Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 61; Numer/Number 5/2010
ISSN 0423–104X

Case report of a woman with monoclonal gammapathy and papillary thyroid carcinoma, diagnosed because of detection of CHEK2 (I157T) mutation in genetic examinations

Opis przypadku chorej z monoklonalną gammapatią i rakiem brodawkowatym tarczycy, u której diagnostykę tyreologiczną podjęto ze względu na obecność mutacji CHEK2 (I157T)

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Abstract

The *CHEK2* gene encodes the CHK2 protein, which is kinase involved in DNA repair processes. By activating a lot of cell substrates, it can regulate the cell cycle, demonstrates suppressive effects, and participates in the senescence and apoptosis processes. Mutations in the *CHEK2* gene are associated with increased risk of numerous cancers. The case described herein is that of a woman with a missense mutation that results in the substitution of isoleucine for threonine at position 157. This variant of the mutation doubles the risk of papillary thyroid carcinoma two times and causes up to 9% of these cancer. It is also associated with a two-fold increased risk of cancers of the kidney (10%), colon (10%), and ovary (10% — G1), a 1.6-fold increased risk of prostate cancer (8% of all of them and 12% of familiar ones), and a 1.5--fold increased risk of breast cancer (7%). The screening procedures were initiated in a carrier who revealed papillary thyroid carcinoma. Genetic screening of the family diagnosed her daughter as the carrier of this mutation. Until now no active cancer disease has been recognized in the daughter. On the example of the presented case we discuss indications for screening in cases of positive family history. The group especially predisposed seem to be patients with at least two coexisting carcinomas. Having diagnosed the mutation, it is necessary to do genetic screening of family members. Continuous oncological observation of the carriers of CHEK 2 mutation is essential. **(Pol J Endocrinol 2010; 61 (5): 502–506)**

Key words: *gene CHEK2, protein CHK2, missense mutation CHEK2 (I157T), papillary thyroid carcinoma*

Streszczenie

Ludzki gen *CHEK2* koduje białko CHK2, będące kinazą efektorową zaangażowaną w naprawę DNA. Aktywując wiele substratów komórkowych, bierze udział w regulacji cyklu komórkowego, wykazuje działanie supresyjnie, wpływa również na proces apoptozy i starzenia się komórek. Mutacje genu *CHEK2* są związane z ryzykiem licznych nowotworów. Opisywany przypadek chorej dotyczy mutacji typu missens, gdzie dochodzi do zamiany izoleucyny na treoninę w pozycji 157. Mutacja ta zwiększa 2-krotnie ryzyko raka brodawkowatego tarczycy. Predysponuje do występowania 2-krotnie częściej raka nerki (10%), jelita grubego (10%), jajnika (10% — G1), 1,6-krotnie częściej raka prostaty (8% wszystkich i 12%występujących rodzinnie) oraz 1,5-krotnie częściej raka piersi (7%). Na podstawie diagnostyki w kierunku predysponowanych nowotworów wykryto u chorej raka brodawkowatego tarczycy. Skrining genetyczny rodziny pozwolił na wykazanie nosicielstwa tej mutacji u córki pacjentki — dotychczas nie stwierdzono u niej czynnej choroby nowotworowej. Opisywany przypadek chorej wskazuje na celowość przeprowadzania badań genetycznych w przypadku dodatniego wywiadu rodzinnego w kierunku chorób nowotworowych. Szczególnie predysponowaną grupą wydają się być chorzy z co najmniej dwoma współistniejącymi nowotworami. Wykazanie mutacji nakłada obowiązek badań genetycznych u pozostałych członków rodziny, jak również bezterminowy nadzór onkologiczny u nosicieli mutacji. **(Endokrynol Pol 2010; 61 (5): 502–506)**

Słowa kluczowe: *gen CHEK2, białko CHK2, mutacja missens CHEK2 (I157T), rak brodawkowaty tarczycy*

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Introduction

Human gene CHEK2 encodes CHK2 protein, a protein kinase engaged in DNA-repair. Activating cell substrates, it regulates the cell cycle and affects apoptosis and aging of cells [1, 2]. Mutations of the CHEK2 gene lead to the development of various cancers [1–3]. The two main groups of mutations of this gene are characterized by either truncation of the encoded protein or the missense type, with the substitution of one amino acid into another. The described case refers to the missense mutation which leads to substitution of isoleucine at position 157 with threonine. CHEK2 mutation (I157T) doubles the risk of papillary thyroid carcinoma and causes up to 9% of these cancers [3, 4]. It predisposes to twice as frequent incidence of cancers of the kidney (10%), colon (10%), and low grade ovary cancer (10%), 1.6-times more frequent prostate cancer (8% of all and 12% of familial cases), and 1.5-times more frequent breast cancer (7%) [3, 4]. In 4.8% of cases it affects the Polish population [2, 3]. The frequency of incidence of this mutation, as well as the variety of cancers to which it predisposes, makes genetic testing and genetic counselling advisable, especially in patients with positive familiar history. Genetic supervision should be implemented in cases where at least two cancers were diagnosed. In families of carriers of CHEK2 mutations, DNA testing is necessary.

Description

A woman of 56 years was referred to the Genetic Clinic due to a positive familial history for monoclonal gammapathy. Her father and her father's brother and sister were diagnosed with multiple myeloma. Since 1999 the patient has been under observation owing to monoclonal gammapathy, without treatment. Familial history for thyroid diseases is positive: the patient's mother and her second sister were diagnosed with nodular goitres, while her 26-year-old daughter has been treated with substitutive doses of L-T4 since childhood, due to hypothyroidism due to Hashimoto's disease. In genetic testing the patient was diagnosed with CHEK2 mutation (I157T). Oncological diagnostics was conducted according to the recommendations of the International Centre For Hereditary Cancers at the Department of Genetics and Pathomorphology of the Pomeranian Medical University. Thyroid diagnostics indicated Hashimoto's disease: TSH — 1.41 uIU/mL (N: 0.4–4.0 uIU/mL), a/TPO — 378 uIU/mL (N: 0–35 uIU/mL).

In thyroid ultrasound there were described in the right lobe a hypoechogenic solid nodule with micro calcifications of 10 × 9 mm (P2), in a hypoechogenic nodule of 10 × 7 mm (P3), and in the left lobe a normoechogenic nodule of 25 × 17 mm (L3).

In cytological examination (FNAB) of the thyroid nodules there were diagnosed: P2 — papillary thyroid cancer, P3 — nodule of suspicious character, and L3 — benign tumour. The operation that followed was a total thyroidectomy. In the histopathological examination papillary carcinoma was confirmed in the P2 as the pT3N0Mx tumour. Adjuvant treatment with ^{131}I was implemented and LT-4 was instituted in a suppressive dose. Oncology diagnostics for other cancers did not show any pathologies.

Genetic testing in the patient's daughter treated for hypothyroid Hashimoto's disease found her to be a carrier of CHEK2 mutation (I157T), but no presence of cancers was found to which this mutation predisposes. The patient remains under endocrinological observation. The other family members rejected genetic diagnostics.

Discussion

Human gene CHEK2 encodes CHEK2 protein, a protein kinase active in DNA-repair. The protein product regulates the cell response to DNA-damage by phosphorylation of a number of cell substrates [1, 2]. The locus of CHEK2 gene is in the long arm of chromosome 22 (22q12.1). The first identification of CHEK2 was in budding yeast Saccharomyces cerevisiae as Rad53, and in Schizosaccharomyces pombe as Cds1 [1]. Both these proteins were then found to be serine/threonine-kinases controlling DNA replication and activating inhibition of the cell cycle as a response to DNA damage. In 2002, mutation truncating CHEK2 (1100del1C) was first described in a patient with breast cancer. In 2003, CHEK2 mutation was proven to be associated with prostate cancer. In 2004, mutation of this gene was, for the first time, revealed to increase the risk of numerous cancers [1–3].

As a response to damage of both strands of DNA, CHEK2 protein is activated through its dimerisation and autophosphorylation. Activated CHEK2 starts a number of cell mechanisms with the result of DNA repair, inhibition of the cell cycle, or aging and apoptosis of the cell (Fig. 1).

The mechanism of DNA repair occurs through activation of BRCA1 by CHEK2 [1, 2, 5, 6]. Phosphorylation of CDC25C phosphatase causes the inhibition of cell cycle in the G2 phase [1, 2], and indirect phosphorylation of CDC25C phosphatase causes inhibition of S phase [1]. CHEK2 also indirectly regulates inhibition of the G1 phase of the cell cycle and cell apoptosis activating phosphorylation of protein p53 [1, 2, 7, 8]. It has recently been found to be essential for regulating p53 and not for its direct activation [1]. CHEK2 may also

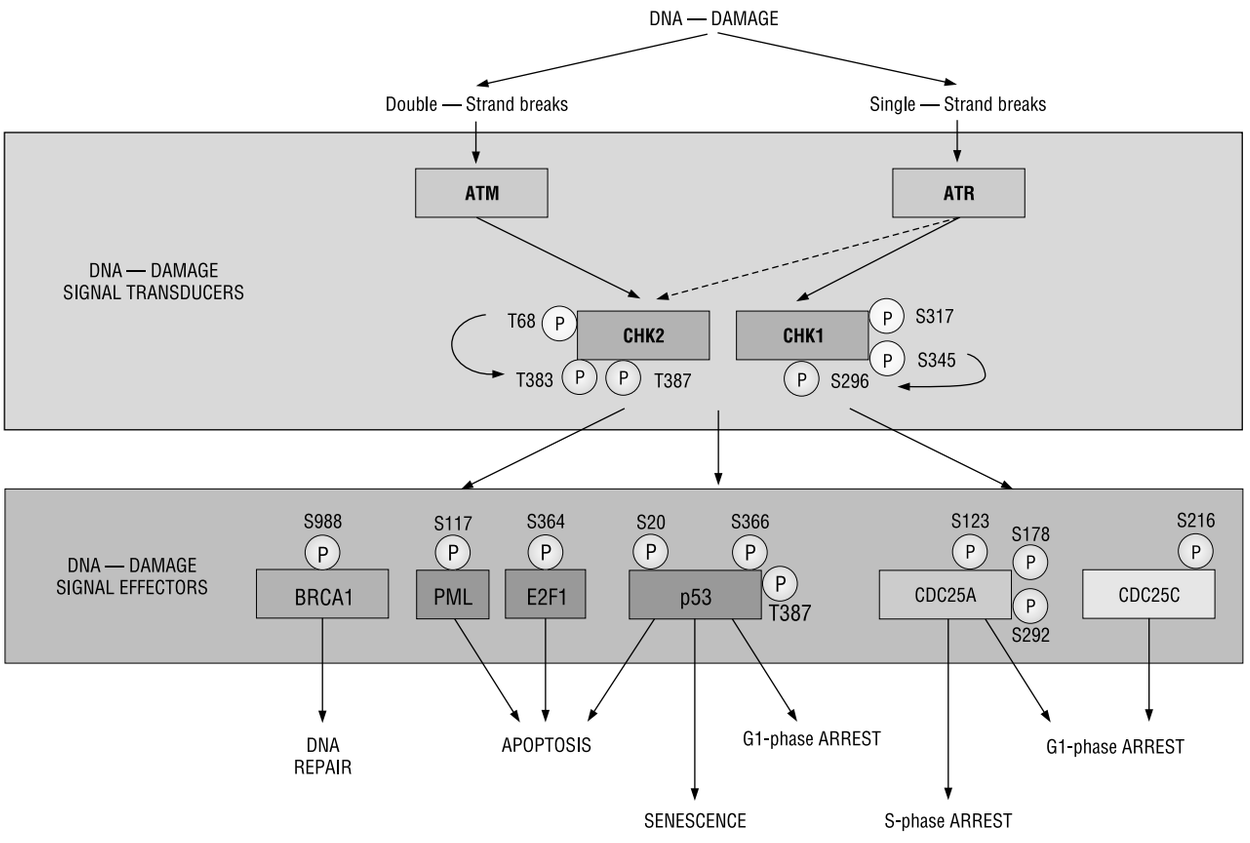

Figure 1. *Schematic overview of the DNA-damage response signalling pathway*
Rycina 1. *Schemat przedstawiający drogi odpowiedzi komórki na uszkodzenie DNA*

promote apoptosis through interaction with other cell substrates. It also influences the process of cell aging. Telomere damage activates CHEK2, which triggers further mechanisms, among others through p53 and p21, CKD inhibitor in undamaged cells. CHEK2 acts as an anti-cancer barrier because it induces cancer cell aging, suppressing their proliferation and, as a result, the process of oncogenesis [9].

Illustration 1

Constitutive mutations and polymorphisms in CHEK2 gene are associated with the risk of numerous cancers. Two main groups of CKEK2 gene mutations have been described:

— protein truncating mutation:
  - 1100delIC,
  - IVS2+1G > A,
  - Del 5395;

— missense mutations: the most frequent mutation is I157T, in which on the nucleotide level thymine is substituted with cytosine at position 433. This changes the reading frame and on the amino acid level isoleucine at position 157 is substituted with threonine. Missense mutation is located in a functional domain of CHEK2 gene and the protein which it produces is defective in recognition and phosphorylation of CDC25A, protein p53, and BRCA1 [10, 11].

These mutations increase the risk of occurrence of some cancers [1–3]. Cancer of the prostate and breast and papillary cancer of the thyroid are associated with both types of mutations, while cancer of the kidney, colon, and ovary occur only in the case of I157T mutation [3]. Carriers of kidney cancer present themselves histopathologically as clear cell carcinoma [3]. Cancers associated with the most common mutations are presented in Table I.

In the described case, detecting CHEK2 mutation (I157T) was incidental. So far in the literature, an association of this mutation with monoclonal gammapathy has not been described although there are reports of its association with leukaemia [12]. According to the recommendations presented below, the patient was screened for the carcinoma to which this mutation predisposes. Apart from the diagnosed papillary thyroid carcinoma, no other pathologies were found. Genetic screening of the family members was positive only in a daughter with long-standing Hashimoto's disease, who was also the mutation carrier. The conducted tests

Table I. *Typical cancers associated with the most frequent CHEK2 mutations (data taken from refs [4])*
Tabela I. *Nowotwory związane z nosicielstwem najczęstszych mutacji (CHEK2) (na podstawie [4])*

Organ	Truncating mutation (1100delC i IVS2+1G > A)		Missense mutation (I 157 T)	
	Increasing the risk of incidence	% participation between cancers of this organ	Increasing the risk of incidence	% participation between cancers of his organ
Breast	2.4 ×	2.5%	1.5 ×	7%
Prostate	2.3 ×	2.5% (5% familiar)	1.6 ×	8% (12% familiar)
Papillary thyroid carcinoma	5 ×	4%	2 ×	9%
Kidney	–	–	2 ×	10%
Colon	–	–	2 ×	10%
Ovary (G1)	–	–	2 ×	10%

did not find any other pathologies. Both patients will remain under permanent oncological observation.

In the case of carriers of I157T mutation, no age differences were found in developing the carcinoma in comparison with the cancer-free population [3]. Unlike these observations, the protein-truncating mutations demonstrated that the average age of developing cancer of the colon and thyroid was lower than in the case of patients with sporadic cancers [3]. In the case of breast cancer, the examined women with this carcinoma were carriers of BRCA1 and CHEK2 I157T. It seems that carrying both these mutations does not increase the risk of breast cancer in comparison with carrying only the BRCA1 mutation [13]. It was noticed that this mutation decreased the risk of nicotine-related cancers, including lung and nasopharynx [14].

The International Centre for Hereditary Cancers of Pomeranian Medical University recommends the following screening for the carriers of CHEK2 mutation I157T [4]:

— for women:
  - systematic breast self-control;
  - medical breast examination after 40 years of age, twice a year;
  - breast ultrasound after 40 years of age, yearly;
  - MRI of breast, or possibly mammography after 40 years of age, once a year alternately with breast ultrasound;
  - vaginal ultrasound of the reproductive organ after 25 years of age, yearly;

— for men:
  - palpation of prostate, PSA after 50 years of age, yearly;
  - prostate saturation biopsy to be considered after 60 years of age, only if, in the family history, relatives of first degree had prostate cancer;

— for both genders:
  - abdominal ultrasound after 40 years of age yearly, particularly the kidneys;
  - colonoscopy or colon contrast enema after 60 years of age, every 5 years or more often, should any intestinal disorders appear;
  - thyroid ultrasound after 20 years of age, yearly.

However, it should be stressed that until now there are no indications to investigate this germline mutation in patients with thyroid cancer, when no other cancers are diagnosed in the proband or in the family.

Conclusions

Missense mutation of CHEK2 (I157T) is related to an increased predisposition to some cancers, including a two-fold greater risk of papillary thyroid cancer. It occurs in 4.8% of the Polish population. When the family history for carcinoma is positive, genetic diagnostics of the family members is recommended. The presented family illustrates that haematological malignancies may also be observed in CHEK2 mutation carriers.

Referrences

1. Antoni L, Sodha N, Collins I. et al. CHK2 kinase: cancer susceptibility and cancer therapy — two sides of the same coin? Nature Reviews Cancer 2007; 7: 925–935.
2. Bartek J, Lukas J. Chk1 and CHK2 kinases in checkpoint control and cancer. Cancer Cell 2003; 3: 421–427.
3. Cybulski C, Górski B, Huzarski T et al. CHEK2 is a multiorgan cancer susceptibility gene. Am J Hum 2004; 75: 1131–1135.

4. Kurzawski G, Suchy J, Cybulski I et al. DNA Tests for the moderately increased risk of malignant tumors. In: Lubiński J (ed.). Genetic clinic of Carcinoma 2008. Print Group Sp. z o.o., Szczecin 2008: 52–53.
5. Lee JS, Collins K, Brown A et al. hCds 1 — mediated phosphorylation of BRCA1 regulates the DNA damage response. Nature 2000; 404: 201–204.
6. Zhang J, Willers H, Feng Z et al. CHK2 phosphorylation of BRCA1 regulates DNA double-strand break repair. Mol Cell Biol 2004; 24: 708–718.
7. Shieh SY, Ahn J, Tamai K et al. The human homologs of checkpoint kinases Chk1 and Cds 1 (Chk2) phosphorylate P53 at multiple DNA damage-inducible sites. Genes Dev. 2000; 14: 289–300.
8. Hirao A, Kong YY, Matsuoka S et al. DNA damage-induced activation of P53 by checkpoint kinase Chk2. Science 2000; 287: 1824–1827.
9. Di Micco R, Fumagalli M, Cicalese A et al. Oncogene-induced senescence is a DNA damage response triggered by DNA hyper-replication. Nature 2006; 444: 638–642.
10. Falck J, Lucas C, Protopopova M et al. Functional impact on concomitant versus alternative defects in the Chk2-P53 tumour suppressor pathway. Oncogene 2001; 20: 5503–5510.
11. Falck J, Mailand N, Syljuåsen RG et al. The ATM-Chk2-Cdc25A checkpoint pathways guard against radio-resistant DNA synthesis. Nature 2001; 410: 842–847.
12. Rudd M, Sellick G, Webb EL et al. Variants in the ATM-BRCA2-CHEK2 axis predispose to chronic lymphatic. Leukemia Blood 2006; 108: 638–644.
13. Cybulski C, Górski B, Huzarski T et al. Effect of CHEK2 missense variant I157T on the risk of breast cancer in carriers of other CHEK2 or BRCA1 mutations. J Med Genet 2009; 46: 132–135.
14. Brennan T, McKay J, Zaridze D et al . Uncommon CHEK2 mis-sense variant and reduced risk of tobacco-related cancers: case control study. Hum Mol Genet 2007; 16: 1794–1801.