, Myrhoj T, Jarvinen HJ, et al. Characteristics of small bowel carcinoma in hereditary nonpolyposis colorectal carcinoma. International Collaborative Group on HNPCC. Cancer 1998;83:240−4. https://doi.org/10.1002/(sici)1097-0142(19980715)83:2<240::aid-cncr6>3.0.co;2-u.
[23] ten Kate GL, Kleibeuker JH, Nagengast FM, Craanen M, Cats A, Menko FH, et al. Is surveillance of the small bowel indicated for Lynch syndrome families? Gut 2007;56:1198−201. https://doi.org/10.1136/gut.2006.118299.
[24] Arnold CN, Nagasaka T, Goel A, Scharf I, Grabowski P, Sosnowski A, et al. Molecular characteristics and predictors of survival in patients with malignant neuroendocrine tumors. Int J Cancer 2008;123:1556−64. https://doi.org/10.1002/ijc.23690.
[25] Arnold CN, Sosnowski A, Blum HE. Analysis of molecular pathways in neuroendocrine cancers of the gastroenteropancreatic system. Ann N Y Acad Sci 2004;1014:218−9. https://doi.org/10.1196/annals.1294.023.
[26] Arnold CN, Sosnowski A, Schmitt-Graff A, Arnold R, Blum HE. Analysis of molecular pathways in sporadic neuroendocrine tumors of the gastro-entero-pancreatic system. Int J Cancer 2007;120:2157−64. https://doi.org/10.1002/ijc.22569.
[27] Ghimenti C, Lonobile A, Campani D, Bevilacqua G, Caligo MA. Microsatellite instability and allelic losses in neuroendocrine tumors of the gastro-entero-pancreatic system. Int J Oncol 1999;15:361−6. https://doi.org/10.3892/ijo.15.2.361.
[28] Kidd M, Eick G, Shapiro MD, Camp RL, Mane SM, Modlin IM. Microsatellite instability and gene mutations in transforming growth factor-beta type II receptor are absent in small bowel carcinoid tumors. Cancer 2005;103:229−36. https://doi.org/10.1002/cncr.20750.
[29] Andersson E, Sward C, Stenman G, Ahlman H, Nilsson O. High-resolution genomic profiling reveals gain of chromosome 14 as a predictor of poor outcome in ileal carcinoids. Endocr Relat Cancer 2009;16:953−66. https://doi.org/10.1677/ERC-09-0052.
[30] Cunningham JL, Diaz de Stahl T, Sjoblom T, Westin G, Dumanski JP, Janson ET. Common pathogenetic mechanism involving human chromosome 18 in familial and sporadic ileal carcinoid tumors. Genes Chromosomes Cancer 2011;50:82−94. https://doi.org/10.1002/gcc.20834.
[31] Di Domenico A, Wiedmer T, Marinoni I, Perren A. Genetic and epigenetic drivers of neuroendocrine tumours (NET). Endocr Relat Cancer 2017;24:R315−34. https://doi.org/10.1530/ERC-17-0012.
[32] Karpathakis A, Dibra H, Pipinikas C, Feber A, Morris T, Francis J, et al. Prognostic impact of novel molecular subtypes of small intestinal neuroendocrine tumor. Clin Cancer Res 2016;22:250−8. https://doi.org/10.1158/1078-0432.CCR-15-0373.
[33] Kulke MH, Freed E, Chiang DY, Philips J, Zahrieh D, Glickman JN, et al. High-resolution analysis of genetic alterations in small bowel carcinoid tumors reveals areas of recurrent amplification and loss. Genes Chromosomes Cancer 2008;47:591−603. https://doi.org/10.1002/gcc.20561.
[34] Lollgen RM, Hessman O, Szabo E, Westin G, Akerstrom G. Chromosome 18 deletions are common events in classical midgut carcinoid tumors. Int J Cancer 2001;92:812−5. https://doi.org/10.1002/ijc.1276.
[35] Jakobovitz O, Nass D, DeMarco L, Barbosa AJ, Simoni FB, Rechavi G, et al. Carcinoid tumors frequently display genetic abnormalities involving chromosome 11. J Clin Endocrinol Metab 1996;81:3164−7. https://doi.org/10.1210/jcem.81.9.8784062.
[36] Lubensky IA, Debelenko LV, Zhuang Z, Emmert-Buck MR, Dong Q, Chandrasekharappa S, et al. Allelic deletions on chromosome 11q13 in multiple tumors from individual MEN1 patients. Cancer Res 1996;56:5272−8.
[37] Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012;97:2990−3011. https://doi.org/10.1210/jc.2012-1230.
[38] Zhuang Z, Vortmeyer AO, Pack S, Huang S, Pham TA, Wang C, et al. Somatic mutations of the MEN1 tumor suppressor gene in sporadic gastrinomas and insulinomas. Cancer Res 1997;57:4682−6.
[39] Crona J, Gustavsson T, Norlen O, Edfeldt K, Akerstrom T, Westin G, et al. Somatic mutations and genetic heterogeneity at the CDKN1B locus in small intestinal neuroendocrine tumors. Ann Surg Oncol 2015;22:S1428−35. https://doi.org/10.1245/s10434-014-4351-9.
[40] Francis JM, Kiezun A, Ramos AH, Serra S, Pedamallu CS, Qian ZR, et al. Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. Nat Genet 2013;45:1483−6. https://doi.org/10.1038/ng.2821.
[41] Maxwell JE, Sherman SK, Li G, Choi AB, Bellizzi AM, O'Dorisio TM, et al. Somatic alterations of CDKN1B are associated with small bowel neuroendocrine tumors. Cancer Genet 2015. https://doi.org/10.1016/j.cancergen.2015.08.003.
[42] Garbrecht N, Anlauf M, Schmitt A, Henopp T, Sipos B, Raffel A, et al. Somatostatin-producing neuroendocrine tumors of the duodenum and pancreas: incidence, types, biological behavior, association with inherited syndromes, and functional activity. Endocr Relat Cancer 2008;15:229−41. https://doi.org/10.1677/ERC-07-0157.
[43] Noe M, Pea A, Luchini C, Felsenstein M, Barbi S, Bhaijee F, et al. Whole-exome sequencing of duodenal neuroendocrine tumors in patients with neurofibromatosis type 1. Mod Pathol 2018;31:1532−8. https://doi.org/10.1038/s41379-018-0082-y.
[44] de Mestier L, Pasmant E, Fleury C, Brixi H, Sohier P, Feron T, et al. Familial small-intestine carcinoids: chromosomal alterations and germline inositol polyphosphate multikinase sequencing. Dig Liver Dis 2017;49:98−102. https://doi.org/10.1016/j.dld.2016.10.007.
[45] Sei Y, Zhao X, Forbes J, Szymczak S, Li Q, Trivedi A, et al. A hereditary form of small intestinal carcinoid associated with a germline mutation in inositol polyphosphate multikinase. Gastroenterology 2015;149:67−78. https://doi.org/10.1053/j.gastro.2015.04.008.
[46] Dumanski JP, Rasi C, Bjorklund P, Davies H, Ali AS, Gronberg M, et al. A MUTYH germline mutation is associated with small intestinal neuroendocrine tumors. Endocr Relat Cancer 2017;24:427−43. https://doi.org/10.1530/ERC-17-0196.
[47] Weidner TK, Kidwell JT, Glasgow AE, Menias CO, Ahn DH, Pai RK, et al. Small intestine neuroendocrine tumor in a patient with MUTYH adenomatous polyposis-case report and SEER analysis. Clin Colorectal Cancer 2018;17:e545−8. https://doi.org/10.1016/j.clcc.2018.05.002.
[48] Nielsen M, Morreau H, Vasen HF, Hes FJ. MUTYH-associated polyposis (MAP). Crit Rev Oncol Hematol 2011;79:1−16. https://doi.org/10.1016/j.critrevonc.2010.05.011.
[49] Jones N, Vogt S, Nielsen M, Christian D, Wark PA, Eccles D, et al. Increased colorectal cancer incidence in obligate carriers of heterozygous mutations in MUTYH. Gastroenterology 2009;137:489−94. https://doi.org/10.1053/j.gastro.2009.04.047. 494 e481; quiz 725-486.
[50] Casparie M, Tiebosch AT, Burger G, Blauwgeers H, van de Pol A, van Krieken JH, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29:19−24. https://doi.org/10.1155/2007/971816.

[51] Suerink M, Kilinc G, Terlouw D, Hristova H, Sensuk L, van Egmond D, et al. Prevalence of mismatch repair deficiency and Lynch syndrome in a cohort of unselected small bowel adenocarcinomas. J Clin Pathol 2020. https://doi.org/10.1136/jclinpath-2020-207040.

[52] Mojtahed A, Schrijver I, Ford JM, Longacre TA, Pai RK. A two-antibody mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin sebaceous tumors, and gynecologic tract carcinomas. Mod Pathol 2011;24:1004−14. https://doi.org/10.1038/modpathol.2011.55.

[53] Stelloo E, Jansen AML, Osse EM, Nout RA, Creutzberg CL, Ruano D, et al. Practical guidance for mismatch repair-deficiency testing in endometrial cancer. Ann Oncol 2017;28:96−102. https://doi.org/10.1093/annonc/mdw542.

[54] Elsayed FA, Kets CM, Ruano D, van den Akker B, Mensenkamp AR, Schrumpf M, et al. Germline variants in POLE are associated with early onset mismatch repair deficient colorectal cancer. Eur J Hum Genet 2015;23:1080−4. https://doi.org/10.1038/ejhg.2014.242.

[55] Elsayed FA, Grolleman JE, Ragunathan A, Ns group, Buchanan DD, van Wezel T, et al. Monoallelic NTHL1 loss-of-function variants and risk of polyposis and colorectal cancer. Gastroenterology 2020;159:2241−2243 e2246. https://doi.org/10.1053/j.gastro.2020.08.042.

[56] Grolleman JE, de Voer RM, Elsayed FA, Nielsen M, Weren RDA, Palles C, et al. Mutational signature analysis reveals NTHL1 deficiency to cause a multi-tumor phenotype. Cancer Cell 2019;35:256−266 e255. https://doi.org/10.1016/j.ccell.2018.12.011.

[57] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67:93−9. https://doi.org/10.3322/caac.21388.

[58] Popa O, Taban SM, Pantea S, Plopeanu AD, Barna RA, Cornianu M, et al. The new WHO classification of gastrointestinal neuroendocrine tumors and immunohistochemical expression of somatostatin receptor 2 and 5. Exp Ther Med 2021;22:1179. https://doi.org/10.3892/etm.2021.10613.

[59] Viale G, Trapani D, Curigliano G. Mismatch repair deficiency as a predictive biomarker for immunotherapy efficacy. BioMed Res Int 2017;2017:4719194. https://doi.org/10.1155/2017/4719194.

[60] Raphael MJ, Chan DL, Law C, Singh S. Principles of diagnosis and management of neuroendocrine tumours. CMAJ 2017;189:E398−404. https://doi.org/10.1503/cmaj.160771.

[61] Scarpa A, Chang DK, Nones K, Corbo V, Patch AM, Bailey P, et al. Whole-genome landscape of pancreatic neuroendocrine tumours. Nature 2017;543:65−71. https://doi.org/10.1038/nature21063.

[62] Nielsen MLH, Infante E, Brand R. MUTYH-associated polyposis. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. GeneReviews((R)); 1993. Seattle (WA).