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Genotype-phenotype correlations in *NTHL1*-associated tumour syndrome: case report and literature review

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Summary

NTHL1-associated tumour syndrome, formerly known as *NTHL1*-associated polyposis, is a rare autosomal recessive tumour predisposition in which biallelic carriers of pathogenic *NTHL1* variants develop multiple, predominantly adenomatous, polyps and have an increased risk of colorectal cancer and extracolonic tumour manifestations. The Nth like DNA glycosylase 1 *(NTHL1)* gene encodes for an enzyme involved in the base excision repair pathway which plays an important role in the maintenance of genomic integrity in the cell.

Upon identification of our first Swiss biallelic *NTHL1* carrier, we performed a literature survey on mono- and biallelic *NTHL1* carriers, followed by genotype-phenotype correlations in order to delineate the clinical manifestations and review current screening recommendations. A comprehensive literature search was conducted to identify all individuals with *NTHL1* variants reported since the initial discovery in 2015 to 2022, followed by a genotype-phenotype analysis on a total of 216 individuals, 59 being biallelic and 157 monoallelic *NTHL1* carriers. 81.4% of biallelic *NTHL1* carriers presented with colon polyps, the majority (69%) exhibiting between 5 and 99 polyps. Interestingly, though not statistically significant, 19% (6/31; p = 0.0766) of carriers homozygous for the recurrent p.Gln90Ter variant displayed a classical (>100 polyps) polyposis phenotype compared to none of the compound heterozygous patients (n = 20); additionally, compound heterozygotes were diagnosed with breast cancer twice as often as homozygous women (75% vs 38.9%, p = 0.0717). Among biallelic carriers, colorectal carcinomas were reported in 50.8% (n = 30; median age at diagnosis: 49 years) and extracolonic malignancies in 55.9% (n = 33), with breast (53.3%), skin (27.1%), endometrial (16.7%) and bladder cancer (8.5%) being the most frequent. Among monoallelic *NTHL1* carriers, 15.3% (n = 24) presented with colon polyps and 17.8% (n = 28; median age at diagnosis: 55 years) with colon carcinomas.

Timely surveillance measures are essential for early colorectal and breast cancer detection, treatment and prognosis. Prospectively gathered data are needed to further establish and refine clinical guidelines for individuals with *NTHL1*-associated tumour syndrome.

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Introduction

Pathogenic variants in DNA repair genes have been associated with a greatly increased risk for colon cancer, e.g. tumour predispositions such as *MUTYH*-associated polyposis (MAP) and Lynch syndrome. In 2015, Weren et al. reported seven individuals from three different families with colon polyposis and colorectal carcinoma which could be attributed to pathogenic germline variants in the base excision repair (BER) gene *NTHL1* (MANE Select: NM_002528.7) [1]. *NTHL1*-associated tumour syndrome (NATS), initially also referred to as *NTHL1*-associated polyposis (NAP), is an autosomal recessive tumour predisposition with a reported phenotype of adenomatous polyposis coli, colorectal cancer and extracolonic manifestations such as breast cancer, endometrial cancer, urothelial cancer and brain tumours [2]. The estimated frequency of *NTHL1*-associated tumour syndrome in Europe is about 1:114,700, which is approximately five times less frequent than the autosomal recessive *MUTYH*-associated polyposis, which encodes for another component of the base excision repair system [3].

NTHL1, located on chromosome 16p13.3 next to the tuberous sclerosis 2 *(TSC2)* gene, consists of six protein-coding exons and encodes a bifunctional DNA N-glycosylase in the base excision repair system. It removes DNA bases damaged by alkylation, deamination or oxidation [4, 5].

Defects in DNA repair pathways such as base excision repair lead to an accumulation of somatic alterations and thus an increased cancer risk in susceptible tissues [6]. The glycosylases in base excision repair, monofunctional and bifunctional alike, recognise the impaired DNA base and remove it. The resulting DNA gap is then repaired by the short-patch or long-patch repair pathway [7]. The glycosylase NTHL1 is mostly responsible for the removal of ox-

ABBREVIATIONS

MAP:	*MUTYH*-associated polyposis
NTHL1:	Nth like DNA glycosylase 1

idised pyrimidines such as thymine glycol, formamidopyrimidine lesions (FapyG), 5-hydroxycytosine and 5-hydroxyuracil [4]. Accordingly, NTHL1 deficiency has been found to result in a distinct mutational signature, signature 30 of the COSMIC database, characterised by C>T transitions at non-CpG sites and present across tumours from different organs of biallelic germline *NTHL1* carriers [8]. The identification of a Swiss *NTHL1* patient in our clinic prompted us to comprehensively gather published genotype and phenotype data on mono- and biallelic *NTHL1* carriers reported thus far, and to perform a genotype-phenotype analysis. The goal was to further delineate the clinical phenotype and to review current screening recommendations for carriers of the *NTHL1*-associated tumour syndrome.

Case report

A 44-year-old man underwent colonoscopy as part of an investigation of blood in the stool. Over one hundred polyps were found in the entire colon, as well as a 3 cm wide, moderately differentiated, microsatellite-stable adenocarcinoma in the ascending colon (pT2 pN0 (0/35) L0 V0 Pn0 G2). A right-sided hemicolectomy was performed, showing approximately 15–20 polyps consisting mainly of tubular and tubulovillous adenomas: 1 tubulovillous low-grade adenoma in the cecum (3.5 cm), 8 low-grade tubular adenomas (max. 0.9 cm), a hyperplastic polyp (0.8 cm), as well as approximately 10 histologically uncharacterised polyps. Additionally, 2 serrated lesions of the appendix were identified.

Half a year later, the patient underwent a subtotal colectomy after renewed lower gastrointestinal bleeding and due to the inability to remove the remaining polyps endoscopically because of unstoppable bleeding caused by newly discovered Von Willebrand disease. Among the over 100 polyps found, a high-grade differentiated 0.4 cm wide tubular adenocarcinoma was discovered in the descending colon (pT1 pN0 (0/42) L0 V0 Pn0 G1). The histologically examined polyps consisted of a tubulovillous adenoma with high-grade epithelial dysplasia and multiple tubular low-grade dysplastic adenomas. Additionally, an unspecified number of hyperplastic polyps were observed.

A comprehensive gene panel analysis of 13 polyposis genes *(APC*, *BMPR1A, GREM1, MSH3, MUTYH, NTHL1, POLD1, POLE, PTEN, RNF43, RPS20, SMAD4, STK11)* identified the homozygous *NTHL1* variant c.244C>T, p.(Gln90Ter). This variant, formerly known as c.268C>T, p.(Gln90Ter) leads to a premature stop codon undergoing nonsense-mediated decay [1, 9].

Except for a paternal aunt, who suffered from an alleged brain tumour at age 45, family history was unremarkable. His healthy, non-consanguineous parents and his two brothers had inconspicuous colonoscopies.

Literature search

To identify all reported *NTHL1* carriers, bi- and monoallelic alike, a literature search covering all published articles from 2015 to 2022 was conducted. PubMed, EMBASE and the Cochrane Library were used to gather the pertinent data, as well as additional references listed in the relevant articles. First, an open search without any criteria except the publishing date revealed 253 eligible papers. Second, the search terms were restricted to medical and case reports, to omit merely functional *NTHL1* data. More information on the exact search terms is given in appendix table S1. Finally, 30 articles provided the necessary clinical information, such as sex, gene variant, allelic status, clinical manifestations (polyps, colorectal cancer, tumour spectrum, age at onset) and family history. Together with our newly identified Swiss *NTHL1* patient, data on a total of 244 individuals from 200 different families were gathered.

To conduct genotype-phenotype analyses, only patients harbouring at least one pathogenic variant (PV) in *NTHL1*, namely class 4 (likely pathogenic) or class 5 (pathogenic), were included. This led to the exclusion of 14 individuals whose *NTHL1* variant was reported as either benign, likely benign or as a variant of unknown significance (VUS) (classes 1, 2, 3). Furthermore, 14 additional patients with variants in genes other than *NTHL1* were excluded. Our final cohort thus consisted of 216 individuals from 200 families, 59 biallelic and 157 monoallelic *NTHL1* carriers. Appendix table S4 depicts the complete dataset from all 216 individuals.

Polyp numbers were grouped using the following system: “few”, “some” for 1–4 polyps; “multiple”, “numerous”, “several”, “many” for 5–99 polyps; and “massive”, “diffuse”, “carpeted”, “lots” for ≥100 polyps [10].

Statistically, the characteristics of the phenotype and the variant status were compared using the Fisher’s exact and chi-squared test for non-parametric variables. A p-value <0.05 was considered statistically significant. Stat View v.4.5 (Abacus concepts) and Microsoft Excel 2021 were used to perform the calculations mentioned above.

Except for polyps, only malignant tumours were included in the analysis. The benign tumours are listed in table S4.

Results of the literature search

A total of 216 individuals with at least one pathogenic variant in the *NTHL1* gene were identified, encompassing 59 (27.3%) biallelic carriers, 39 homozygous and 20 compound heterozygous, and 157 monoallelic carriers (72.7%). In contrast to the balanced female-male ratio in biallelic carriers (30:29), females were statistically significantly overrepresented in the monoallelic carrier group (117:33; p = 0.0001).

Although 17 different pathogenic loss-of-function *NTHL1* germline variants have been reported to date, c.244C>T p.(Gln90Ter) – formerly known as c.268C>T, p.(Gln90Ter) – was the most frequent in our literature search (81.5% or 176/216) [1, 11]. This nonsense variant was presented at least once in 52 (88.1%)of biallelic and in 125 (79%) of monoallelic carriers (table 1). Furthermore, the c.244C>T p.(Gln90Ter) variant contributed to 76% of all pathogenic mutations found in this cohort (209/275). Except for a (1/59) homozygous *NTHL1* carrier harbouring a biallelic splice variant, all other biallelic carriers carried pathogenic variants which are predicted to result in an immediate stop codon. Detailed information on the *NTHL1* variants is depicted in table S4.

Biallelic *NTHL1* carriers

Among biallelic carriers, 52 (88.1%) displayed either colon polyps or colorectal carcinomas (CRC) or both, 2 (3.4%) had an inconspicuous colonoscopy and in 5 (8.5%) no information was given (table 2). Colonic polyps were present in 48 biallelic carriers (81.4%), in 79.5% of homozygotes and 85% of compound heterozygotes, with most individuals (70%) displaying between 5 and 99 polyps, corresponding to an attenuated polyposis phenotype. Another 13% presented with a classical polyposis phenotype (appendix table S2). Interestingly, although not reaching statistical significance (p = 0.0766), patients with more than 100 polyps (classical polyposis) were only observed in the homozygous group (6/31; 19%), but not among the compound heterozygotes (0/17) (figure 1).

Colorectal carcinoma was reported in 30 (50.8%) patients of the biallelic carrier group; 46.2% of homozygous and 60% of compound heterozygous carriers had developed at least one colorectal carcinoma. Slightly more individuals were diagnosed with colorectal carcinoma before the age of 50 (53.3%). The median age at diagnosis for colorectal carcinoma (49 years, interquartile range [IQR]: 21) was similar to the median age for polyps (48 years, IQR: 14). The age distribution for polyps and colorectal carcinoma is depicted in figure 2.

Extracolonic malignant tumours occurred in 33 (55.9%; 10 M + 23 F) biallelic carriers, in 56.4% of homozygous and 55% of compound heterozygous individuals (table 2). At 53.3% (16 of 30 female carriers), breast cancer constituted the most frequently reported extracolonic cancer manifestation in women, whereas squamous cell cancer was the most frequent one in male carriers (3/29). More detailed information is depicted in table S4. Interestingly, compound heterozygous biallelic females were diagnosed with breast cancer twice as often (75%; 9/12) as homozygous biallelic females (38.9%; 7/18), albeit not statistically significantly (p = 0.0717) (table 2). The median age at diagnosis of breast cancer was 47 years (IQR: 14.5), with an age range of 36 to 63 years. Skin cancer was reported in 13 (22.0%) patients and at a median age at diagnosis of 49 years (IQR: 21). At 61.5% (8 of 13 biallelic carriers), basal cell carcinoma was the most frequent type of skin cancer reported, occurring at a median age at diagnosis of 47.5 years (IQR: 18.5). Endometrial cancer was observed in 16.7% (5/30) of female biallelic carriers (22% [4/18] of homozygotes and 8.3% [1/12] of compound heterozygotes; p = 0.6221) and at a median age at diagnosis of 57 years (IQR: 10.5) (table 5). Finally, bladder cancer was reported in 5 (8.5%) biallelic carriers (10.3% [4/39] of *NTHL1* homozygotes and 5% [1/20] of compound heterozygotes) at a median age of 52 years (IQR: 5.0). The remainder of the reported malignancies (28.8% of biallelic carriers) are listed in table S4.

Monoallelic *NTHL1* carriers

The 157 monoallelic *NTHL1* carriers consisted of two subgroups: 22 had been identified through carrier testing because of an affected biallelic relative, whereas 135 individuals were index patients, who were tested because of their phenotype (appendix table S3).

Looking at the subgroup of monoallelic carriers identified through carrier testing, 13.6% (3/22) presented with colon polyps: two of them had fewer than 5 polyps, while no further details were provided for the third individual. No colorectal carcinomas were observed in this subgroup. Two had an inconspicuous colonoscopy. Unfortunately, no data were provided as to whether the remaining 17 had had a colonoscopy or not. Four of the patients (18.2% or 4/22) presented with extracolonic cancers, as follows: renal cancer at age 61 and bladder cancer at age 64; ovarian cancer

Table 1:
Sex distribution and frequency of *NTHL1* PV p.Gln90Ter in bi- and monoallelic *NTHL1* carriers.

Distribution	Total n (% of total in category)	Biallelic	
		Homozygous n (% of biallelic)	Compound heterozygous n (% of biallelic)
Total	59 (27.3)	39 (66.1)	20 (33.9)
Female	30 (50.8)	18 (46.2)	12 (40)
Male	29 (49.2)	21 (53.8)	8 (60)
NTHL1 PV p.Gln90Ter	52 (88.1)	33 (84.6)	19 (95)

PV: pathogenic variant.

Figure 1: Polyp occurrence in biallelic *NTHL1* carriers.

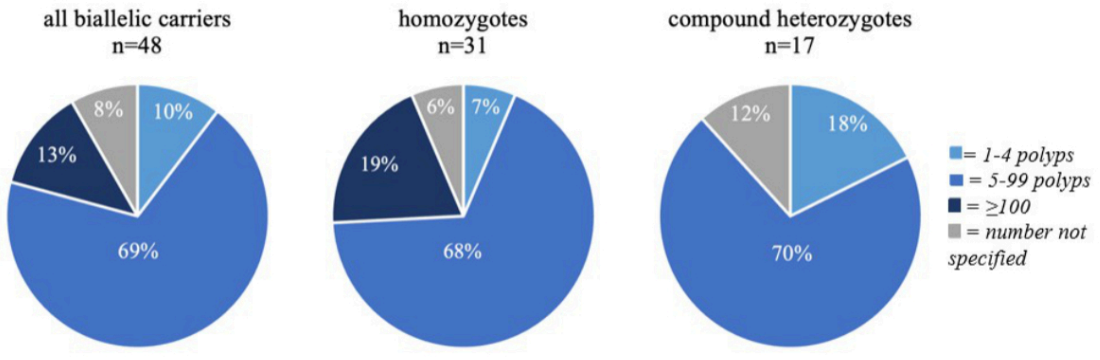

Figure 2: Age at diagnosis of colon polyps and colorectal cancer in biallelic *NTHL1* carriers.

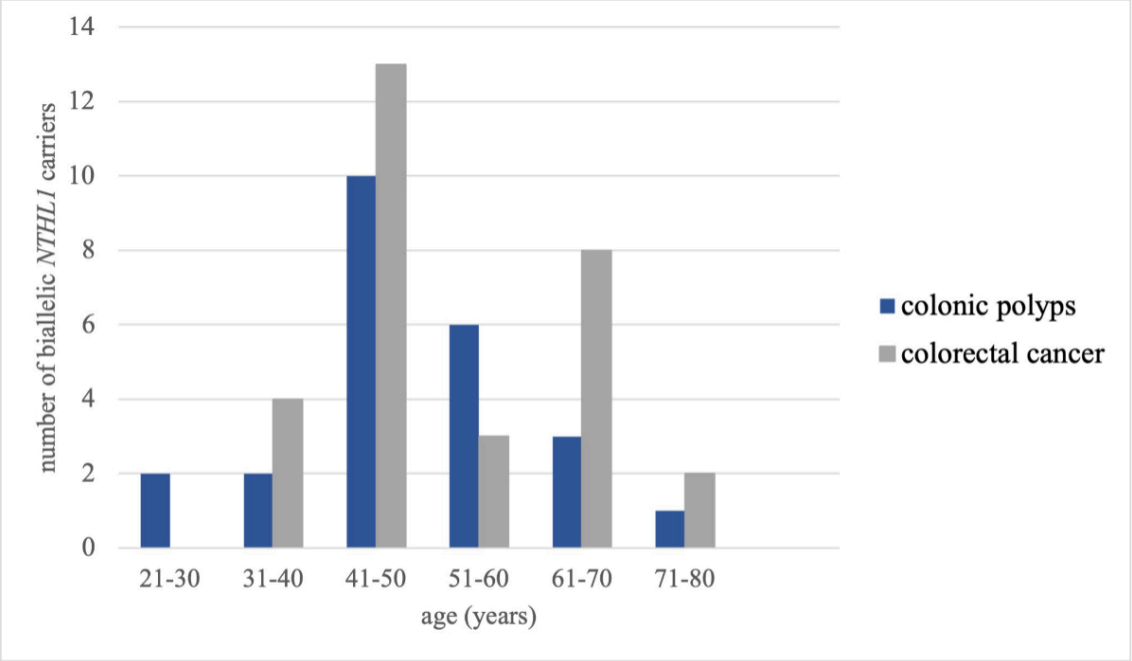

Table 2:
Polyp and cancer occurrence in 59 biallelic *NTHL1* carriers.

Manifestation		**All *NTHL1* biallelic carriers, n = 59**	**Homozygotes, n = 39**	**Compound, heterozygotes n = 20**	**p-value***
Colon manifestations: polyps and/or CRC (%)		52 (88.1)	33 (84.6)	19 (95)	0.4045
Polyps (%)		48 (81.4)	31 (79.5)	17 (85)	0.7337
Number (%)	1–5	5 (10)	2 (7)	3 (18)	
	5–99	33 (69)	21 (68)	12 (70)	
	≥100	6 (13)	6 (19)	0	
	Not specified	4 (8)	2 (6)	2 (12)	
Age at diagnosis, in years	Median (IQR)	48 (14.0)	48 (12.3)	44 (20.8)	
	Range	25–72	25–72	37–63	
Colorectal cancer (%)		30 (50.8)	18 (46.2)	12 (60)	0.4118
Age at diagnosis, in years	Median (IQR)	49 (21.0)	48 (21.3)	51 (18.5)	
	Mean (SD)	51.9 (12.2)	51.5 (13)	52.5 (11.5)	
	Range	31–73	31–72	37–73	
Extracolonic cancers**		33 (55.9)	22 (56.4)	11 (55)	>0.999
Breast cancer (%)***		16 (53.3)	7 (38.9)	9 (75)	0.0717
Age at diagnosis, in years	Median (IQR)	47 (14.5)	47 (2.5)	47 (18.3)	
	Mean (SD)	48.1 (8.7)	46.1 (5.9)	49.6 (10.5)	
	Range	36–63	36–56	36–63	
Skin cancer (%)		13 (22.0)	7 (17.9)	6 (30)	0.3316
Age at diagnosis, in years	Median (IQR)	49 (21.0)	50 (23.0)	49 (14.0)	
	Range	24–68	24–68	39–63	
Endometrial cancer (%)***		5 (16.7)	4 (22.2)	1 (8.3)	0.6221
Age at diagnosis, in years	Median (IQR)	57 (10.5)	57 (15.8)	57 (0.0)	
	Range	53–74	53–74	57–57	
Bladder cancer (%)		5 (8.5)	4 (10.3)	1 (5)	0.6532
Age at diagnosis, in years	Median (IQR)	52 (5.0)	54.5 (9.5)	47 (0.0)	
	Range	47–66	52–66	47–47	
Other cancers (%)****		17 (28.8)	13 (33.3)	4 (20)	0.3698
Age at diagnosis, in years	Median (IQR)	58 (15.5)	56.5 (24.0)	58 (5.0)	
	Range	27–70	27–70	54–62	

* p-value calculated for tumour occurrence in homozygous vs compound heterozygous carriers.

** Further information on all reported extracolonic cancers is shown in appendix figure S2.

*** Number of female biallelic *NTHL1* carriers: total = 30, homozygous = 18, compound heterozygous = 12.

**** A detailed list of all reported carcinomas can be found in appendix table S4.

at age 58; thyroid cancer at age 68; and pulmonary squamous cell carcinoma at age 58 with a smoking history of 67.5 pack-years.

Examining the subgroup of 135 monoallelic carrier index patients, 31.1% (42/135) presented with either colon polyps and/or colorectal carcinoma (table S3). Polyps were present in 21 (15.6%) individuals, the majority (66.7%) reported as having between 5 and 99 polyps. None of the monoallelic carriers in this subgroup presented with a classical polyposis phenotype. Colorectal carcinoma was reported in 28 (20.7%) of monoallelic carriers. The median age at diagnosis for polyps and for colorectal carcinoma was 55 years (IQR for polyps: 12.0, IQR for colorectal carcinoma: 19.3). Extracolonic cancers in this subgroup were reported in 94 patients (69.6%; 13 M + 80 F; one patient's sex unassigned). These malignancies consisted for the most part of breast cancer patients with 56 of the 104 (53.8%) female monoallelic individuals having developed breast cancer. The median age at diagnosis of breast cancer was 51 years (IQR: 23; range: 24–84). Prostate cancer was reported in 25% (6/24) of male monoallelic individuals. Ovarian cancer was found in 10.6% (11/104) and uterine or endometrial cancer in 8.7% (9/104) of female monoallelic *NTHL1* carriers (table S3). Further information on extracolonic malignancies in monoallelic *NTHL1* carriers is given in table S4.

Discussion

This article provides a comprehensive overview of the clinical manifestations and genotype-phenotype correlations in 216 *NTHL1* carriers. It corroborates previous findings, namely that biallelic *NTHL1* carriers are at high risk of adenomatous polyposis (81.4%) and consequently colorectal cancer (50.8%) as well as of certain extracolonic malignancies (55.9%) [12]. 70% of the biallelic individuals showed an attenuated polyposis coli phenotype (5–99 polyps), similar to *MUTYH*-associated polyposis (MAP), where about 76% of biallelic carriers have fewer than 100 colon polyps [13]. Interestingly, though not statistically significant, we found that in the compound heterozygous group (n = 20), nobody was actually presenting with a classical polyposis phenotype (>100 polyps), in contrast to 19% (6/31) of biallelic individuals homozygous for the *NTHL1* founder variant p.Gln90Ter. It is therefore conceivable that certain *NTHL1* variants are associated with a less severe phenotype, i.e. an attenuated polyposis phenotype. Larger, ideally prospective *NTHL1* patient cohorts will be necessary to further substantiate this observation.

The median age at diagnosis of colorectal cancer was 49 years, which is almost 20 years earlier than in the general population (USA: 66 years in men and 69 years in women; Switzerland: 71 years in men and 73 years in women) [14, 15]. Therefore, early colorectal cancer screening measures are essential in biallelic *NTHL1* carriers. Considering that the earliest colorectal carcinoma diagnosis in our cohort was 31 years (and colon polyposis detected at age 25), the proposal of Grolleman et al. to start screening at age 18–20 with a surveillance interval of 2 years, depending on the polyp burden, appears appropriate [8].

Breast cancer represented the most frequent extracolonic cancer manifestation in female biallelic carriers (53.3%; 16/30). At 47 years, the median age at diagnosis was also considerably earlier than in the general population (USA: 62 years; Switzerland: 64.2 years) [15, 16]. Since the earliest breast cancer in our cohort was diagnosed at age 36, our findings support the recommendation by Kuiper et al. to start annual breast cancer surveillance at age 30 [9]. Moreover, *NTHL1* should be considered as a possible cause of early breast cancer in females with inconspicuous results in traditional hereditary breast and ovarian cancer genes such as *BRCA1* and *BRCA2* [17].

The median age at diagnosis of endometrial cancer, reported in 16.7% of biallelic carriers, was 57 years with an age range from 53 to 74 years. This observation rather argues against the screening suggestion from Kuiper et al., who recommended starting with transvaginal ultrasounds at age 40 (and at an interval of two years) [9]. Based on our findings, surveillance starting around age 45–50 would appear more appropriate, unless the family history suggests otherwise. It should, however, be emphasised that, with only five reported cases of endometrial cancer in biallelic carriers, the data remain too limited to support strong, evidence-based recommendations.

To further assess and substantiate cancer risks for extracolonic malignancies in biallelic *NTHL1* carriers, more data will clearly be needed. Intriguingly, the *NTHL1*-associated tumour syndrome cancer spectrum appears to be largely similar to the one reported in *MUTYH*-associated polyposis. Both carry an increased risk of attenuated adenomatous polyposis of the colon and colorectal carcinoma. However, extracolonic cancer seems to occur more frequently in *NTHL1*-associated tumour syndrome than in *MUTYH*-associated polyposis, even though *MUTYH*, an adenine DNA glycosylase, is part of the same DNA repair pathway. Vogt at al. observed in their cohort (276 biallelic *MUTYH* carriers) a 13% occurrence of extracolonic malignant cancers compared to 55.9% in our *NTHL1* biallelic carrier cohort. Breast (7% vs 53.3%), skin (5% vs 22%), endometrial (1.7% vs 16.7%) and bladder cancer (1.5% vs 8.5%) were found to be the most frequent tumour manifestations, in addition to ovarian cancer (2.5%) observed in their *MUTYH* cohort [3, 19]. The risk of gastric cancer appears to be low in both *NTHL1*-associated tumour syndrome and *MUTYH*-associated polyposis: no biallelic carriers in our cohort and only 1% of *MUTYH* patients presented with stomach cancer. Similarly to *MUTYH*-associated polyposis patients (4%), 3.4% (2/59) of biallelic *NTHL1* patients developed cancer of the small intestine [13].

The possible phenotypic impact of monoallelic *NTHL1* variants on cancer development remains unclear. Current data suggest that *NTHL1* heterozygotes are not at increased risk of colon polyposis or colorectal cancer, thus no specific surveillance is thought to be necessary at present [20, 21]. With regard to breast cancer, however, Li et al. suspect that a low-risk effect in monoallelic carriers might be possible [16]. The high breast cancer occurrence in our literature search (47.9%), however, does not necessarily support this statement. While the female-to-male ratio was balanced among biallelic *NTHL1* carriers, monoallelic females were statistically significantly overrepresented (F:M = 117:33). It is likely that this imbalance is due to ascertainment bias since some of the larger studies exclusively focused on genetic testing of female breast cancer patients

contributing 73 (62.4%) of monoallelic *NTHL1* females [16, 22].

Similarly, the observed variety of other malignancies in *NTHL1* heterozygotes may be largely the result of ascertainment error or chance, reflecting differences in environmental exposures, lifestyle and familial differences in individual genetic makeup. Therefore, surveillance measures other than those recommended for the general population do not appear to be justified for monoallelic carriers at this time.

In conclusion, biallelic *NTHL1* carriers are at high risk of adenomatous polyposis coli and different malignancies, in particular colorectal and breast cancer before age 50. Timely surveillance measures are important for early cancer detection, treatment and prognosis. International collaborative studies, ideally performed in a prospective manner, are needed to further delineate cancer risks and timely surveillance measures in patients with *NTHL1*-associated tumour syndrome.

Data sharing statement

All supporting and used data can be found in the manuscript and the supplementary files.

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Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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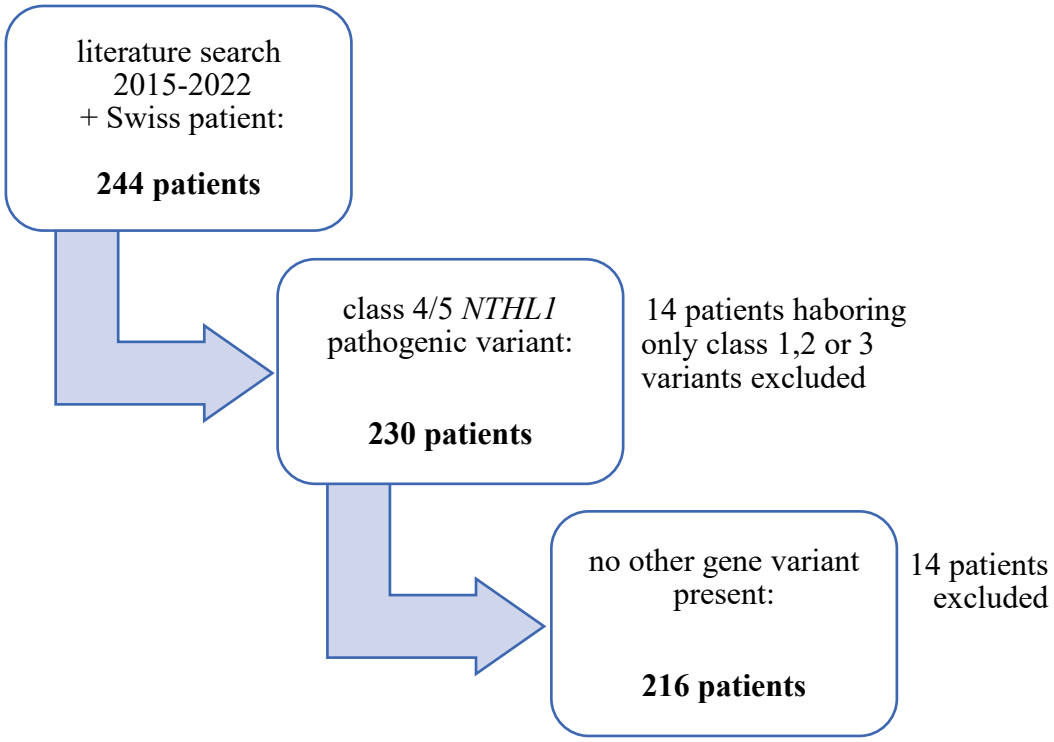
Appendix

Supplementary Table S1: Literature search terms used.

- NTHL1 AND (1998:py OR 2000:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py) AND ('article'/it OR 'article in press'/it OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'preprint'/it OR 'review'/it OR 'short survey'/it)
- nthl1 AND ('cancer'/exp OR cancer OR 'tumor'/exp OR tumor OR 'carcinoma'/exp OR carcinoma OR 'neoplasia'/exp OR neoplasia OR 'adenoma'/exp OR adenoma OR 'polyps'/exp OR polyps OR 'nthl1-associated polyposis' OR ('nthl1 associated' AND ('polyposis'/exp OR polyposis)) OR 'nthl1 associated tumor syndrome' OR (nthl1 AND associated AND ('tumor'/exp OR tumor) AND ('syndrome'/exp OR syndrome))) AND ('colon'/exp OR colon OR crc OR colorectal OR 'bowel'/exp OR bowel) AND (hereditary OR familial OR multitumor OR pancancer OR 'breast'/exp OR breast) AND (2006:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py) AND ('Article'/it OR 'Article in Press'/it OR 'Chapter'/it OR 'Conference Review'/it OR 'Editorial'/it OR 'Letter'/it OR 'Note'/it OR 'Review'/it OR 'Short Survey'/it)
- NTHL1 AND ((cancer) OR (tumor) OR (carcinoma) OR (neoplasia) OR (adenoma) OR (polyps) OR (NTHL1-associated polyposis) OR (NTHL1 associated tumor syndrome)) AND ((colon) OR (CRC) OR (colorectal) OR (bowel)) AND ((hereditary) OR ((familial)) OR (multitumor) OR (pancancer) OR (breast))
  → Filter by publication date 1990-2022

Supplementary Figure S1: Flow chart describing the *NTHL1* literature search and exclusion criteria applied.

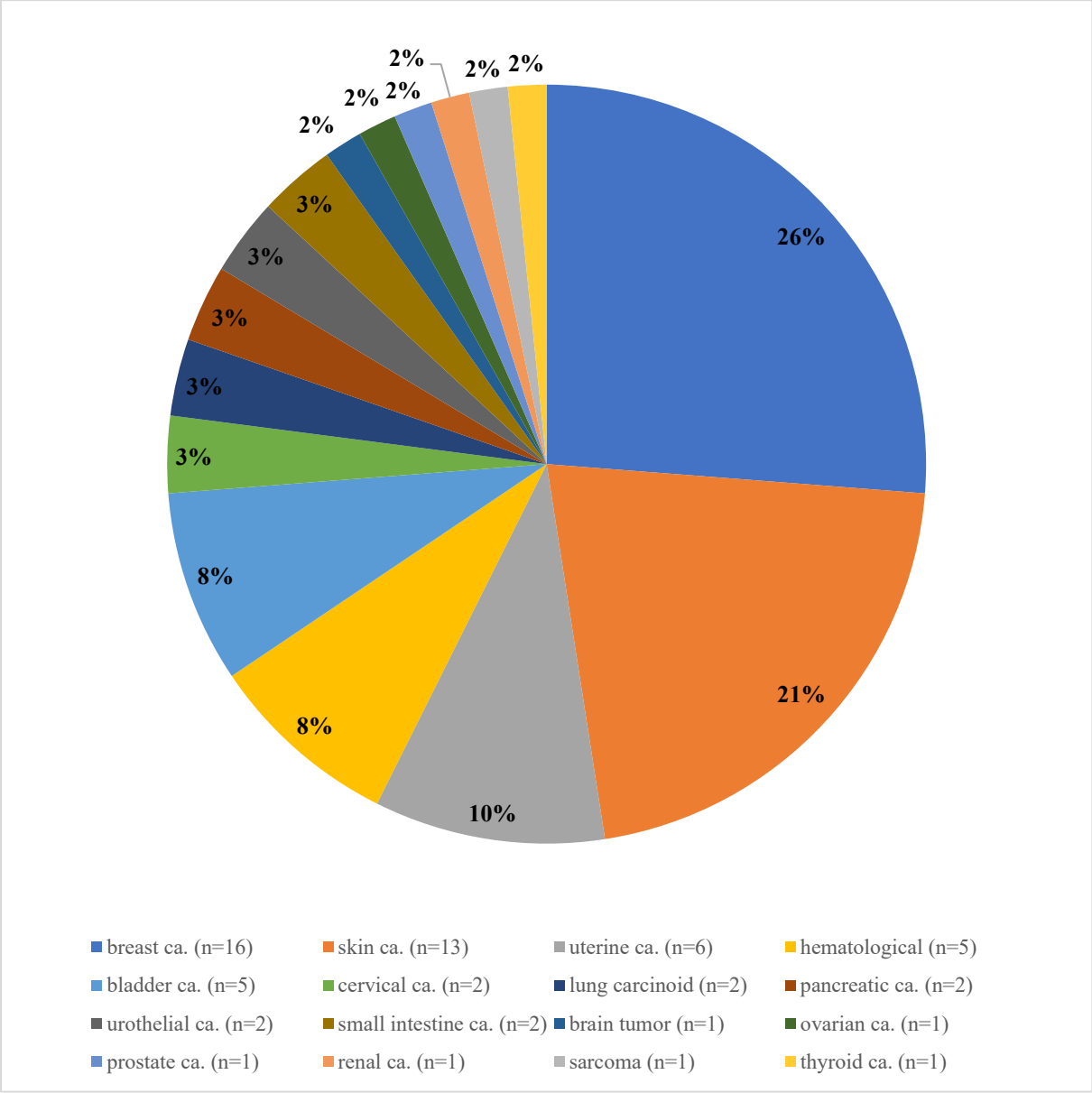


Supplementary Table S2: Median age at diagnosis (years) for polyps in biallelic *NTHL1* carriers

		All *NTHL1* Biallelic carriers n=59	**Homozygotes n=39**	**Compound heterozygotes n=20**	P-value[1]
Number (%)	1 to 5	5 (10)	2 (7)	3 (18)	
	median (IQR)	44 (0)	-	44 (0)	
	5 to 99	33 (69)	21 (68)	12 (70)	
	median (IQR)	56 (13.0)	56 (15.0)	49 (19.0)	
	≥100	6 (13)	6 (19)	0	0.0766
	median (IQR)	47 (9.0)	47 (9.0)	-	
	not specified	4 (8)	2 (6)	2 (12)	
	median (IQR)	58 (12.8)	51 (14.0)	61 (0)	

[1] *P-value calculated for polyp occurrence in homozygous vs. compound heterozygous carriers.*

Supplementary Figure S2: Occurrence of extracolonic cancers in biallelic *NTHL1* carriers.



Supplementary Table S3: Polyp and cancer occurrence in 157 monoallelic *NTHL1* carriers.

		All n=157	**Index patients[1] n=135**	**Relatives[2] n=22**
Colon affected *= polyps and/or CRC (%)*		45 (28.7)	42 (31.1)	3 (13.6)
Polyps (%)		24 (15.3)	21 (15.6)	3 (13.6)
number (%)	1 to 5	2 (8.3)	0	2 (66.7)
	5 to 99	14 (58.3)	14 (66.7)	0
	>100	0	0	0
	not specified	8 (33.3)	7 (33.3)	1 (33.3)
age at diagnosis *in years*	median (IQR)	55 (12.0)	55 (12.0)	
	age range	43-71	43-71	
CRC (%)		28 (17.8)	28 (20.7)	0 (0)
age at diagnosis *in years*	median (IQR)	55 (19.3)	55 (19.3)	0
	age range	36-75	36-75	0
Extracolonic malignancies (%)[3]		98 (62.4)	94 (69.6)	4 (18.2)
Breast cancer (%)[4]		56 (47.9)	56 (53.8)	0 (0)
age at diagnosis *in years*	median (IQR)	51 (23)	51 (23)	0
	age range	24-84	24-84	0
Skin cancer (%)		6 (3.8)	6 (4.4)	0 (0)
Endometrium cancer (%)[4]		3 (2.6)	3 (2.9)	0 (0)
Bladder cancer (%)		2 (1.3)	1 (0.7)	1 (4.5)
Ovarian cancer (%)[4]		12 (10.3)	11 (10.6)	1 (7.7)
age at diagnosis *in years*	median (IQR)	58 (9.3)	60 (11.0)	58
	age range	53-83	53-83	58-58
Prostate cancer (%)[5]		6 (18.2)	6 (25)	0 (0)
age at diagnosis *in years*	median (IQR)	54 (13.0)	54 (13.0)	0
	age range	49-71	49-71	0
Uterine cancer (%)[4]		6 (5.1)	6 (5.8)	0 (0)
age at diagnosis *in years*	median (IQR)	66 (39.8)	66 (39.8)	0
	age range	23-68	23-68	0

[1] *Tested and reported for mutations in NTHL1 because of their phenotype.*
[2] *Relative from at least one biallelic NTHL1 carrier.*
[3] *A detailed list of all reported carcinomas can be found in Supplementary Table 4.*
[4] *Number of female monoallelic NTHL1 carriers: total=117, alone=104, from biallelic family=13.*
[5] *Number of male monoallelic NTHL1 carriers: total=33, alone=24, from biallelic family=9.*

Supplementary Table S4: Complete data table on *NTHL1* carriers.

[a] *F = female, M = male.*
[b] *CRC = colorectal carcinoma.*
[c] *Age in brackets.*
[d] *A-P = adenomatous polyps, A = adenomas, V-A = villous adenomas, S-A = serrated adenomas, TV = tubulovillous, T-A = tubular adenomas, H-P = hyperplastic polyps, S-P = serrated polyps, TV-A = tubulovillous adenomas, SS-P = sessile serrated polyps.*
[e] *ca. = carcinoma/cancer, PC = prostate cancer, PaC = pancreatic cancer, DC = duodenal cancer, BCC = basal cell cancer, BC = breast cancer, EC = endometrial cancer, SCC = squamous cell carcinoma, BlC = bladder cancer, TC = thyroid cancer, RC = renal cancer, AML = acute myeloid leukemia, OC = ovarian cancer, CC = cervical cancer, CIS = carcinoma in situ, UC = uterine cancer, LC = lung cancer, LiC = liver cancer, SMC = small bowel cancer.*

Family	Number	Sex[a]		Mutation Allel 1	Allel 2	CRC[b,c]	Colon Polyps[c, d]	Other tumors[c, e]	Source
1	1 (P01)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (40), CRC (49)	15 A-P	duodenal adenomas (62), esophageal adenomas, PC (60)	(Weren et al., 2015)
1	2 (P49)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		40 A-P	Endometrial complex hyperplasia (46), meningioma (54),	(Weren et al., 2015)
2	3 (P07)[1]	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (47)	50 A-P	PaC (47), DC (52), biliary tract hamartoma (52)	(Weren et al., 2015)
2	4 (P71)[1]	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		50 A-P	BCC (55), BC (56), EC (57)	(Weren et al., 2015)
2	5 (P72)[1]	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		10 A-P		(Weren et al., 2015)
2	6[1]	F	heterozygous	c.244C>T, p.Gln90Ter					(Weren et al., 2015)
3	7 (P23)[2]	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (64), CRC (64)	20 A-P	EC (74)	(Weren et al., 2015)
3	8 (P69)[2]	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (63), CRC (63)	8 A-P	BCC (63) 3x, non-hodgkin lymphoma (70)	(Weren et al., 2015)
4	9	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.709+1G-->A	CRC (41)	<30 A: V-A & S-A (41-54)	ovarian cystadenoma (41), Intradermal nevi (42), sebhorrheic keratoses (47),	(Rivera et al., 2015)

								BlC (47), meningioma (47) 3x, BCC (52), intradermal nevi (55), SCC (55), BC (58)	
4	10	F	heterozygous	c.709+1G-->A					(Rivera et al., 2015)
5	11	M	compound heterozygous	c.244C>T, p.Gln90Ter	c.859C>T, p.Gln287Ter	CRC (44)	1 TV (44)		(Chubb et al., 2016)
6	12	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (48)	24 A (48), 12-24 (48-60)		(Belhadj et al., 2017)
7	13	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (67), CRC (67), CRC (67)	>15 T-A (67), 5 H-P (67)	BC (47), BC (50), BlC (66)	Belhadj et al., 2017)
8	14	M	compound heterozygous	c.244C>T, p.Gln90Ter	c.859C>T, p.Gln287Ter	CRC (41)	Yes		(Broderick et al., 2017)
9	15 (2519)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		150 A-P & S-P (49)		(Fostira et al., 2018)
10	16 (2513)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (31), CRC (65)		Small intestine adenomatous polyps	(Fostira et al., 2018)
11	17	M	heterozygous	c.793G>A, p.Glu265Lys		CRC (48)			(Toh et al., 2018)
12	18[3]		heterozygous	c.244C>T, p.Gln90Ter			10 (34)		(Rosenthal et al., 2018)
13	19		heterozygous	c.244C>T, p.Gln90Ter		CRC (45)			(Rosenthal et al., 2018)
14	20 (P01-II:11)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (59), CRC (59)	multiple A-P	TC (70)	(Grolleman et al., 2019)
14	21 (P01-II:7)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (69)	multiple A-P	RC (61), neurofibroma	(Grolleman et al., 2019)
14	22 (P01-II:9)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (63)	>30 A-P		(Grolleman et al., 2019)
14	23 (P01-II:4)	F	heterozygous	c.244C>T, p.Gln90Ter				RC (61), BlC (64)	(Grolleman et al., 2019)

15	24 (P02-II:1)	M	compound heterozygous	c.244C>T, p.Gln90Ter	c.806G>A, p.Trp269Ter	CRC (67)	50-100 A-P		(Grolleman et al., 2019)
16	25 (P03-II:3)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (33)	1 A-P, 2 H-P		(Grolleman et al., 2019)
16	26 (P03-II:5)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		6 A-P, 7 H-P		(Grolleman et al., 2019)
16	27 (P03-I:1)	M	heterozygous	c.244C>T, p.Gln90Ter			3 A-P		(Grolleman et al., 2019)
16	28 (P03-II:1)	F	heterozygous	c.244C>T, p.Gln90Ter					(Grolleman et al., 2019)
17	29 (P04-II:5)	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.733dup, p.Ile245AsnfsTer28	CRC (53)	1 A-P	BC (38), BC (40), AML (59)	(Grolleman et al., 2019)
17	30 (P04-II:2)	F	heterozygous	[4]			2 A-P	OC (58)	(Grolleman et al., 2019)
17	31 (P04-II:8)	M	heterozygous	[4]					(Grolleman et al., 2019)
17	32 (P04-II:4)	F	heterozygous	[4]					(Grolleman et al., 2019)
18	33 (P05-IV:5)[1]	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (49)	>200: A-P & H-P & S-P		(Grolleman et al., 2019)
18	34 (P05-III:3)[1]	F	heterozygous	c.244C>T, p.Gln90Ter				TC (68)	(Grolleman et al., 2019)
18	35 (P05-IV:3)[1]	F	heterozygous	c.244C>T, p.Gln90Ter					(Grolleman et al., 2019)
18	36 (P05-IV:4)[1]	F	heterozygous	c.244C>T, p.Gln90Ter					(Grolleman et al., 2019)
19	37 (P06-III:2)	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.235_236insG, p.Ala79GlyfsTer2	CRC (61)	multiple A-P, >30 H-P	BC (63)	(Grolleman et al., 2019)
20	38 (P07-III:3)	M	compound heterozygous	c.806G > A, p.Trp269Ter	c.859C > T, p.Gln287Ter		>40 A-P	SCC (60), AML (62)	(Grolleman et al., 2019)
21	39 (P08-IV:1)[1]	M	homozygous	c.545G > A, p.Trp182Ter	c.545G > A, p.Trp182Ter			SCC (29), myelodysplastic syndrome (33)	(Grolleman et al., 2019)
21	40 (P08-IV:2)[1]	M	homozygous	c.545G > A, p.Trp182Ter	c.545G > A, p.Trp182Ter			SCC (24)	(Grolleman et al., 2019)

21	41 (P08-IV:3)[1]	F	homozygous	c.545G > A, p.Trp182Ter	c.545G > A, p.Trp182Ter			brain tumor (27)	(Grolleman et al., 2019)
21	42 (P08-III:3)[1]	F	homozygous	c.545G > A, p.Trp182Ter	c.545G > A, p.Trp182Ter			CC (62)	(Grolleman et al., 2019)
21	43 (P08-III:2)[1]	M	heterozygous	c.545G > A, p.Trp182Ter					(Grolleman et al., 2019)
22	44 (P09-III:4)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (42), CRC (55)	11 A-P, >4 H-P	BC (47), BlC (52), endocervical adeno-CIS (52), BC (53), EC (53)	(Grolleman et al., 2019)
23	45 (P10-III:2)[5]	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		13 A-P	liver cyst, skin hemangioma (3x), ovarian cyst, BC (46)	(Grolleman et al., 2019)
23	46 (P10-III:3)[5]	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		2 A-P, 1 H-P		(Grolleman et al., 2019)
23	47 (P10-II:2)	M	heterozygous	c.244C>T, p.Gln90Ter					(Grolleman et al., 2019)
23	48 (P10-II:3)	F	heterozygous	c.244C>T, p.Gln90Ter					(Grolleman et al., 2019)
24	49 (P11-III:4)	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.390 > A, p.Tyr130Ter		13 A-P, 2 H-P	uterine polyps, meningioma (45) BC (47), breast papilloma (49)	(Grolleman et al., 2019)
24	50 (P11-III:5)	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.390 > A, p.Tyr130Ter	CRC (73)		OC (57), EC (57), BC (60), meningioma (64)	(Grolleman et al., 2019)
25	51	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		10 T-A (57), >30: T-A & H-P (65)	BlC (57)	(Groves et al., 2019)
26	52 (Patient 1)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		23: T-A & TV-A (47), 115: T-A & SS-P (58)		(Altaraihi et al., 2019)

26	53 (Patient 2)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		1 T-A (45), 8: T-A & SS-P (55)	thyroid adenoma (40)	(Altaraihi et al., 2019)
26	54 (Person 3)[6]	F	heterozygous	c.244C>T, p.Gln90Ter				pulmonary SCC (58)	(Altaraihi et al., 2019)
26	55 (Person 4)	M	heterozygous	c.244C>T, p.Gln90Ter					(Altaraihi et al., 2019)
27	56 (Patient 9)	F	heterozygous	c.244C>T, p.Gln90Ter				pancreatic insulinoma NET (75), BC (76)	(Larouche et al., 2019)
28	57		heterozygous	c.244C>T, p.Gln90Ter				TC (23)	(Belhadj et al., 2019)
29	58		heterozygous	c.444G>A, p.Ala148=		CRC			(Belhadj et al., 2019)
30	59	F	heterozygous	c.527T>C, p.Ile176Thr				OC (35), stomach ca. (56)	(Belhadj et al., 2019)
31	60	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.550-1G>A	CRC (37)	26 A (37-46), 8 H-P (39-46)	meningioma (45)	(Belhadj et al., 2019)
32	61		heterozygous	c.244C>T, p.Gln90Ter		CRC (40)			(Belhadj et al., 2019)
33	62		heterozygous	c.550-1G>A		CRC (70), CRC (70), CRC (70)	>70		(Belhadj et al., 2019)
34	63		heterozygous	c.769G>A, p.Ala257Thr		CRC (20)			(Belhadj et al., 2019)
35	64		heterozygous	c.527T>C, p.Ile176Thr		CRC (41)			(Belhadj et al., 2019)
36	65		heterozygous	c.527T>C, p.Ile176Thr		CRC (31)	1 A (32)		(Belhadj et al., 2019)
37	66 (83)[7]	F	heterozygous	c.244C>T, p. Gln90Ter			24 A (70)	endometrial hyperplasia	(Lorca et al., 2019)
38	67 (11)[8]	F	heterozygous	c.139+10C>T			polyposis (29)		(Ricci et al., 2019)
39	68 (12)[9, 10]	M	heterozygous	c.140-16G>A			attenuated polyposis (44)		(Ricci et al., 2019)

40	69 (14)[8]	F	heterozygous	c.527T>C, p.Ile176Thr		CRC (44)	polyposis (44)		(Ricci et al., 2019)
41	70 (17)[8]	F	heterozygous	c.550-11_550-10delCT			attenuated polyposis (24)		(Ricci et al., 2019)
42	71 (31)	F	heterozygous	c.244C>T, p.Gln90Ter			polyposis (50)		(Ricci et al., 2019)
43	72 (SP-0129)	F	heterozygous	c.699_700del, p.Ser116ArgfsTer38		CRC (38)			(Chang et al., 2020)
44	73 (Her1)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (34)	(Kumpula et al., 2020)
44	74		heterozygous	c.244C>T, p.Gln90Ter				stomach ca.	(Kumpula et al., 2020)
44	75	F	heterozygous	c.244C>T, p.Gln90Ter				UC	(Kumpula et al., 2020)
45	76 (Her2)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (38)	(Kumpula et al., 2020)
46	77 (Her3)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (38)	(Kumpula et al., 2020)
46	78	F	heterozygous	c.244C>T, p.Gln90Ter				BC (62)	(Kumpula et al., 2020)
46	79 (Her4)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (47)	(Kumpula et al., 2020)
47	80 (Her5)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (49)	(Kumpula et al., 2020)
48	81 (Unsel1)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (79)	(Kumpula et al., 2020)
49	82 (Unsel2)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (71)	(Kumpula et al., 2020)
50	83 (Unsel3)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (50), TC	(Kumpula et al., 2020)
51	84 (Unsel4)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (66)	(Kumpula et al., 2020)
52	85 (Unsel5)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (59)	(Kumpula et al., 2020)
53	86 (Unsel6)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (62)	(Kumpula et al., 2020)

54	87 (Unsel7)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (58)	(Kumpula et al., 2020)
55	88 (Unsel8)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (70)	(Kumpula et al., 2020)
56	89 (Unsel 9)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (69)	(Kumpula et al., 2020)
57	90 (Unsel10)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (62)	(Kumpula et al., 2020)
58	91 (Unsel11)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (64)	(Kumpula et al., 2020)
59	92 (P09708)	M	heterozygous	c.859C>T, p.Gln287Ter		CRC (73), CRC (73)			(Elsayed et al., 2020)
60	93 (P92662)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (53)			(Elsayed et al., 2020)
61	94 (P07001)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (43)			(Elsayed et al., 2020)
62	95 (P58832)	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (46)		UC (29)	(Elsayed et al., 2020)
63	96 (P00387)	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (42)		UC (23), LC (53)	(Elsayed et al., 2020)
64	97 (P0011)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (56)		LiC	(Elsayed et al., 2020)
64	98 (P0011-2)	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (55)			(Elsayed et al., 2020)
65	99 (P0804)	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (50)			(Elsayed et al., 2020)
66	100 (P0468)	M	heterozygous	c.244C>T, p.Gln90Ter			A-P (43)		(Elsayed et al., 2020)
66	101 (P0567)	F	heterozygous	c.244C>T, p.Gln90Ter			A-P (55)		(Elsayed et al., 2020)
66	102 (P0567-2)	F	heterozygous	c.244C>T, p.Gln90Ter			A-P (61)		(Elsayed et al., 2020)
67	103 (P0523)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (58)	A-P (59)		(Elsayed et al., 2020)
68	104 (P0568)	M	heterozygous	c.244C>T, p.Gln90Ter			A-P		(Elsayed et al., 2020)

69	105 (P0602)	F	heterozygous	c.244C>T, p.Gln90Ter			A-P		(Elsayed et al., 2020)
70	106 (K134)	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (49)	A-P (48-56)		(Elsayed et al., 2020)
71	107 (LUMC3333)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (<69), CRC (69)			(Elsayed et al., 2020)
72	108 (LUMC2745)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (72), CRC		SCC (61),	(Elsayed et al., 2020)
73	109 (LUMC0748)	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (56), CRC (56), CRC (68)		OC (56)	(Elsayed et al., 2020)
74	110 (Tcc136)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (75)			(Elsayed et al., 2020)
75	111 (Tcc456)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (72)		PC	(Elsayed et al., 2020)
76	112 (Tcc712)	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (71)	7 A-P (71)	EC (66)	(Elsayed et al., 2020)
77	113 (P05001)	F	compound heterozygous	c.244C>T, p.Gln90Ter	p.(Ala71fs)	CRC (61)	A-P (61), H-P (61)	BCC (63)	(Elsayed et al., 2020)
78	114 (P1)	M	compound heterozygous	c.244C>T, p.Gln90Ter	c.139+1G>A		7 A (<50), 2 H-P (<50)		(Boulouard et al., 2021)
78	115 (P2)	F	homozygous	c.139+1G>A	c.139+1G>A			sinonasal sarcoma (46) uterine fibroma, meningioma	(Boulouard et al., 2021)
79	116 (P3)	M	compound heterozygous	c.244C>T, p.Gln90Ter	c.550-1G>A	CRC (58)	numerous A (58), numerous H-P (58)		(Boulouard et al., 2021)
79	117	F	heterozygous	c.244C>T, p.Gln90Ter					(Boulouard et al., 2021)
79	118	F	heterozygous	c.550-1G>A					(Boulouard et al., 2021)
79	119	M	heterozygous	c.550-1G>A					(Boulouard et al., 2021)
80	120 (P4)	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.550-1G>A		1 A	BCC (40), BC (42)	(Boulouard et al., 2021)

								PaC (54)	
80	121 (P5)	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.550-1G>A	CRC (45)		BCC (39), BC (43)	(Boulouard et al., 2021)
80	122	M	heterozygous	c.244C>T, p.Gln90Ter					(Boulouard et al., 2021)
81	123 (P6)[11]	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		20 A (52)	DC (52)	(Boulouard et al., 2021)
82	124 (P7)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		mixed polyposis (58)		(Boulouard et al., 2021)
83	125 (P8)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (72)	villous layer (72), TV-A (72), 70 A (72)	urothelial carcinoma (65), melanoma (68),	(Boulouard et al., 2021)
84	126 (P9)	M	homozygous	c.550-1G>A	c.550-1G>A		35 (55-73)	2 small intestine desmoid tumors (55), 2 duodenal adenomas (69)	(Boulouard et al., 2021)
85	127 (P10)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		22: T-A & TV-A (58)		(Boulouard et al., 2021)
86	128 (P11)	M	homozygous	c.527T>C, p.Ile176Thr	c.527T>C, p.Ile176Thr			PC (47), femoral head costeosarcoma (54)	(Boulouard et al., 2021)
87	129 (P12)	F	compound heterozygous	c.113C>T, p.Ala38Val	c.527T>C, p.Ile176Thr		30 A (24)	numerous duodenal adenomas (31)	(Boulouard et al., 2021)
88	130 (P13)	M	compound heterozygous	c.244C>T, p.Gln90Ter	c.349C>T, p.Pro117Ser		6 A (63), 4 H-P (63)	duodenal adenoma (63)	(Boulouard et al., 2021)
89	131 (P14)	F	homozygous	c.527T>C, p.Ile176Thr	c.527T>C, p.Ile176Thr			BC (47), BC (49), EC (51), BCC (64)	(Boulouard et al., 2021)
90	132 (2393/20)	F	heterozygous	c.244C>T, p.Gln90Ter				OC (62), PaC	(Doddato et al., 2021)
91	133 (1NN)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter			BC (36)	(Salo-Mullen et al., 2021)
92	134 (1N)	F	heterozygous	c.244C>T, p.Gln90Ter			<10	PaC (65)	(Salo-Mullen et al., 2021)

93	135 (2N)	M	heterozygous	c.244C>T, p.Gln90Ter				BlC (53), PC (54), lymphoma (68)	(Salo-Mullen et al., 2021)
94	136 (3N)	F	heterozygous	c.244C>T, p.Gln90Ter			<10	UC (66), BC (84), vulva ca. (92)	(Salo-Mullen et al., 2021)
95	137 (4N)	M	heterozygous	c.244C>T, p.Gln90Ter				cholangio ca. (45)	(Salo-Mullen et al., 2021)
96	138 (5N)	F	heterozygous	c.244C>T, p.Gln90Ter				OC (58), endobronchial carcinoid (59)	(Salo-Mullen et al., 2021)
97	139 (6N)	F	heterozygous	c.244C>T, p.Gln90Ter			<10	PaC (58)	(Salo-Mullen et al., 2021)
98	140 (7N)	F	heterozygous	c.244C>T, p.Gln90Ter				retinoblastoma (23 months)	(Salo-Mullen et al., 2021)
99	141 (8N)	M	heterozygous	c.244C>T, p.Gln90Ter				PC (49), unknown primary (63)	(Salo-Mullen et al., 2021)
100	142 (9N)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (65)	<10		(Salo-Mullen et al., 2021)
101	143 (10N)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (61)			(Salo-Mullen et al., 2021)
102	144 (11N)	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (53)			(Salo-Mullen et al., 2021)
103	145 (12N)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (54), PaC (84)	(Salo-Mullen et al., 2021)
104	146 (13N)	M	heterozygous	c.244C>T, p.Gln90Ter				PC (71)	(Salo-Mullen et al., 2021)
105	147 (14N)	F	heterozygous	c.244C>T, p.Gln90Ter				OC (67)	(Salo-Mullen et al., 2021)
106	148 (15N)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (63)	(Salo-Mullen et al., 2021)
107	149 (16N)	F	heterozygous	c.244C>T, p.Gln90Ter			<10	UC (67)	(Salo-Mullen et al., 2021)
108	150 (17N)	F	heterozygous	c.244C>T, p.Gln90Ter				UC (78)	(Salo-Mullen et al., 2021)
109	151 (18N)	F	heterozygous	c.244C>T, p.Gln90Ter			<10	BC (46)	(Salo-Mullen et al., 2021)

110	152 (19N)	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (36)			(Salo-Mullen et al., 2021)
111	153 (20N)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (45)	<10	PC (52), SMC (66), melanoma (76)	(Salo-Mullen et al., 2021)
112	154 (21N)	F	heterozygous	c.244C>T, p.Gln90Ter				sarcoma (62)	(Salo-Mullen et al., 2021)
113	155 (22N)	M	heterozygous	c.244C>T, p.Gln90Ter		CRC (63)	<10		(Salo-Mullen et al., 2021)
114	156 (23N)	M	heterozygous	c.244C>T, p.Gln90Ter			<10	PaC (69)	(Salo-Mullen et al., 2021)
115	157 (24N)	M	heterozygous	c.244C>T, p.Gln90Ter				PC (62), melanoma (76)	(Salo-Mullen et al., 2021)
116	158 (25N)	F	heterozygous	c.244C>T, p.Gln90Ter			<10	unknown primary (65)	(Salo-Mullen et al., 2021)
117	159 (26N)	M	heterozygous	c.604G>T, p.Glu202Ter				melanoma (58)	(Salo-Mullen et al., 2021)
118	160 (27N)	M	heterozygous	c.604G>T, p.Glu202Ter				melanoma (61), glioblastoma (67)	(Salo-Mullen et al., 2021)
119	161 (28N)	M	heterozygous	c.718_719delAC, p.Thr240AlafsTer32				sarcoma (46)	(Salo-Mullen et al., 2021)
120	162 (29N)	F	heterozygous	c.806G>A, p.Trp269Ter				sarcoma (13)	(Salo-Mullen et al., 2021)
121	163 (30N)	F	heterozygous	c.819delG, p.Glu273AspfsTer68			<10	OC (62)	(Salo-Mullen et al., 2021)
122	164 (31N)[12]	F	heterozygous	c.244C>T, p.Gln90Ter				BC (34)	(Salo-Mullen et al., 2021)
123	165 (32N)[12]	F	heterozygous	c.244C>T, p.Gln90Ter				BC (42), BC (44)	(Salo-Mullen et al., 2021)
124	166 (33N)[12]	F	heterozygous	c.244C>T, p.Gln90Ter				BC (64)	(Salo-Mullen et al., 2021)
125	167 (34N)[13]	F	heterozygous	c.244C>T, p.Gln90Ter				OC (44)	(Salo-Mullen et al., 2021)
126	168 (35N)[14]	F	heterozygous	c.244C>T, p.Gln90Ter		CRC (47), CRC (74)	<10	SMC (57), BC (64), LC (67), SMC (73),	(Salo-Mullen et al., 2021)

								BC (75)	
127	169 (36N)[15]	M	heterozygous	c.484delG, p.Asp162ThrfsTer25				retinoblastoma (5 months), stomach ca. (54)	(Salo-Mullen et al., 2021)
128	170 (37N)[16]	M	heterozygous	c.244C>T, p.Gln90Ter				germ cell tumor (22)	(Salo-Mullen et al., 2021)
129	171 (38N)[17]	F	heterozygous	c.244C>T, p.Gln90Ter				OC (14)	(Salo-Mullen et al., 2021)
130	172 (39N)[18]	F	heterozygous	c.244C>T, p.Gln90Ter				CC (26)	(Salo-Mullen et al., 2021)
131	173 (C35612)	F	heterozygous	c.64_83del, p.Ser22AlafsTer5				BC (45), BC (60)	(Li et al., 2021)
132	174 (C31266)	F	heterozygous	c.244C>T, p.Gln90Ter				OC (53)	(Li et al., 2021)
133	175 (C20960)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (35)	(Li et al., 2021)
134	176 (C21261)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (56)	(Li et al., 2021)
135	177 (C30667)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (37)	(Li et al., 2021)
136	178 (C21552)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (42), CRC (55)		BC (47), BlC (52), BC (53), UC (53)	(Li et al., 2021)
137	179 (C21570)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (52)	(Li et al., 2021)
138	180 (C30165)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (54)	(Li et al., 2021)
139	181 (C21835)	F	heterozygous	c.244C>T, p.Gln90Ter				OC (54), BC (55)	(Li et al., 2021)
140	182 (C31362)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (47)	(Li et al., 2021)
141	183 (C35407)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (38), BC (47)	(Li et al., 2021)
142	184 (C35456)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (68)	(Li et al., 2021)
143	185 (C36876)	F	heterozygous	c.244C>T, p.Gln90Ter				non-melanoma, BC (68)	(Li et al., 2021)
144	186 (C37500)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (30)	(Li et al., 2021)
145	187 (C37696)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (33)	(Li et al., 2021)
146	188 (C36922)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (45)	(Li et al., 2021)
147	189 (C31544)	F	heterozygous	c.244C>T, p.Gln90Ter				peritoneal ca. (62)	(Li et al., 2021)
148	190 (C31956)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (24)	(Li et al., 2021)
149	191 (C32018)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (57)	(Li et al., 2021)
150	192 (C32110)	F	heterozygous	c.244C>T, p.Gln90Ter				OC (58)	(Li et al., 2021)

151	193 (C32170)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (44)	(Li et al., 2021)
152	194 (C32815)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (55)	(Li et al., 2021)
153	195 (C32819)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (51)	(Li et al., 2021)
154	196 (C33461)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (39)	(Li et al., 2021)
155	197 (C34180)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (40)	(Li et al., 2021)
156	198 (C34833)	F	heterozygous	c.244C>T, p.Gln90Ter				BC (31)	(Li et al., 2021)
157	199 (N36632)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
158	200 (N30349)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
159	201 (N34375)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
160	202 (N34388)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
161	203 (N35792)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
162	204 (N30392)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
163	205 (N37007)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
164	206 (N33080)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
165	207 (N35136)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
166	208 (N33892)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
167	209 (N37075)	F	heterozygous	c.244C>T, p.Gln90Ter					(Li et al., 2021)
168	210 (C30797)	F	heterozygous	c.380_383dup, p.Arg129ThrfsTer42				BC (31)	(Li et al., 2021)
169	211 (N33902)	F	heterozygous	c.390C>A, p.Tyr130Ter					(Li et al., 2021)
170	212 (N35337)	F	heterozygous	c.390C>G, p.Tyr130Ter					(Li et al., 2021)
171	213 (C33562)	F	heterozygous	c.457C>T, p.Arg153Ter				BC (42)	(Li et al., 2021)
172	214 (C34178)	F	heterozygous	c.457C>T, p.Arg153Ter				BC, OC (83)	(Li et al., 2021)
173	215 (C34086)	F	heterozygous	c.760A>T, p.Lys254Ter				OC, BC (51)	(Li et al., 2021)
174	216 (C31264)	F	heterozygous	c.859C>T, p.Gln287Ter				BC (51)	(Li et al., 2021)
175	217 (C21256)	F	heterozygous	c.859C>T, p.Gln287Ter				BC (57)	(Li et al., 2021)
176	218 (C20188)	F	heterozygous	c.859C>T, p.Gln287Ter				mouth ca. (46), BC (51), mouth ca. (59)	(Li et al., 2021)
177	219 (C21809)	F	heterozygous	c.859C>T, p.Gln287Ter				BC (36)	(Li et al., 2021)
178	220 (C21298)	F	heterozygous	c.859C>T, p.Gln287Ter				BC (28)	(Li et al., 2021)
179	221 (C37112)	F	heterozygous	c.859C>T, p.Gln287Ter				BC (49)	(Li et al., 2021)
180	222 (C32774)	F	heterozygous	c.859C>T, p.Gln287Ter				OC (68)	(Li et al., 2021)
181	223 (C33342)	F	heterozygous	c.859C>T, p.Gln287Ter				BC (28)	(Li et al., 2021)

182	224 (C33351)	F	heterozygous	c.859C>T, p.Gln287Ter				BC (41)	(Li et al., 2021)
183	225 (N35940)	F	heterozygous	c.859C>T, p.Gln287Ter					(Li et al., 2021)
184	226 (N33964)	F	heterozygous	c.859C>T, p.Gln287Ter					(Li et al., 2021)
185	227 (TCGA_UCEC_041)	F	heterozygous	c.244C>T, p.Gln90Ter				EC	(Kondrashova et al., 2021)
186	228 (TCGA_UCEC_045)	F	heterozygous	c.244C>T, p.Gln90Ter				EC	(Kondrashova et al., 2021)
187	229	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.859C>T, p.Gln287Ter		17: TV-A & T-A & H-P (39)	meningioma (39), meningioma (39)	(Liu et al., 2021)
188	230 (FAP347)[19]	M	heterozygous	c.274C>T, p.Arg92Cys			30-100 A (46)		(Dell'Elice et al., 2021)
189	231 (Patient 4)[8]	M	heterozygous	c.244C>T, p.Gln90Ter				several BCC, gallbladder ca. (70)	(Rosenblum et al., 2021)
190	232 (family #4)		heterozygous	c.244C>T, p.Gln90Ter		CRC (62)			(Djursby et al., 2022)
191	233 (family #5)		heterozygous	c.244C>T, p.Gln90Ter		CRC (51)			(Djursby et al., 2022)
192	234 (Patient 1)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		Yes (44)	BCC (43), DCIS (44), BC (44)	(Weatherill et al., 2022)
192	235	M	heterozygous	c.244C>T, p.Gln90Ter			Yes		(Weatherill et al., 2022)
193	236 (Patient 2)[20]	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter		Clusters (48), (72), (73)	lung carcinoid (31), skin ca. (40), skin ca. (45), meningioma (63), neuroma (71), duodenal adenoma (72), meningioma (76) 2x, lung carcinoid (76), CML (76)	(Weatherill et al., 2022)
194	237 (Patient 3)	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.859C>T, p.Gln287Ter			cervical dysplasia (31), BC (36)	(Weatherill et al., 2022)

195	238 (Patient 4)[21]	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.859C>T, p.Gln287Ter	CRC (42)	profuse polyposis (51)	BC 39), meningioma (45) 3x, DCIS (50)	(Weatherill et al., 2022)
196	239 (Patient 5)	F	compound heterozygous	c.244C>T, p.Gln90Ter	c.366C>A, p.Tyr122Ter		multiple	melanoma (41), SCC (46), sweat gland ca. (48), BCC (50), BC (59)	(Weatherill et al., 2022)
196	240	M	heterozygous	c.244C>T, p.Gln90Ter					(Weatherill et al., 2022)
197	241 (Patient 6)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (43), CRC (51)	>100 (25-52)	meningioma (37) meningioma (49)	(Weatherill et al., 2022)
198	242 (FAP1015)	F	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC	10 (47)	duodenal adenomas, papilla vater ca., urothelial ca., EC, CC	(Olkinuora et al., 2022)
199	243	M	compound heterozygous	c.244C>T, p.Gln90Ter	c.649_650del, p.Val217TrpfsTer55	CRC (49), CRC (57)	numerous, 5 T-A (57)	sebaceous cyst 2x	(Wakeling et al., 2022)
200	244 (Index)	M	homozygous	c.244C>T, p.Gln90Ter	c.244C>T, p.Gln90Ter	CRC (44), CRC (44)	>100: TV-A & T-A & H-P & S-P & A (44)	MGUS type IgG lambda (44)	this study

[1] *consanguinity*
[2] *possible consanguinity*
[3] *pathogenic variant in BRCA2*
[4] *not sure which genetic variant (c.244C>T, p. Gln90Ter vs. c.733dup, p.Ile245AsnfsTer28)*
[5] *twins*
[6] *67.5 pack years*
[7] *pathogenic variant in POLE*
[8] *pathogenic variant in APC*
[9] *pathogenic variant in MUTYH*
[10] *VUS in STK11*
[11] *heterozygous pathogenic variant in M2H2*
[12] *variant in BRCA2*
[13] *variant in BRCA1*
[14] *variant in M2H2*
[15] *variant in RB1*

[16] *variant in SDHB*
[17] *variant in SMARCA4*
[18] *variant in ERCC3*
[19] *3 VUS in MUTYH*
[20] *VUS in TERT*
[21] *pathogenic variant in NF1*

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