”Cyclin D1 and CHEK2 polymorphic variants as low risk susceptibility alleles in DTC patients”

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Differentiated thyroid cancer (DTC) originates from thyroid follicular epithelial cells and belongs to a group of slowly progressing tumors with relatively good prognosis. However, optimal results in the treatment of these tumors via coordinated multimodal therapy are achieved mostly by early diagnosis. A serious problem in course of DTC are recurrences and metastasis. Conversion from well differentiated thyroid cancer to aggressive anaplastic carcinoma is possible, what underline importance of effective diagnosis and characteristics at the molecular level as well. A genetic background of DTC is not clear. There are known several mutations detected in the thyroid tumors cells, but genetic factors predisposing to promotion of carcinogenesis of thyroid gland are still unexplained.

CHEK2 gene (checkpoint kinase 2) is located in the position 22q12.1 and spanning 54,6 kb. It encodes the human ortholog of the yeast checkpoint kinases Cds1 and Rad53. In response to the damage of genetic material and inhibition of the replication process, protein is activated by phosphorylation. Mutations in *CHEK2* gene are evidenced to be a multi cancer predisposition factor. Protein product of this gene is a cell cycle checkpoint regulator, tumor suppressor and is a member of subfamily of serine/threonine protein kinases.

The *CCND1* gene (11q13) encodes the cyclin D1, a protein which belongs to the highly conserved cyclin family, that serve as regulators of CDK kinases. Cyclin D1 is a key regulatory protein which plays an important role in the transition from G1 to S phase of cell cycle during cell division. The cancer relevance of the cyclin D1 gene was apparent upon its identification in 1991. The cyclin D1 locus was initially identified based on its involvement in a chromosomal rearrangement of benign parathyroid tumors. The *CCND1* gene alterations which influence on the cell cycle progression, are observed frequently in a variety of tumors and may contribute to tumorigenesis.

The aim of the study was to examine two sequence variants in *CHEK2* p.R145W (c.433C>T, rs137853007 and p.I157T c.470T>C, rs17879961) and *CCND1 (*c.723G>A (rs9344; p.Pro241= and c.669C>T, rs3862792; p.Phe223=) genes in a group of Polish patients with differentiated thyroid cancer and control individuals from Polish population. We examined a cohort of 647 Polish patients diagnosed with differentiated thyroid carcinoma and Polish population included 799 subjects (615 females and 184 males).

As a genotyping technique we used pyrosequencing. In order to determine statistical significance of differences in genotypic and allelic frequency, observed among compared groups, we used GraphPad Prism 4 (chi-square distribution and Fisher exact test).

We did not observe noteworthy variability in p.R145W (c.433C>T, rs137853007), but in analysis of p.I157T sequence variant (c.470T>C, rs17879961) we demonstrated statistically significant differences in allele frequencies (p=0,005, OR=2,014, C.I.=[1,348-3,010]).

In a case of *CCND1* gene we observed statistically higher frequency of allele A in rs9344 locus in DTC patients (p=0,02498, OR=1,191, C.I.=[1,022-1,387]). We observed also a statistically significant difference between genotypes in subjected group. Genotype AA occurs significantly to be more frequent in patients with DTC (p=0,02023, OR=1,452, C.I.=[1,059-1,989]) than in control population group. We did not notice any statistically important differences in frequencies of genotypes or alleles in rs3862792 locus in subjected groups.

In conclusion the allele c.470C *CHEK2* gene and c.723A variant *CCND1* gene may be a risk alleles in the development of differentiated thyroid cancer in Polish population.