CLINICAL STUDY

CDC73-related hereditary hyperparathyroidism: five new mutations and the clinical spectrum

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Abstract

Objective: Hyperparathyroidism-jaw tumour (HPT-JT) syndrome is a rare autosomal dominant cause of benign and malignant parathyroid tumours, ossifying jaw tumours, various cystic and neoplastic renal abnormalities and benign and malignant uterine tumours. Disease-causing mutations have been localised in the tumour suppressor gene *CDC73*. There is limited information available on the mutations, and resulting phenotypes and long-term follow-up data are especially scarce.

Design: We analysed the clinical data from 16 patients (including three families) carrying mutations in the *CDC73* gene. We describe five new mutations/gene variants, the corresponding phenotypes of these carriers and the long-term follow-up.

Methods: The 16 patients were evaluated at an endocrine outpatient clinic and at a surgical department. DNA samples were obtained for sequence analysis of the *CDC73* gene.

Results: Clinical features of HPT-JT syndrome were detected in 13 of the 15 carriers with germline *CDC73* mutations. The major features were benign ($n=7$; 47%) or cancerous ($n=3$; 20%) HPT-JT was present in eight cases (53%). Most patients had severe hypercalcaemia, and median serum calcium levels were 3.36 mmol/l. A patient with non-secretory parathyroid carcinoma was included. HPT was diagnosed at a median age of 28.5 years. Mutational analysis of the *CDC73* gene identified eight sequence changes, three of them have been reported previously, whereas five are novel: c.1346delG, c.88_94delTTCTCCT, the non-coding variants, c.307 + 5G > T and c.424 – 5T > C and c.*12C > A of unknown significance.

Conclusions: This study significantly increases the information available on the mutations and phenotypes of HPT-JT syndrome.

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Introduction

In patients with *CDC73* mutations (formerly known as *HRPT2*), a spectrum of parathyroid tumour-associated phenotypes is described as follows: hyperparathyroidism-jaw tumour syndrome (HPT-JT), familial isolated hyperparathyroidism (FIHP) and parathyroid carcinoma (1). HPT-JT is a rare autosomal dominant cause of benign and malignant parathyroid tumours, ossifying fibromas of the mandible and maxilla, various cystic and neoplastic renal abnormalities and benign and malignant uterine tumours. The disease is caused by inactivating germline mutations in the tumour suppressor gene *CDC73* with subsequent loss of parafibromin expression (2, 3). *CDC73* encodes parafibromin, a regulator of gene expression. Several reports have demonstrated a loss of parafibromin expression in HPT-JT-related parathyroid adenomas (4) and also by somatic *CDC73* mutations in sporadic parathyroid carcinomas (5). To date, more than 100 independent *CDC73*

mutations have been identified (germline and somatic), and these occur throughout the coding region and splice sites of the *CDC73* gene (1). Primary HPT, the main finding in HPT-JT syndrome, occurs in 80–90% of affected individuals. In about 10–15% of *CDC73*-associated cases, HPT is caused by parathyroid carcinoma and even nonfunctioning parathyroid carcinomas have been reported (6). Cemento-ossifying fibromas of the mandible and maxilla occur in 30–40% of individuals with HPT-JT syndrome, whereas ~20% show kidney lesions, most commonly renal cysts, but rarely malignant tumours have been reported. Uterine tumours appear to be common in women with HPT-JT (7). Incomplete penetrance of gnathic, renal and uterine expression of HPT-JT is known to occur.

Familial primary HPT is a heterogeneous disease; the main hereditary forms of HPT are multiple endocrine neoplasia (MEN) type 1 and type 2, HPT-JT syndrome and FIHP (8), which is characterised by HPT without other associated features. FIHP is rarely caused by

CDC73 mutations (9, 10). Sporadic parathyroid carcinomas frequently have somatic *CDC73* mutations that are likely to be pathogenetic. Somatic mutations have been detected in 57–100% of patients with sporadic parathyroid carcinoma (5, 11, 12). About 20% of patients with apparently sporadic parathyroid carcinoma carry germline mutations in the *CDC73* gene (5). There is considerable variability in the penetrance and expressivity of truncating *CDC73* mutations, making it difficult to develop comprehensive and efficient guidelines for carrier therapy and surveillance. *CDC73* mutation analysis in affected families offers the unique chance to diagnose hereditary parathyroid cancer at an early stage.

In this study, we investigated the phenotypic characteristics of 16 patients carrying mutations in the *CDC73* gene and provide significant new data about this group of patients and their families. In particular, the long-term follow-up data are crucial for formulating appropriate management guidelines. In this study, we describe five new mutations/gene variants, the corresponding phenotype in these carriers, and the long-term follow-up for up to 17 years.

Materials and methods

The study population consisted of 16 patients evaluated at the endocrine outpatient clinic in Heidelberg, Germany, and operated at the Surgical Department of the University of Halle, Germany. DNA samples were obtained and sent, with clinical data, for mutation analysis at the Molecular Laboratory in Heidelberg, Germany. Informed consent for collection of clinical, biochemical and genetic data was obtained from all patients. HPT-JT syndrome was diagnosed in cases with familial primary HPT, evidence of parathyroid adenoma or carcinoma, cemento-ossifying jaw tumours and germline *CDC73* mutations. Criteria used for diagnosis of parathyroid carcinoma were vascular and/or capsular invasion of tumour tissue and/or metastatic disease. Selection criteria to identify index cases for *CDC73* sequencing was established: familial HPT and/or HPT plus an HPT-JT associated lesion (i.e. jaw tumour and renal cysts). Germline and somatic *CDC73* sequencing was only done for patient H. Clinical, biochemical and histological data were collected and follow-up included clinical and laboratory re-evaluation. Family A was included in a former study (13), whereas the index case of family C was included in several studies (3, 12, 14). The clinical findings and family data were extended and long-term follow-up was outlined.

Germline and somatic mutation analysis of the *CDC73* gene

DNA was extracted from tumour samples and peripheral blood leucocytes according to standard procedures. The 17 exons of the *CDC73* gene were amplified by PCR as

described previously (5). The PCR products were purified using the AMPure system (Beckman Coulter, Brea, CA, USA) and sequenced with the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's protocol. All mutations were confirmed by a second independent PCR amplification and sequencing reaction.

Results

The study population consisted of 16 patients of which 15 carried germline mutations in the *CDC73* gene, whereas in one patient (H), only a somatic *CDC73* mutation was detected in parathyroid cancer tissue. In this study, four patients with parathyroid carcinomas were included, three with germline *CDC73* mutations (A II.1, B I.1 and C II.1) and patient H with only the somatic mutation.

Patients

The study population included three families (with three, five, and three affected members/mutation carriers) carrying different germline mutations (Fig. 1). The index cases of families A, B and C all had parathyroid carcinoma; therefore, sequence analysis of the *CDC73* gene was performed. In all of the single patients (D, E, F and G), the combination of HPT with jaw tumours led us to sequence the *CDC73* gene. Clinical features of HPT-JT syndrome were detected in 13 of the 15 carriers of germline mutations (Table 1). Disease manifestation was exhibited in two family members of family B (B II.2 and B II.3), but germline testing was not yet performed; therefore, we considered them to be affected family members. To date, two subjects (A I.1 and B II.1), aged 72 and 43 years, have no clinical manifestation of the disease and are considered healthy mutation carriers.

The major clinical features in our 15 patients carrying germline *CDC73* mutations were benign ($n=7$, 47%) or cancerous ($n=3$, 20%) HPT. Of the total patients, one underwent surgery for benign HPT but the exact histology was not available, and four patients had no parathyroid involvement. No criteria for atypical parathyroid adenomas were identified. HPT was the first manifestation leading to the diagnosis of the disease in all but two patients. Aetiology in all but one patient with benign parathyroid disease was a single parathyroid adenoma; hyperplasia of three glands was identified in one patient (C II.2). HPT was diagnosed at a median age of 28.5 years (range 16–58), whereas carcinoma patients had a median age at diagnosis of 30 years (range 22–57). In affected patients, median serum calcium levels were 3.36 mmol/l (range 2.9–4.3 mmol/l; normal 2.2–2.65 mmol/l) and median PTH levels were 39.8 pmol/l (range 12.5–235 pmol/l; normal 1.3–5.4 pmol/l). In patients exhibiting parathyroid carcinoma, median serum calcium

Figure 1 Pedigrees of families A, B and C. For details see Table 1. Index cases are denoted by arrow; and symbols with a slash indicate the individual is deceased.

and PTH levels were even higher (4.05 mmol/l and 189 pmol/l respectively). During a median follow-up time of 10 years (range 0.5–11 years) in the patients carrying benign parathyroid disease, no recurrence was observed; one patient with parathyroid cancer (A II.1) was suspected to be disease free (follow-up time 9 years). Recurrent non-secretory parathyroid cancer was detected in one patient (C II.1). This patient had multiple recurrences and

re-operations in the neck and mediastinum and, therefore, impaired lung function and increased risk for pneumonia and pulmonary complications. She died from severe pneumonia at the age of 40 years after 17 years of follow-up. One patient suffered from severe hypercalcaemia related to lung and bone metastases (B I.1).

Jaw tumours were present in eight cases (53%), and half of them were histologically proven as cemento-ossifying fibromas. In two members of family B, jaw tumours (one proven histologically) were diagnosed before other disease manifestations. Renal cysts were found by ultrasound in one patient and uterine myoma in two patients. Of the six females carrying germline mutations in our study, myomas were detected in two patients, gynaecological ultrasound was normal in three patients and information was unavailable in one patient. Of the 15 cases, two cases were assigned the status of apparent silent carrier.

In one patient with parathyroid cancer (H), only a somatic novel *CDC73* mutation was detected in the tumour tissue, no germline mutation was found. The diagnosis of this patient was based on hypercalcaemia, and during follow-up, recurrent cancer tissue was re-operated several times. This patient suffered from persistent hypercalcaemia due to parathyroid cancer and died as a result of lung metastases, hypercalcaemia and cachexia after 8 years of follow-up.

Mutational analysis of the *CDC73* gene

In this study, mutational analysis of the *CDC73* gene identified eight sequence changes, three of which have been previously reported. Of the *CDC73* sequence changes, five encountered in this study are novel: c.1346delG, c.307+5G>T, c.424–5T>C, c.*12C>A and c.88_94delTTCTCCT in Exon 1 in the parathyroid tumour tissue of patient H causes premature termination of protein synthesis; this mutation was detected only in the tumour tissue of this patient, not in her germline. This mutation occurs either as a homozygous variant or more likely in a hemizygous state (loss of heterozygosity). In two index cases (B I.1, E 1), a known *CDC73* polymorphism, c.1418–17C>G in intron 15, was detected. No polymorphisms were detected in the four other index cases.

Discussion

Clinical findings

The major clinical features in our 15 patients carrying germline *CDC73* mutations were benign (47%) or cancerous (20%) HPT, similar to the findings of Simonds *et al.* (8). HPT was the first manifestation of the disease in all but two of our patients. This is in concordance with recently published studies (15, 16). Aetiology in all but one patient with benign parathyroid disease was

Table 1 Clinical and laboratory findings in patients with HPT-JT syndrome/parathyroid carcinoma.

Patient no. (reference)	Sex/current age (years)	Age at diagnosis of HPT (years)	Initial calcium mmol/l (2.2–2.65)	Initial PTH pmol/l (1.3–5.4)	Parathyroid tumours	Outcome/follow-up years	Associated diseases
A I.1 (13)	M/72	–	2.4	2.9	–	No disease manifestation/5	–
A II.1 (13)	M/39	30	4.3 (renal failure)	143	Carcinoma	Disease-free/9	Jaw-tumour
A II.2 (13)	F/43	32	3.3	48.9	Adenoma	Disease-free/11	Uterine myoma
B I.1	M/63	57	3.8	235	Carcinoma	Persistent HPT metastases: lung, bone/6	–
B I.2	M/51	–	2.2	Normal	–	No HPT, no kidney disease/8	Jaw-tumour ^a
B II.1	F/43	–	2.2	Normal	–	No disease manifestation/6	–
B II.2	M/36	–	Normal	Normal	–	No HPT/6	Jaw-tumour
B II.3	M/22	16	3.46	25	Adenoma	Disease-free /6	–
C I.2	M/61	50	3.27	39.6	Single adenoma	Disease-free /10	–
C II.1 (3, 12, 14)	F/DWD	22 ^b	Normal, NSC	Normal, NSC	Carcinoma	Multiple recurrences DWD/17	Jaw tumour ^a
C II.2	M/31	20	3.36	12.5	3 Hyperplastic glands	Disease-free/11	–
D 1	F/33	20	3.6	39.8	Adenoma	Disease-free/10	Jaw tumour
E 1	M/25	NA	Elevated	Elevated	NA	NA	Jaw tumour
F 1	F/29	27	2.9	15	Adenoma	Disease-free/2	Jaw tumour ^a
G 1	F/58	58	3.2	54.5	Adenoma	Disease-free/0.5	Jaw-tumour ^a Uterine myoma
Somatic mutation H 1	F/DFD	25	3.4	39.1	Carcinoma	Persistent HPT metastases: lung/8	Renal cysts

DWD, dead with disease; DFD, dead from disease; NSC, non-secretory carcinoma; NA, not available.

^aHistologically proven cemento-ossifying fibroma.^bAge at diagnosis of non-secretory parathyroid carcinoma.

a single parathyroid adenoma. Jaw tumours were present in eight cases (53%) in our study. In two patients, jaw tumours were diagnosed first without any other disease manifestations. Cemento-ossifying fibromas have been reported to occur in 25–50% of cases (2, 15), but it is not clear whether the jaw tumours were the first manifestations. If family screening is established in an appropriate manner, early findings of jaw tumours may allow for earlier diagnosis of HPT-JT syndrome.

Renal cysts were detected in one patient. In the two patients diagnosed with uterine myomas, hysterectomy was not necessary. This is in contrast to the findings of Bradley *et al.* (7) who described uterine involvement and a decrease in reproductive fitness in up to 75% of women with HPT-JT syndrome. Of the 15 cases, two were assigned the status of apparent silent carrier, while the degree of non-penetrance has been described to be more than 30% (7).

The average age of onset of HPT in HPT-JT syndrome is not well established and is usually in late adolescence or early adulthood but subjects younger than 10 years of age have been reported (8). In one study, a mean age at diagnosis of 36 years is reported (17). The median age at diagnosis of HPT was 28.5 years (range 16–58)

in our study; this is in accordance with recently published data (17). We suggest biochemically screening asymptomatic mutation carriers beginning at the age of 15 years, because very early manifestation is rare. However, some may argue that a baseline screening Ca/PTH, panoramic jaw X-rays and renal ultrasound any time after the age 5 years would be appropriate, because any equivocal or positive features would invoke more careful screening for other disease manifestations (18).

HPT in HPT-JT syndrome is usually caused by a single parathyroid adenoma, but recurrence of HPT after selective parathyroidectomy occurred in about 20% of cases after 10–15 years (17). In HPT-JT patients with HPT, long periods of postsurgical normocalcaemia could be documented; therefore, selective parathyroidectomy may be an effective strategy, but long-term follow-up is necessary (19). In our patients, predominantly single parathyroid adenomas were detected at the primary operation. After a median follow-up of 10 years (range 0.5–11 years), no recurrence was observed in patients carrying benign parathyroid disease. The reason for this lack of recurrences might be the relatively short follow-up period. In 20% of cases in our study, HPT in HPT-JT syndrome was caused by parathyroid cancer. A 15%

Table 2 *CDC73* mutations in patients with HPT-JT syndrome/parathyroid carcinoma.

Family	Mutation	Region	Mutation type	Predicted effect	Reference
A	c.700C>T p.Arg234X	Exon 7	Germline	Mutation/premature stop codon	Shattuck <i>et al.</i> 2003 (5)
B	c.1346delG p.Gly449ValfsX30	Exon 15	Germline	Frame shift premature stop codon	Novel
C	c.76delA p.Ile26SerfsX11	Exon 1	Germline	Mutation/deletion premature stop codon	Howell <i>et al.</i> 2003 (12)
D	c.1432_1433delCT p.Leu478GlufsX	Exon 16	Germline	Mutation/frame shift premature stop codon	Haag <i>et al.</i> 2008 (21)
E	c.307+5G>T	IVS 3	Germline	VUS/splice site	Novel
F	c.424-5T>C	IVS 5	Germline	VUS/splice site	Novel
G	c.*12C>A	3'-UTR	Germline	VUS/expression	Novel
H	c.88_94delTTCTCCT p.Phe30GlyfsX5	Exon 1	Somatic	Mutation (homozygous)/deletion premature stop codon	Novel

VUS, variants of unknown significance.

occurrence of parathyroid carcinoma was detected in a large study (8); in this study, the number of operations per case was highest in the HPT-JT subgroup because of the high prevalence of parathyroid carcinoma. In this study, one patient (8) had parathyroid carcinoma in two separate glands at initial cervical exploration, and the highest proportion of cystic parathyroid tumours was among the HPT-JT patients. An index patient (C II.1) with non-secretory parathyroid carcinoma was included in our study. Another normocalcaemic patient with parathyroid cancer has been described (6), and these two patients carry different mutations. From these two cases, we conclude that longitudinal surveillance by serum calcium biochemistry alone may not be sufficient; routine neck ultrasound should also be performed.

Some findings in the HPT-JT patients in this and other studies differ from the findings typical for patients with sporadic HPT or other varieties of hereditary HPT. First, there is a unique high frequency (three of 15 cases) of parathyroid cancer in HPT-JT in our study. The frequency of parathyroid carcinoma is virtually 0 in MEN1 and clearly below 1% in sporadic cases of HPT (8, 20). Secondly, the majority of patients with HPT-JT have single gland involvement, similar to patients with the sporadic variety. This is in contrast to HPT in MEN1, which involves several glands simultaneously and asymmetrically. Thirdly, in our study, the severity of parathyroid involvement in relation to serum calcium and PTH elevation was more severe in HPT-JT than in sporadic HPT, which nowadays is often mild and asymptomatic.

Genetic characteristics

In this patient cohort, we identified eight *CDC73* mutations in four of the 17 exons. Of the eight mutations, one resulted directly in a premature stop codon, four gave rise to an altered reading frame and two mutations involved a splice site and therefore are likely to cause a change in the resulting protein.

The mutation p.Arg234X of family A has been previously reported in several unrelated patients with parathyroid carcinomas (5, 11) and also in HPT-JT patients (1, 15). Clinical data are limited in these studies; therefore, a comparison of phenotypes is not possible. The mutations p.Ile26SerfsX11 of family C and p.Leu478GlufsX of patient D have been previously reported by the authors (3, 12, 21). In this study, five of the *CDC73* sequence changes encountered are novel (Table 2). The newly described heterozygous deletion c.1346delG p.Gly449ValfsX30 in Exon 15 in family B causes a frameshift and premature stop codon and, therefore, is predicted to cause a loss of gene function. This *CDC73* mutation segregated with the disease within this family; therefore, it is very likely to be involved in the pathogenesis of the disease. The novel c.307+5G>T sequence change in intron 3 of patient E and the unreported mutation c.424-5T>C in patient F involve a splice site and, therefore, might affect the resulting protein. The variant of unknown significance, c.*12C>A in the 3'-UTR in patient G, may be involved in the regulatory processes of expression. The co-occurrence of HPT and a jaw tumour in the single patients E, F and G suggest a pathogenetic role of the newly described gene variants in these patients.

In the relatively short time since the identification of *CDC73* in 2002, nearly 70 germline mutations have

Table 3 When should *CDC73* mutation analysis be considered?

Parathyroid carcinoma
Cemento-ossifying fibroma of the jaw
Young patient with hyperparathyroidism when MEN1 mutation analysis is negative
Multiglandular parathyroid involvement when MEN1 mutation analysis is negative
Recurrent hyperparathyroidism when MEN1 mutation analysis is negative
Familial hyperparathyroidism when MEN1/2 mutation analysis is negative
If in mild asymptomatic familial hypercalcaemia, <i>CASR</i> and MEN1/2 mutation analysis is negative, <i>CDC73</i> mutation analysis may be considered

been reported (1). Mutations in exons 1, 2 and 7 are overrepresented (about 80%), but there is no apparent genotype–phenotype correlation (1). Our data support this finding. Non-penetrance of the *CDC73* mutations in HPT-JT kindreds has been reported in >30% of mutation carriers (15) and the latest clinical manifestation of HPT was reported after the age of 60 years. In our study, the oldest asymptomatic gene carrier was 72 years old.

How to involve genetic information in clinical practice

Familial HPT has been associated with mutant *MEN1* and *MEN2*, mutant calcium-sensing receptor (*CASR*) and mutant *CDC73* genotypes. *CDC73* mutation analysis is reasonable in patients with parathyroid carcinoma or in patients with HPT and cemento-ossifying fibromas of the mandible and maxilla (Table 3). Also, in young patients with HPT, *CDC73* mutation analysis may be undertaken when *MEN1* mutation analysis is negative. Of the HPT-JT families described, the youngest patient with HPT was 10 years of age (8), whereas the youngest patient in our study was 16 years of age. In patients with multiglandular involvement, HPT-JT syndrome may be a rare causative disease, as was found for one case in our study. Recurrent HPT is described in HPT-JT syndrome especially during long-term follow-up (17); therefore, in patients with multiglandular involvement or recurrent HPT, *CDC73* mutation analysis may be considered. Among the different variants of hereditary HPT, *MEN1*–HPT is the most frequent and carries the highest recurrence rate. Therefore, *MEN1* gene analysis should be completed first in suspected hereditary HPT; if *MEN1* mutation analysis is negative, *CDC73* analysis should be considered. In 5–10% of cases, *MEN1* phenocopies may be present and it is important to be aware of their presence in the clinical setting of hereditary HPT (22). Some of these cases have been attributed to mutations in the cyclin-dependent kinase inhibitor genes (23). In *MEN2*, the higher penetrance of medullary thyroid cancer and pheochromocytoma dominates the clinical presentation. HPT in *MEN2* usually is mild and usually occurs only in RET 634 carriers. A 20% penetrance rate is documented for *MEN2*; therefore, it is not the primary consideration in the differential diagnosis of hereditary HPT (24). *CASR* mutation screening in FIHP should be considered when there is mild asymptomatic hypercalcaemia without other pathologies.

Conclusions

The identification of *CDC73* mutations in patients with HPT-JT syndrome and the ability to perform genetic testing offer the unique chance to diagnose hereditary

parathyroid cancer at an early stage. Also, early diagnosis of HPT in these families is possible, preventing hypercalcaemic crisis, nephrolithiasis and renal insufficiency and osseous complications like fractures due to osteoclastic ‘brown’ tumours or osteoporosis. Excision of the identified parathyroid tumour is usually sufficient in HPT-JT syndrome. There is no evidence supporting prophylactic parathyroid surgery in *CDC73* mutation carriers. Long-term follow-up is required because of the risk of recurrent HPT and parathyroid carcinoma.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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