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**ASSOCIATION OF PAX3 AND TMTC2 GENE POLYMORPHISM ON THE FACE MORPHOLOGY CHANGE AFTER EXCISION OF SKIN TUMORS**

**POVEZANOST POLIMOFIZMA PAX3 I TMTC2 GENA NA PROMENU MORFOLOGIJE LICA NAKON EKSCIZIJE TUMORA KOŽE**

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ASSOCIATION OF PAX3 AND TMTC2 GENE POLYMORPHISM ON THE FACE MORPHOLOGY CHANGE AFTER EXCISION OF SKIN TUMORS

POVEZANOŠT POLIMORFIZMA PAX3 I TMTC2 GENA NA PROMENU MORFOLOGIJE LICA NAKON EKSCIZIJE TUMORA KOŽE

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Abstract

**Background/Aim.** The group of genes, known as PAX (Paired box), has a great role in organogenesis, as well as in maintaining the normal function of certain cells after the birth. In addition to these genes, the impact on the organogenesis, at the cellular level, has a transmembrane tetratricopeptid group of genes (TMTC). The term polymorphism in the human genome implies variations in the hereditary basis that occur in human populations, the presence of two or more different alleles of one genome in the population. The aim of the work is to determine whether there is an association of PAX3 and TMTC2 genes polymorphism with changes of face morphology after the skin tumor excision and direct suture closure. **Methods.** The study included 130 patients of both sexes, older than 50 years, with the medical indication for the elliptical surgical excision of skin tumor. DNA was isolated from 5ml of peripheral blood. Gene polymorphisms were analyzed with pre-designed SNP assays, by allelic discrimination method on REAL-TIME apparatus. The patients had a laser scanning preoperatively, 7 days and 90 days postoperatively, giving x, y and z coordinates of 5 cephalometric points on the face, for every patient, which determined the shape of the medial cheek region. The shape of the medial cheek region, as well as the coordinates of 5 cephalometric points, among genotypes was compared, preoperatively, 7 days and 90 days postoperatively, in both genes. **Results.** A statistically significant difference in the shape of the medial cheek region between wild-type and mutant of PAX3 gene was found preoperatively, while the statistically significant difference in the shape of the medial cheek region was not found between wild-type and heterozygote, nor between wild-type vs. heterozygote and mutant of PAX3 gene, nor among genotypes of TMTC2 gene. Post-operatively, 7 days and 90 days, there was no statistically significant difference in the shape of the examined region among genotypes in both genes. **Conclusion.** Polymorphisms of PAX3 and TMTC2 genes are not associated with the change in the morphology of the face after the skin tumor excision and direct suture closure of the defect.

Key words: polymorphism, PAX3 and TMTC2 gene, facial morphology

Apstrakt

**Uvod/Cilj.** Grupa gena, poznata pod nazivom PAX (eng. paired box), ima velikog udela u organogenezi, kao i u održavanju normalne funkcije izvesnih ćelija nakon rođenja. Pored ovih gena, utiču na organogenezu, na ćelijskom nivou, ima i transmembransko-tetratrikopeptidna grupa gena (TMTC). Pod pojmom polimorfizam u genomu čoveka podrazumevaju se varijacije u naslednoj osnovi koje se javljaju u humanim populacijama, prisutnost dva ili više različitih alela jednog gena u populaciji. Cilj rada je da se utvrdi da li postoji povezanost polimorfizma PAX3 i TMTC2 gena sa promenom morfologije lica nakon ekscizije tumora kože i postekscizione direktna suture. **Metode.** Istraživanjem je obuhvaćeno 130 ispitanika, oba pola, starijih od 50 godina, kod kojih je postavljena medicinska indikacija za hiruršku elipsastu eksciziju tumora kože lica. DNK je izolovana iz 5ml periferne krvi. Polimorfizmi gena su analizirani predizajniranim SNP esejima, metodom alelske diskriminatorije na REAL-TIME aparatu. Ispitanici su skenirani laser skenerom preoperativno, 7 dana i 90 dana postoperativno, čime su se za svakog ispitanika.
dobile x, y i z koordinate 5 kefalometrijskih tačaka na licu, koje su određivale oblik medijalne obrazne regije. Uporedjivan je oblik medijalne obrazne regije, kao i koordinate 5 kefalometrijskih tačaka, izmedju genotipova, preoperativno, 7 dana i 90 dana postoperativno, kod oba gena. **Rezultati.** Preoperativno je nadjena statistički visoko značajna razlika oblika medijalne obrazne regije izmedju wild type i mutanata PAX3 gena, dok statistički značajna razlika oblika ispitivane regije nije nadjena izmedju wild type i heterozigota, kao ni izmedju genotipova TMTC2 gena. Postoperativno, 7 dana i 90 dana, nije nadjena statistički značajna razlika oblika ispitivane regije izmedju genotipova, kod oba gena. **Zaključak.**

Polimorfizmi PAX3 i TMTC2 gena nisu povezani sa promenom morfologije lica nakon ekscizije tumora kože lica i zatvaranja defekta direktnom suturom.

**Ključne reči:** polimorfizam, PAX3 i TMTC2 gen, morfologija lica

**Introduction**

In recent years, efforts have been intensified to determine the influence of polymorphism of genes on the morphological characteristics of the face.

It has been demonstrated that a group of genes, known as PAX (Paired box), has a great role in organogenesis, as well as in maintaining the normal function of certain cells after the birth. There are four groups of PAX genes (1). In the first group are PAX 1 and 9, in the second group are PAX 2, 5 and 8, in the third group are PAX 3 and 7, while in the fourth group are PAX 4 and 6. During embryonic development, PAX 3 gene is active in the cells of the neural crest. These cells migrate from the spinal cord in certain regions in the embryo (2). The protein encoded by PAX 3 gene influences the activity of other genes, inducing cells to form neural crest limb muscles, the bones of the face and scalp, certain neural structures and melanocytes, which presence determines the color of hair, eyes, and skin. Melanocytes are also found in some regions of the brain and the inner ear. Therefore, the PAX 3 gene, associated with the development of the ear, eye and facial development, is highly expressed in melanoma, and also contributes to the survival of tumor cells (alveolar rhabdomyosarcoma, which is more common in adolescents). It is located on the second chromosome (2q36.1). Mutations in the gene lead to the Waardenburg syndrome. The disease is characterized by varying degrees of deafness, minor defects in the structures that originate from the neural crest and anomalies in pigmentation (3).

In addition to these genes, a transmembrane tetratricopeptid - group of genes (TMTC 1, 2, 3, 4) has the impact on the organogenesis, of which TMTC 2 gene encodes a protein 2, which is a transmembrane building element of the cell membrane, and endoplasmic reticulum. TMTC 2 gene is located on chromosome 12 (12q21.31) (4). At the molecular level, it has a role in binding of one molecule with one or more specific sites of other molecules (5). The specific role of TMTC 2 gene has not yet been established, although it is known that it has a role in cellular calcium homeostasis (6).

DNA polymorphisms are now widely studied as markers of possible genetic susceptibility for certain diseases. The Genome-Wide Association Studies (GWAS) explain the genetic basis of complex diseases by comparing the frequency of different genetic variants in the population in relation to healthy-population. One of the most common types of genetic
polymorphisms is the polymorphism of the single nucleotide sequence (SNP), replacing one of the four nucleotides in the DNA molecule. Substitutions may occur in the coding (exon) or non-coding (intron) portion of the gene, or in the promoter region. SNPs are commonly used in genetic studies of the association. Previous research has shown that SNPs can be associated with the development of various types of disease, response to pathogens, drugs and other agents. Besides, in some works, an association between SNP of PAX3 (rs7559271, G/A) and TMTC2 (rs10862567, T/A) and differences of face morphology (1) were found, but there were no studies about the association between PAX3 and TMTC2 SNP and postoperatively differences in face morphology, after skin tumor excision.

In accordance with the reconstructive ladder, in plastic and reconstructive surgery after facial skin tumor excision, we primarily use the direct closure, as this is the simplest method of covering defects (7).

However, in addition to general medical and surgical principles, it is necessary to take into account the aesthetics of the face, and the consequential symmetry after excision. If the symmetry is violated, direct suture does not apply, and we use skin graft or flap (8).

The aim of the study was to determine the association of polymorphisms of PAX3 (rs7559271, G/A) and TMTC2 (rs10862567, T/A) gene with changes of face morphology after skin tumor excision and direct suture closure of the defect.

Methods.

The study included 130 patients of both sexes, older than 50 years, with the medical indication for the surgical elliptical excision of facial region skin tumors.

Before the surgical elliptical excision, 5ml of peripheral blood of all the patients was taken by venipuncture. All the patients signed the consent to participate in research, by the decision of the Ethics Committee of Military Medical Academy Belgrade. Peripheral blood with anticoagulant was kept in a freezer at -20°C. Deoxyribonucleic acid (DNA) from peripheral blood was isolated by commercial kit PureLink® Genomic DNA Kit (Invitrogen, Thermo Fisher, USA), according to the manufacturer instructions.

Polymorphism of genes was determined with pre-designed SNP (single nucleotide polymorphism) assays (TaqMan ® Pre-designed SNP Genotyping Assay, Applied Biosystems, for PAX3 rs7559271, and TMTC2 rs10862567), by allelic discrimination method on REAL-TIME apparatus (ABI Prism 7500, USA).

Immediately preoperatively, in all patients, the elliptical excision of skin tumors lines around the margin of clinically unaffected skin 2mm width was marked and the elliptical excision, parallel to the lines of minimum tension, was done, after which patients were scanned preoperatively with laser scanner (Laserscanner, the Institute for Robotics and Process Control, University of Braunschweig, Germany, 2009). The patients were also scanned postoperatively, 7 and 90 days after surgery (9).
Five cephalometric points (nasion, endocanthal central point, pronazale, lower palpebral point, endocanthion), and their x, y and z coordinates, were determined from scans of the patients’ face, using extraction of coordinates by C++ software, and using the characteristics of cephalometric points: nasion is the most anterior point of the junction of the nasal and frontal bones in the midsagittal plane, endocanthal central point is in the middle between bilateral most deep points of endocanthus, pronasale is the most prominent point on tip of nose, lower palpebral point is the lowest point of lower eyelid, endocanthion is the most deep point of endocanthus. For five cephalometric points we got 15 coordinates (x1-5, y1-5, z1-5). Those coordinates determined the shape of the polygonal line, as a border of the space of operated region, in the region of the medial cheek of the face. Changes of the shape of the operated region were assessed by using Procrustes analysis. As the first, superimposition of landmark points was done by translation, rotation and scaling, after what we used Procrustes distance (Pd), given by Procrustes coordinates (x, y, z), as a squared root of sum of squared distances between corresponding landmarks of two shapes, which is a measure of shape difference between two groups of shapes. We compared Procrustes distances, as a measure of shape differences, among all the genotypes, and among all three scanning times (preoperatively, 7 and 90 days postoperatively), using ANOVA and Post Hoc Scheffe test. Besides, as we wanted to know which coordinate has influence on changing the shape of the operated region, we compared x, y and z coordinates of five cephalometric points among the groups of patients with different genotypes of PAX3 and TMTC2 genes, using MANOVA. Determination of Procrustes distances was done in software program MorphoJ, version 1.06d, 2014, while ANOVA, Post Hoc Scheffe test, and MANOVA, were done in SPSS 23, IBM, 2015 (10).

Results

Distribution of genotypes of PAX3 and TMTC2 gene was presented in Table 1. The most presented genotype was wild-type, in both of genes.

Table 1.

**Distribution of genotypes of PAX3 and TMTC2 gene in the examined group of patients**

<table>
<thead>
<tr>
<th>genotypes</th>
<th>PAX3</th>
<th>TMTC2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>wild type</td>
<td>72</td>
<td>55,4</td>
</tr>
<tr>
<td>heterozygote</td>
<td>34</td>
<td>26,1</td>
</tr>
<tr>
<td>mutant</td>
<td>24</td>
<td>18,5</td>
</tr>
<tr>
<td>total</td>
<td>130</td>
<td>100</td>
</tr>
</tbody>
</table>
The value of Procrustes distances means between the coordinates of each patient and average coordinates, in all of three genotypes of PAX3 gene (wild-type (G/G), heterozygote (G/A), and mutant (A/A)), preoperatively, 7 days after surgery and 90 days after surgery, was presented in Graph 1. We found the highest value of Procrustes distances in all of three genotypes seven days postoperatively, while 90 days postoperatively the value of Procrustes distances were lower than preoperatively. The preoperative median was lower than mean in all of the genotypes, while the median was higher than mean 7 and 90 days postoperatively, with the exception of mutants 90 days postoperatively.

Table 2.

<table>
<thead>
<tr>
<th>genotypes</th>
<th>days</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>7</td>
<td>90</td>
</tr>
<tr>
<td>p value of Procrustes distances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wt vs. het</td>
<td>0.419</td>
<td>0.847</td>
<td>0.248</td>
</tr>
<tr>
<td>wt vs. het + mut</td>
<td>0.738</td>
<td>0.924</td>
<td>0.597</td>
</tr>
<tr>
<td>wt vs. mut</td>
<td><strong>0.005</strong></td>
<td>0.868</td>
<td>0.128</td>
</tr>
</tbody>
</table>

*p values<0,01 are bolded, *Pd=Procrustes distance, *wt=wild type; het=heterozygote; mut=mutant

The statistical significance of Procrustes distances differences among the patients with different PAX3 genotypes in all of three scanning times was analyzed using ANOVA and Post Hoc Scheffe test and was presented in Table 2. We found the statistically high significant difference only between wild-type and mutant preoperatively, while 7 and 90 days postoperatively there was no statistically significant difference among the genotypes.
Results of MANOVA testing differences among the coordinates of PAX3 genotypes in all three scanning times (0, 7, 90 days) were presented in Table 3. We found the statistically high significant difference between wild-type and mutant in y2-4, z2 and z4, preoperatively, in z2 and z4 7 days postoperatively, and in y3, z2 and z4 90 days postoperatively, as well as in y2 and y4 between wild-type vs. heterozygote and mutant. The statistically significant difference was found between wild-type and mutant 7 days postoperatively in y3, as well as between wild type vs. heterozygote and mutant preoperatively and 90 days postoperatively, in y3, z2 and z4.
The value of Procrustes distances means between the coordinates of each patient and average coordinates, in all of three genotypes of TMTC2 gene (wild type (T/T), heterozygote (T/A), and mutant (A/A)), preoperatively, 7 days after surgery and 90 days after surgery, are presented in Graph 2. We found the highest value of Procrustes distances seven days postoperatively in all of three genotypes, while 90 days postoperatively the value of Procrustes distances were lower than preoperatively. Preoperatively, the median was lower than mean in all of the genotypes, while the median was higher than mean 7 and 90 days postoperatively.

The statistical significance of Procrustes distances differences between TMTC2 genotypes in all of three scanning times was analyzed using ANOVA and Post Hoc Scheffe test. There was no statistically significant difference among the genotypes of TMTC2 gene in all three scanning times (results not presented).

Using MANOVA, we tested the statistically significant difference among the coordinates of TMTC2 genotypes in all three scanning times (0, 7, 90 days). There was no statistically significant difference among the genotypes of TMTC2 gene in all three scanning times, for all the coordinates (results not presented).

Discussion

Previous studies have shown that polymorphisms of PAX3 and TMTC2 gene have a role in the determination of the morphology of the face (11). The genetic-phenotypic relationship of the PAX3 gene is characterized by gene expression in the craniofacial syndrome, as well as in the alveolar rhabdomyosarcoma 2, and in Waardenburg syndrome (type 1 and 3) (12).

In previous works (1, 12, 13), it was found that PAX3 gene has a role in the growth of the endocanthal region. This provokes the difference in landmark coordinates in this region. As
the shape difference is dependent on x, y and z coordinates of landmarks, it is expected that different genotypes could be associated with the difference in the shape of that region (1, 21, 22, 23). On the other hand, there were no works about the associations between PAX3 SNP and postoperatively x, y and z coordinates of cephalometric points.

In our study, we found that there was the statistically high significant difference in the shape of the examined region between patients with PAX3 wild-type and mutants, preoperatively, while there was no statistically significant difference in the shape between wild-type and heterozygotes as well as between wild-type vs. heterozygotes and mutants. That showed that PAX3 alleles were expressed differently in facial morphology in the examined region, which was correlated with the expression of the PAX3 gene in the Waardenburg syndrome (24, 25, 26).

PAX3 gene product is a DNA-binding protein that is expressed during early neurogenesis (13). Transfection experiments have shown that PAX3 and SOX10 have a direct binding effect for the proximal region of the MITF promoter, which contains sites for both factors (14, 15). The mutated SOX10 or PAX3 proteins cannot transact this promoter, directly indicating that the two genes directly affect the regulation of MITF expression (16, 17). Hybridization experiments in dominant mouse megacolon have confirmed that SOX10 dysfunction reduces MITF expression, as well as the development and survival of melanocytes (18). Authors have suggested that the interaction between the three genes that have been altered in Waardenburg syndrome can explain the auditory and pigment symptoms of the disease (19). The MITF and PAX3 gene mutations, encoding transcription factors, are responsible for Waardenburg syndrome 2A (20). Also, in previous works, it was found that PAX3 and TMTC2 SNP were associated with cephalometric points’ distances in the endocanthal region (1).

Analyzing x, y, and z coordinates of the cephalometric points, we found that there was the statistically significant difference between wild-type and mutants, preoperatively in y2-4, z2 and z4, on the basis of which could be concluded that the PAX3 gene had a role in defining the morphology of the medial canthus region, and in the nasion-endocanthion angle. Postoperatively, a statistically significant difference in y2 and y4 was not found, and it could be concluded that other factors affected the postoperative change of z2 and z4 and not PAX3 gene polymorphism. The above could be explained by the influence of surgical intervention on the change in the morphology of the medial canthus due to the concavity of the medial canthus.

The significant difference among the shapes of examined region postoperatively due to the genotypes of PAX3 gene was not found. As there was also no significant difference between wild-type and mutants, postoperatively, we could conclude that there was a role of PAX3 gene to the facial morphometric characteristics, but only preoperatively. As there was no significant correlation between preoperative and postoperative results in general, we could assume that there was no association between PAX3 gene polymorphism and postoperative facial morphometric characteristic.
Also, we did not find any difference in the shape of the examined region among TMTC2 genotypes preoperatively, neither postoperatively (27, 28). Besides, like in PAX3 gene, there was no correlation between preoperative and postoperative results, so we could suppose that there was no association between TMTC2 gene and facial morphology in the medial cheek region (29, 30).

Postoperative results are based on preoperative morphology, but also are dependent on the postsurgical healing process. Accordingly, we can assume that other factors affect the changes of three-dimensional coordinates of tested cephalometric points and not just the genetic influence of PAX3 gene.

Conclusion

Based on the obtained results, we can conclude that polymorphisms of PAX3 and TMTC2 gene are not associated with the change in the morphology of the face after the skin tumor excision and direct suture closure of the defect, but other factors have a role in changes of postoperative three-dimensional coordinates of cephalometric points.

References


SUPPLEMENT

Table 4.

<table>
<thead>
<tr>
<th>genotypes</th>
<th>days</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>7</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p value of Procrustes distances</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>wt vs. het</td>
<td>0.976</td>
<td>0.992</td>
<td>0.724</td>
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<tr>
<td>wt vs. het + mut</td>
<td>1.000</td>
<td>0.908</td>
<td>0.983</td>
<td></td>
</tr>
<tr>
<td>wt vs. mut</td>
<td>0.719</td>
<td>0.535</td>
<td>0.819</td>
<td></td>
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</table>

*p values<0.01 are bolded, *Pd=Procrustes distance, *wt=wild type; het=heterozygote; mut=mutant

Table 5.
### P value of difference of x, y and z coordinates among the patients with different TMTC2 genotypes (preoperatively (0), postoperatively 7 and 90 days)

<table>
<thead>
<tr>
<th></th>
<th>wt vs. het</th>
<th>wt vs. het + mut</th>
<th>wt vs. mut</th>
</tr>
</thead>
<tbody>
<tr>
<td>days</td>
<td>0 7 90</td>
<td>0 7 90</td>
<td>0 7 90</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x1</td>
<td>0.934 0.934 0.934</td>
<td>0.972 0.972</td>
<td>0.972 0.846 0.846</td>
</tr>
<tr>
<td>x2</td>
<td>0.814 0.977 0.842</td>
<td>0.894 0.827</td>
<td>0.679 0.998 0.849 0.837</td>
</tr>
<tr>
<td>x3</td>
<td>0.861 0.861 0.908</td>
<td>0.988 0.988</td>
<td>0.988 0.825 0.825 0.866</td>
</tr>
<tr>
<td>x4</td>
<td>0.934 0.934 0.934</td>
<td>0.972 0.972</td>
<td>0.972 0.846 0.846 0.846</td>
</tr>
<tr>
<td>x5</td>
<td>0.934 0.934 0.934</td>
<td>0.972 0.972</td>
<td>0.972 0.846 0.846 0.846</td>
</tr>
<tr>
<td>y1</td>
<td>0.934 0.934 0.934</td>
<td>0.972 0.972</td>
<td>0.972 0.846 0.846 0.846</td>
</tr>
<tr>
<td>y2</td>
<td>0.934 0.909 0.986</td>
<td>0.972 0.968</td>
<td>0.705 0.846 0.808 0.523</td>
</tr>
<tr>
<td>y3</td>
<td>0.722 0.954 0.722</td>
<td>0.652 0.765</td>
<td>0.652 0.892 0.815 0.892</td>
</tr>
<tr>
<td>y4</td>
<td>0.934 0.932 0.991</td>
<td>0.972 0.956</td>
<td>0.694 0.846 0.805 0.525</td>
</tr>
<tr>
<td>y5</td>
<td>0.934 0.934 0.934</td>
<td>0.972 0.972</td>
<td>0.972 0.846 0.846 0.846</td>
</tr>
<tr>
<td>z1</td>
<td>0.687 0.954 0.954</td>
<td>0.935 1.000</td>
<td>1.000 0.970 0.976 0.976</td>
</tr>
<tr>
<td>z2</td>
<td>0.722 0.779 0.722</td>
<td>0.652 0.541</td>
<td>0.652 0.892 0.739 0.892</td>
</tr>
<tr>
<td>z3</td>
<td>0.942 0.986 0.986</td>
<td>0.981 0.974</td>
<td>0.974 0.999 0.920 0.920</td>
</tr>
<tr>
<td>z4</td>
<td>0.722 0.779 0.722</td>
<td>0.652 0.541</td>
<td>0.652 0.892 0.739 0.892</td>
</tr>
<tr>
<td>z5</td>
<td>0.934 0.934 0.934</td>
<td>0.972 0.972</td>
<td>0.972 0.846 0.846 0.846</td>
</tr>
</tbody>
</table>

*wt=wild type; het=heterozygote; mut=mutant, *x1-5, y1-5, z1-5=coordinates of 5 cephalometric points

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