The Influence of Polymorphisms in Tumor Suppressor Genes in Thyroid Carcinomas

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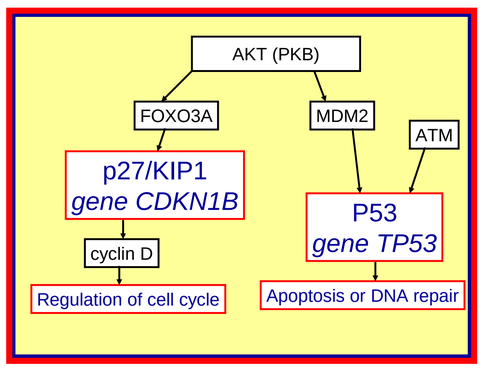
Introduction:

Thyroid carcinomas are the most often endocrine malignancy and their incidence is still growing. But the genetic predisposition to the development of thyroid cancer is still unknown. Beside mutations in the specific oncogenes, the genetic predisposition to the thyroid cancer could be influenced by risk variants in tumor suppressor genes encoding key proteins in regulation of cell cycle and cell surviving.

CDKN1B (12p13.1-p12)

- Encoding cyclin-dependent kinase inhibitor 1B (p27, Kip 1)
- Localized in the cell nucleus
- Controls cell proliferation, differentiation and division



TP53 (17p13.1)

- Encoding protein p53
- Localized in the cell nucleus
- Regulation of cell division and proliferation
- „The guardian of the genome“

Aim of the study:

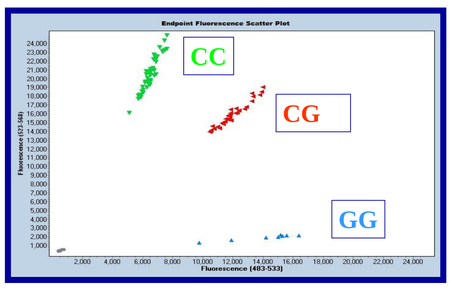
To determine the influence of polymorphisms Val109Gly (T/G) in the gene *CDKN1B* encoding protein p27/Kip1 and Arg72Pro (C/G) in the gene *TP53* encoding protein p53 on the development of the thyroid cancer.

Our cohorts:

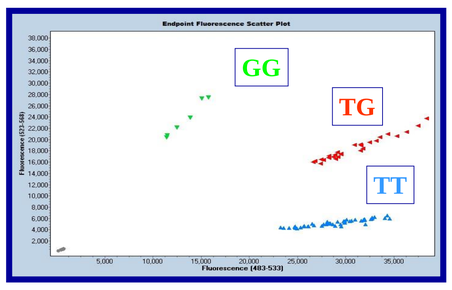
- 345 patients with sporadic medullary thyroid carcinoma (MTC)
- 269 patients with papillary thyroid carcinoma (PTC)
- 374 healthy controls

Methods:

- DNA isolation from peripheral leukocytes or from thyroid cancer tissues - QIAamp DNA Blood Kit or Trizol
- Detection of polymorphisms Val109Gly (T/G) in the gene *CDKN1B* and Arg72Pro (C/G) in the gene *TP53* - TaqMan specific assays; Real Time PCR (Light Cycler 480, Roche)
- Statistical evaluation - NCSS 2004 programme (Statistical Solutions, Saugus, MA, USA) and Chi-square test



analysis Arg72Pro (C/G) in *TP53*

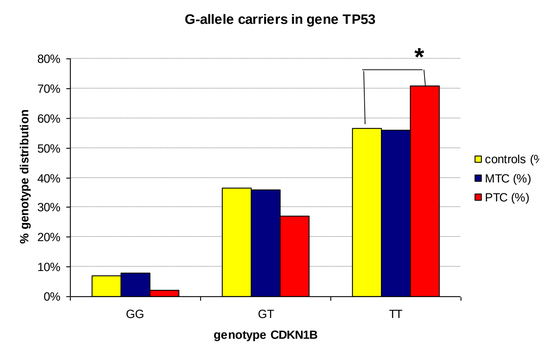


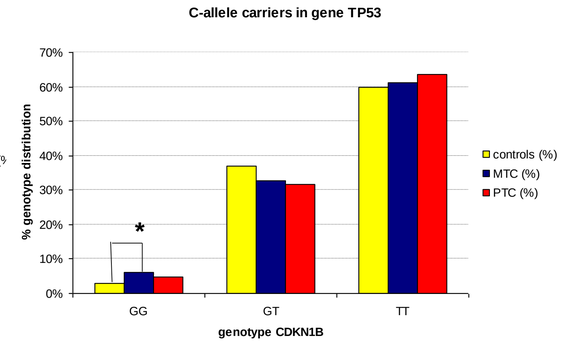
analysis Val109Gly (T/G) in *CDKN1B*

Results:

TP53	Controls	%	MTC	%	PTC	%
CC	206	54,8	187	54,2	145	53,7
CG	142	37,8	127	36,8	106	39,3
GG	28	7,5	31	9,0	19	7,1
C	554	73,7	501	72,6	396	73,3
G	198	26,3	189	27,4	144	26,7

CDKN1B	Controls	%	MTC	%	PTC	%
GG	15	4,0	23	6,7	11	4,0
GT	138	36,9	116	33,6	83	30,4
TT	221	59,1	206	59,7	179	65,6
G	168	22,5	162	23,5	105	19,2
T	580	77,5	528	76,5	441	80,8





G-allele carrier in the gene *TP53*								
	PTC	%	Controls	%	OR	CI 95%		P Yates
***CDKN1B* genotypic distribution**								
GG	3	2,1	14	7,1	0,28	0,08	0,99	0,065
GT	39	27,1	72	36,4	0,65	0,41	1,04	0,090
TT	102	70,8	112	56,6	**1,86**	**1,18**	**2,94**	**0,010**
***CDKN1B* allelic distribution**								
G	45	15,6	100	25,3	**0,55**	**0,37**	**0,81**	**0,003**
T	243	84,4	296	74,7	**1,82**	**1,23**	**2,70**	**0,003**

C-allele carriers in the gene *TP53*								
	MTC	%	Controls	%	OR	CI 95%		P Yates
***CDKN1B* genotypic distribution**								
GG	31	6,2	16	2,9	**2,20**	**1,19**	**4,08**	**0,016**
GT	164	32,7	204	37,1	0,83	0,64	1,06	0,157
TT	306	61,1	330	60,0	1,05	0,82	1,34	0,769
***CDKN1B* allelic distribution**								
G	226	22,6	236	21,5	1,07	0,87	1,31	0,578
T	776	77,4	864	78,5	0,94	0,76	1,15	0,578

Conclusion:

Although total distributions of alleles of each gene were not statistically different in patients compared to controls, the remarkable risk is in combination of specific alleles of these genes. G allele in *TP53* in combination with T allele in *CDKN1B* is more often in patients with PTC than in controls (84,4 % vs. 74,7 %, OR=1,82; CI95% (1,23-2,70); p=0,003) and specifically the TT genotype in *CDKN1B* is the most risk in comparison with controls (70,8 % vs. 56,6 %, OR=1,86; CI95% (1,18-2,94); p=0,01). In MTC patients, C allele in *TP53* with GG genotype in *CDKN1B* is more frequent compared to controls (6,2 % vs. 2,9 %, OR=2,2; CI95% (1,19-4,08); p=0,016). It seems that genetic variants of tumor suppressor genes and mainly their cumulative risk effect play a role in the development of PTC and MTC.

This work was supported by IGA MH CZ NT/13901-4 and MH CZ 00023761.

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