Familial Cancer (2014) 13:57–63
DOI 10.1007/s10689-013-9674-3

ORIGINAL ARTICLE

Cancer risk and genotype–phenotype correlations in *PTEN* hamartoma tumor syndrome

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Published online: 11 August 2013

Abstract Patients with germline *PTEN* mutations are at high risk of developing benign and malignant tumours. We aimed to evaluate the cumulative risk of several types of cancer and of dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease, LDD). In addition, genotype–phenotype correlations in *PTEN* hamartoma tumour syndrome (PHTS) were assessed. Data on patients with *PTEN* mutations were collected from clinical genetic centres in Western Europe, Australia, and the USA. The cumulative risk of developing cancers of the breast, thyroid, endometrium, skin, kidneys, colorectum, and lungs, and also LDD was calculated by Kaplan–Meier methods. Associations between mutations and cancer were assessed by Chi square means. A total of 180 germline *PTEN* mutation carriers, 81 males (45 %), from nine countries were included. The cumulative risk of developing any cancer and/or LDD at age 60 was 56 % for males and 87 % for females ($p = 0.001$). Females had significant higher risks of developing breast cancer, thyroid cancer, and LDD than males. The only genotype–phenotype correlation identified was a lower frequency of thyroid cancer in patients with missense mutations ($p = 0.014$). In conclusion, PHTS patients, particularly females, have a substantial risk of developing one or more

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tumours from a broad tumour spectrum. Major genotype–phenotype associations could not be identified.

Keywords PTEN phosphohydrolase · Multiple hamartoma syndrome · Neoplasms

Introduction

PTEN hamartoma tumor syndrome (PHTS) is the collective term for clinical syndromes caused by germline mutations in the tumor suppressor phosphatase and tensin homologue, situated on chromosome 10 (*PTEN*). These syndromes include Cowden syndrome, Lhermitte-Duclos disease (LDD), Bannayan-Riley-Ruvalcaba syndrome, and Proteus (-like) syndrome, and although they appear to be different disease entities, they share overlapping characteristics including hamartomatous tumours [1]. The tumors observed in PHTS derive from all embryonic layers. Recently, a risk of 89 % for any cancer diagnosis was found, with particularly high risks of carcinomas of the breast, thyroid, endometrium, kidney, colorectum, and cerebellar gangliocytoma (Lhermitte-Duclos disease) [3, 4]. Expression of the clinical features is variable [2].

The functional role of the *PTEN* gene has been partially elucidated. In many types of (sporadic) human cancers, somatic *PTEN* mutations have been identified [5]. *PTEN* appears to act as a tumor suppressor gene by counteracting the PI3K/Akt signalling network, an important cancer promoting pathway. Furthermore, PTEN is involved in maintaining genomic stability, DNA repair, stem cell self-renewal, cellular senescence, and cell migration/metastasis [6].

Several studies have assessed the possibility of genotype–phenotype correlations in *PTEN* mutation carriers, but such associations were not demonstrated [2, 7]. One study found that specific germline mutations in mouse models did have a strong influence on the variable predisposition to cancer, however [8]. Furthermore, recent studies using mouse models and human clinical data have provided support for the idea that PTEN protein dosage may influence the PHTS phenotype [9, 10].

The aim of the current study was to assess the cumulative risk of developing cancer in a large international cohort of patients with *PTEN* mutations, and to evaluate if specific cancer types were associated with certain mutations (i.e. genotype–phenotype associations).

Methods

Patients

Clinical genetic centres from United Kingdom, France, Norway, Germany, Switzerland, USA (Rochester, MN), Australia, Denmark, and The Netherlands contributed to this study by providing data on patients with a proven germline mutation in the *PTEN* gene. Information was obtained on several variables including gender, date of birth, date of last contact, result of *PTEN* mutation testing, number of affected relatives, ethnicity, and the year of diagnosis of clinical symptoms. The involved geneticists were asked to report tumours and other relevant findings in *PTEN* mutation carriers.

Statistical analysis

Patient characteristics were analysed and delineated. Cumulative cancer risks were calculated by Kaplan–Meier methods, with observation time from date of birth to date of tumour diagnosis, date of death, or date of last observation, whichever came first. Differences between males and females were assessed by the log rank test.

Univariate analyses were performed to predict the effect and classify the mutation. The frequency of tumours was

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compared for both groups by the Chi square test. Statistical analysis was performed by using, PASW version 18.0 (SPSS, Chicago, Illinois, USA). The threshold of statistical significance was set at $p < 0.05$.

Classification of mutations

All mutations were reviewed and classified by a clinical molecular geneticist (HGY). Only variants that are classified as likely to be pathogenic according to the guidelines of the CMGS and VKGL (British and Dutch molecular genetic societies), are included as mutations in this paper (see http://www.cmgs.org/BPGs/pdfs%20current%20bpgs/UV%20GUIDELINES%20ratified.pdf).

These criteria include among others the Grantham score, SIFT and PolyPhen analysis, splice site analysis, and analysis of frequency of the mutation in the population.

The location of mutations in the two key *PTEN* domains were reported: either the protein tyrosine phosphatase domain (exons 2–6) or the C2 calcium lipid binding region domain (exons 6–8). Mutations in the other domains (PDZ-binding domain (amino acids 401–403) and the carboxy-terminal region (amino acids 351–400) were grouped into an "other mutations group". The *PTEN* mutations were considered to be deleterious based upon the type of the mutation (nonsense, frameshift, splice site, missense, deletions) [11]. Subgroups were formed based on the type of the mutation, existing literature, location in a domain, and prediction of nonsense-mediated decay (NMD). NMD is a quality-control mechanism that selectively degrades mRNAs harbouring premature termination (nonsense) codons and thereby these mutations do not lead to aberrant PTEN protein formation but haploinsufficiency. For mutations that have not been described and were not predicted to lead to NMD, an in silico-based method (Alamut software) was used to assess the effect of the mutation (http://www.interactivebiosoftware.com/alamut/doc/1.5/index.html).

Results

Clinical characteristics

A total of 180 patients with mutations (81 males, 45 %), born between the years 1928 and 2008 were included. The mean age at the date of last contact was 32 years (range 1–73 years). Fifty-four patients (30 %) were younger than 18 years at the end of the observation time. The majority of patients had macrocephaly, which was reported in 150 patients (83.3 %). Benign mucocutaneous lesions (including trichilemmomas, papillomatous papules, and acral keratoses) were reported in 83 patients (46.1 %), with a cumulative risk of 80 % at age 60. Mental retardation, including developmental delay and learning difficulties, was reported in 31 patients (17.2 %).

Mutations

Data on 119 families were available. All patients tested positively for a germline *PTEN* gene mutation. A total of 92 different mutations were identified in 114 families. Five families were known to have a mutation, but no information was available. The most frequent mutation was exon 5, c.388C>T, resulting in p.Arg130X, which was found in seven families. Mutations in exon 8, c.1003C>T resulting in p.Arg335X and exon 2, c.144C>A resulting in p.Asn48Lys, occurred in four families. All other mutations were found less frequently.

Figure 1 shows the distribution of mutations. The molecular genetic defect was reported for 107 families and included 40 missense mutations (37.4 %), 29 nonsense mutations (27.1 %), 17 splice site mutations (15.9 %), 14 frameshift mutations (13.1 %), and 7 deletions (6.5 %).

A total of 62 (63.9 %) families had a mutation in the protein tyrosine phosphatase domain (exons 2–6), and 35 (36.1 %) families had mutations in the C2 calcium lipid binding region (exons 6–9). One large deletion included both domains, and precise data on domain location were missing in 21 families.

Sixty-one (53.5 % of 114 families, complete data on 5 families missing) of the families had a mutation that was predicted to lead to nonsense-mediated decay (NMD).

Cumulative risk of cancer and/or Lhermitte-Duclos disease (LDD)

A total of 56 patients had developed a malignant tumour and/or LDD; 35 patients had one tumour, 14 patients had two

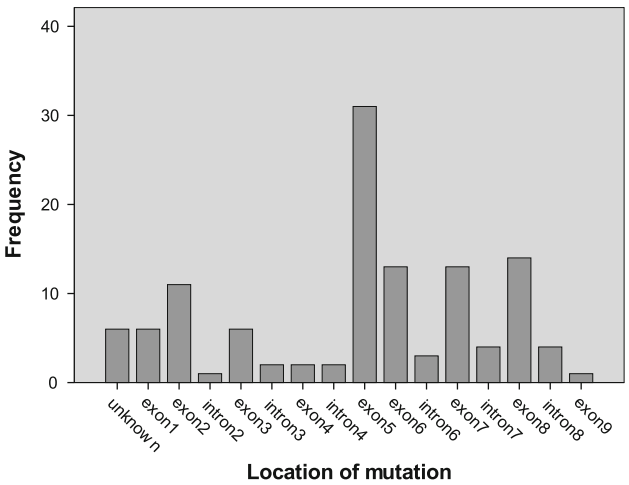

Fig. 1 Distribution of *PTEN* mutations

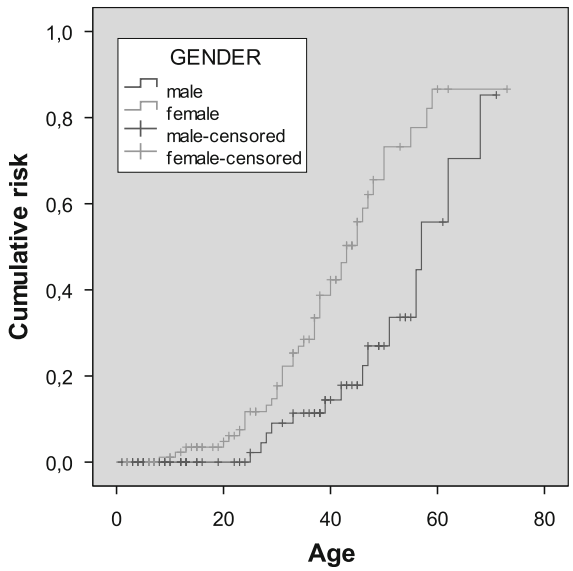

Fig. 2 Cumulative risk of developing cancer and/or Lhermitte-Duclos disease in *PTEN* mutation carriers

tumours, and in 7 patients three metachronous or synchronous tumours were reported. Figure 2 shows the cumulative risk of developing cancer and/or LDD. Females had a significantly higher risk of developing cancer and/or LDD than males (log rank test, p value 0.001). At the age of 60 years, males and females had respectively a five- and seven-fold increased risk of developing cancer compared with the general population (data extracted from the Globocan Database of the World Health Organization [12]).

Table 1 displays the cumulative risk (up to age 60 years) of developing different tumour types for males and females separately. No breast cancers were observed in males. Six of the twenty-four patients (25 %) with breast cancer had bilateral tumours. Beside the 17 patients with Lhermitte-Duclos disease (LDD), 19 patients had other abnormal findings at brain imaging, including pineal gland tumor, meningioma, microgyria, abnormalities of the white matter, cavernous hemangioma, cysts, and vestibular schwannoma. Benign thyroid lesions were reported in 80 patients (44.4 %), at a mean age of 33 years (range

Table 1 Frequency and cumulative risk (up to age 60 years) of cancer and Lhermitte-Duclos disease (LDD) in a cohort of 180 *PTEN* mutation carriers, separately presented and compared for males and females

Cancer type	N	Cumulative risk				Log rank test p value
		Age 30 (%)	Age 40 (%)	Age 50 (%)	Age 60 (%)	
Any cancer and/or LDD						
Male	14/81	9	14.4	27	55.7	0.001
Female	42/99	17.7	42.3	73.2	86.6	
Breast cancer						
Male	0/81	–	–	–	–	0.000
Female	24/99	6.1	20.4	54.2	67.3	
Thyroid cancer						
Male	2/81	2.3	5.7	5.7	5.7	0.043
Female	12/99	6.5	14.3	19.6	24.9	
LDD						
Male	3/81	2.3	2.3	11	11	0.048
Female	14/99	5.3	12.3	23	43.5	
Melanoma						
Male	1/81	2.3	2.3	2.3	2.3	0.219
Female	0/99	–	–	–	–	
Endometrial cancer						
Female	7/99	1.6	6.5	20.7	20.7	–
Colorectal cancer						
Male	2/81	–	–	–	20	0.531
Female	2/99	–	–	–	16.7	
Renal cancer						
Male	2/81	2.3	2.3	2.3	2.3	0.697
Female	2/99	–	2.4	2.4	8.5	
Lung cancer						
Male	1/81	–	–	–	–	0.634
Female	2/99	–	–	2.5	12.2	

One male patient developed lung cancer at age 68

Not included in this table: two males with seminoma at age 25 and a cancer of unknown primary origin at age 33; five basalioma cases, 2 squamous cell carcinoma cases

5–63 years). At age 40, the cumulative risk of benign thyroid lesions was 50 % (figure not shown). Breast cancer, thyroid cancer, and LDD often occurred together, but no specific combination of three tumours was seen twice. All patients who developed colorectal cancer (n = 4) or renal cancer (n = 4) also had syn- or metachronous cancers.

Genotype–phenotype correlations

To evaluate genotype–phenotype associations, the *PTEN* gene was divided into domains as described in the Methods section. The frequency of occurrence of several tumours was compared between patients with mutations leading to NMD and non-NMD mutations. In both groups, similar cancer frequencies were found. Comparison of cancer frequencies in the protein tyrosine phosphatase domain (exons 2–6) with the C2 calcium lipid binding region domain (exons 6–8) also showed no significant genotype–phenotype correlations. Analysis of missense versus other mutations showed a positive correlation between non-missense mutations and thyroid cancer ($p = 0.014$, Table 2). Excluding the mutations with unknown pathogenicity did not influence the results.

Table 2 Frequency of cancer in the patients with missense versus non-missense mutations

Cancer type	Missense mutations	Other mutations	*p* value Chi square test
Any cancer			
Yes	16	31	0.153
No	55	64	
Breast cancer			
Yes	6	16	0.115
No	65	79	
LDD			
Yes	3	10	0.156*
No	68	85	
Thyroid cancer			
Yes	1	11	**0.014***
No	70	84	
Endometrial cancer			
Yes	4	2	0.189*
No	29	54	
Skin cancer			
Yes	5	3	0.289*
No	66	92	
Renal cancer			
Yes	3	1	0.314*
No	68	94	
Colorectal cancer			
Yes	2	2	1.00*
No	69	93	
Lung cancer			
Yes	0	3	0.261*
No	71	92	

* Fisher's exact test if one variable is <5

Bold value indicates $p < 0.05$

Discussion

The present international cohort study shows that female *PTEN* mutation carriers have an approximately eight times increased risk of developing cancer and/LDD, compared to the general population. Male patients showed a five-fold increased risk of developing cancer and/or LDD, compared with the healthy population. Nearly 40 % of the patients developed two or three pathologically different tumours. Beside the well-known tumour spectrum in *PTEN* mutation carriers, including breast cancer, thyroid cancer, endometrial cancer, and cerebellar gangliocytoma (LDD), several patients developed skin cancer, renal cancer, and colorectal cancer. No evident associations between *PTEN* mutation site or mutation type and the phenotypic expression could be identified, except a positive correlation between non-missense mutations and thyroid cancer.

As Cowden syndrome is the most frequent and best characterized syndrome of the disease entities of PHTS, most previous studies focused on this syndrome. One of these reported a cumulative risk at age 70 of 89 % for any cancer diagnosis in patients with Cowden syndrome [3] which is similar to the risk of 87 % at age 70 observed in the present analysis. That study also reported that males had fewer cancers diagnosed than female patients, and that males in particular had cancers not associated with Cowden syndrome, including melanoma, squamous cell cancer, renal cancer, lung cancer, and testicular seminoma [3]. Another study, including 46 patients meeting clinical PHTS criteria, also reported a much wider tumour spectrum including ovarian cancer, vaginal adenocarcinoma, broncheoalveolar adenocarcinoma, and neuroendocrine tumours [7]. A third study, including 368 *PTEN* mutation carriers, also observed a broad spectrum of malignant tumours in *PTEN* mutation carriers, including colorectal cancer, renal cancer, and melanoma [4]. Moreover, that study found a higher cumulative risk of breast cancer and endometrial cancer than was assumed previously [4]. Our study confirms that cancers of the skin, kidney, colorectum, lung, and seminoma occur in patients with PHTS in addition to the characteristic tumor spectrum. However, the frequency of skin cancer (including one case of melanoma, age 27 and several cases of basalioma of which the youngest patient was 23 years), lung cancer, and seminoma seemed not to be significantly different from the general population, if compared with cumulative risks as

reported in the Globocan Database [12]. The risk of colorectal cancer and renal cancer was clearly increased.

Females had significantly higher cancer risks than males in this study, as observed previously [3]. In part, this is due to the typical female cancers, breast and endometrial cancer. However, females were also at higher risk of thyroid cancer and LDD. Remarkably, we and others did not find increased risk of prostate cancer in males, despite the fact that somatic deletions of PTEN are common in human prostate cancers [13].

Although LDD is not a malignancy by histological definition, this tumour causes serious problems, including headaches and other symptoms of increased intracranial pressure, cerebellar ataxia, visual disturbances, and cranial nerve palsies [14]. Therefore, we also assessed LDD in the present study and calculated a substantial detection rate (20 %) of LDD and other cerebral abnormalities at brain scanning. This may even be an underestimate, as brain examinations in most cases will have been performed because of symptoms. A previous study assessing the frequency of asymptomatic LDD showed abnormal brain scans in 35 % of patients with Cowden syndrome, including LDD, hemangiomas, and vascular malformations [15]. As the majority of findings are of benign nature it is questionable whether screening of the brain is indicated in all patients with PHTS. It seems to be appropriate to perform brain imaging on clinical indication, as identification of these disorders may explain clinical symptoms. On the other hand, non-symptomatic abnormalities such as hemangiomas and vascular malformations may cause acute bleeding or seizures [15]. Whether serious consequences of these abnormalities can be prevented by early detection needs careful assessment. Also, further studies are needed to answer the question of whether and when surgery is indicated for LDD.

The distribution of germline mutations in the *PTEN* gene in our cohort resembles roughly that as described in previous studies [5, 10]. Studies in mouse models, and recently also in humans, show that a lower PTEN dosage is correlated with increasing tumour susceptibility [9, 10]. Despite several investigations into an association between certain *PTEN* mutations and the phenotype of PHTS we could not demonstrate any such correlation, except a lower frequency of thyroid cancer in patients with missense mutations, compared with non-missense mutations. The clinical value of this finding appears to be limited. Our findings concerning genotype–phenotype correlations are in accordance with most previous studies on this topic [2, 7, 16].

Germline *PTEN* mutations cause PHTS, but somatic *PTEN* mutations are also frequently found in sporadic tumours. Interestingly, there is overlap between common tumours of the PHTS spectrum and sporadic tumours with frequent *PTEN* mutations, suggesting that *PTEN* mutations are an etiological factor in these tumour types [11]. It is evident that PTEN plays an important role in tumorigenesis, and appears to interact with multiple other genes [17].

As germline *PTEN* mutations are rare (estimated incidence at least 1:200,000) [1], calculation of cancer risks is complicated due to the small numbers of PHTS patients available to study. The present study included a considerable cohort of mutation carriers from nine Western countries. By inclusion of all mutation carriers, even asymptomatic children, the risk of ascertainment bias was reduced. However, as symptomatic patients are usually referred for genetic counselling, we realize that some extent of ascertainment bias can not be excluded. Furthermore, there may be preferential ascertainment of family branches with affected family members. In general, the clinical geneticists reported complete data. In some cases, it was not clear whether the characteristic was missing or that no information was available. Therefore, the risks presented in this study are minimal risks, A shortcoming of this study is that detailed information on *PTEN* mutations was missing in some cases, although we assume that more information would not have changed the results significantly, since information was available for the majority of patients.

Current guidelines include strategies to detect cancers of the breast, thyroid, endometrium, and colorectum in a timely manner [18]. We agree with Tan et al. [4] that clinical guidelines should be changed according to the results of the recent studies, including the present study. Patients and physicians should be aware of the risk of tumours other than those in the well-known Cowden tumour spectrum and screening protocols could be changed to incorporate these. Future studies should also focus on the development of agents that inhibit the PI3K/Akt/mTOR pathway for potential treatment for this condition [19–21].

In conclusion, our study confirms that PHTS patients have a substantially increased risk of developing several types of cancer, compared with the general population, more pronounced in women than in men. At present, no evident association of mutation site and cancer risk has been found.

Conflict of interest The authors declare that they have no conflict of interest.

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