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Topology of the associative cytokine gene network in primary open-angle glaucoma

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INTRODUCTION

Primary open-angle glaucoma (POAG) is one of the leading causes of global irreversible blindness. Therefore, it remains a serious medical and social problem throughout the world [1]. There is an assumption that the predisposition to the development of glaucoma is due to polymorphism of the regulatory regions of coding genes that determine the individual level of production of cytokines, chemokines, and growth factors [2, 3]. The aim of our study was to conduct a comprehensive bioinformatics analysis of polymorphic regions of the cytokine network genes to identify the relationship between the features of the topology of this network with the development of POAG.

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2. Zhang Y.H., Xing Y.Q., Chen Z., Ma X.C., Lu Q. Association between interleukin-10 genetic polymorphisms and risk of primary open angle glaucoma in a Chinese Han population: a case-control study. Intl. J. of Ophthalmol. 2019;12(10):1605–1611. doi: 10.18240/ijo.2019.10.13

3. Shevchenko A.V., Prokof`ev V.F., Konenkov V.I., Chernykh V.V., Ermakova O.V., Trunov A.N. Analysis of IL1B (rs1143627), IL4 (rs2243250), IL6 (rs1800795), IL8 (rs4073), IL10 (rs1800896, rs1800872), IL17A (rs227593) cytokines genes polymorphism and its complex genotypes among Caucasian patients of Western Siberia with primary open-angle glaucoma. Immunologiya. 2021;42(3):211-221. doi: 10.33029/0206-4952-2021-42-3-211-221. (in Russian)

PATIENTS AND METHODS

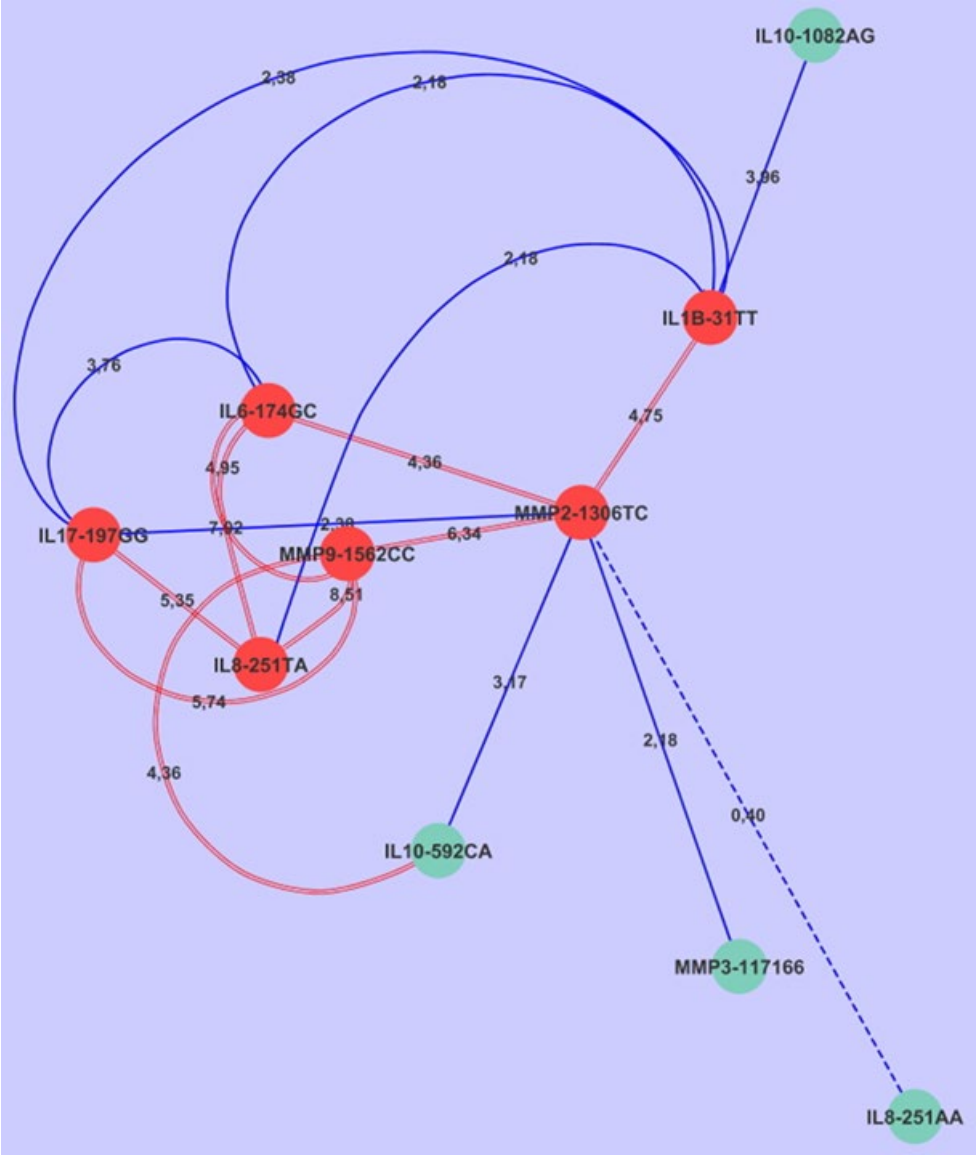
A genetic study was performed on 199 subjects, including 99 patients with POAG and 100 patients without glaucoma of similar gender and age as a comparison control group.

Polymorphisms of the regulatory regions of 10 cytokine genes (*IL1B -31 C/T, IL4 -590 C/T, IL6 -174 C/G, IL8 -251 T/A, IL10 -592 C/A, IL10-1082 A/G, IL17A -197 G/A, MMP2-1306 C/T, MMP3-1171 5A/6A, MMP9-1562 C/T*) were examined.

Statistical processing was performed using specialized software packages StatSoft Statistica 10.0, IBM SPSS Statistics 23 (USA) and package of original programs for bulk processing of bioinformation, including multicomponent genetic analysis, based on combinatorics methods in probability theory. The critical significance level for statistical hypothesis testing was assumed to be 0,05. Visualization of pairwise gene-gene interactions in groups with the presence and absence of UF in the form of an interactome biological network was performed in the program Cytoscape V. 3.7.2 [4]. Interpretation of visualization results was performed on the basis of general global and local topological properties of biological networks.

4. P. Shannon, A. Markiel, O. Ozier, N. S. Baliga, J. T. Wang, D. Ramage, N. Amin, B. Schwikowski, and T. Ideker, “Cytoscape: a software environment for integrated models of biomolecular interaction networks,” Genome Res., 2003, vol. 13(11), pp. 2498–2504.

A FRAGMENT OF THE GENE NETWORK OF CYTOKINES IN PRIMARY OPEN-ANGLE GLAUCOMA



Main intergenic interactions

Polymorphism combinations		%
IL8-251:MMP9-1562	TA-CC	8.51
IL6-174:MMP9-1562	GC-CC	7.92
MMP2-1306:MMP9-1562	TC-CC	6.34
IL17-197:MMP9-1562	GG-CC	5.74
IL8-251:IL17-197	TA-GG	5.35
IL6-174:IL8-251	GC-TA	4.95
IL1B-31:MMP2-1306	TT-TC	4.75
IL10-592:MMP9-1562	CA-CC	4.36
IL6-174:MMP2-1306	GC-TC	4.36
IL10-1082:IL17-197	AG-GG	3.96
IL1B-31:IL10-1082	TT-AG	3.96
IL8-251:IL10-1082	TA-AG	3.96
IL6-174:IL17-197	GC-GG	3.76
IL1B-31:MMP9-1562	TT-CC	3.56
IL4-590:IL17-197	CC-GG	3.56
IL4-590:IL8-251	CC-TA	3.56
IL8-251:MMP2-1306	TA-TC	3.56
IL10-592:MMP2-1306	CA-TC	3.17
IL1B-31:IL4-590	TT-CC	2.97
IL17-197:MMP2-1306	GG-TC	2.38
IL1B-31:IL17-197	TT-GG	2.38
IL1B-31:IL6-174	TT-GC	2.18
IL1B-31:IL8-251	TT-TA	2.18
MMP2-1306:MMP3-1171	TC-66	2.18
IL8-251:MMP2-1306	AA-TC	0.40

RESULTS

Analysis of the topology of the associative gene network of cytokines allowed us to identify the main genes and main intergenic interactions that make the greatest contribution to the development of primary open-angle glaucoma.

In our opinion, six polymorphisms (MMP2-1306CT, IL17-197GG, IL1B-31TT, IL8-251TA, MMP9-1562CC and IL6-174GC) can act as the main genes, which account for 80% of all involved genes.

These genes form the main nodes ("hubs") in the gene network, since they have the largest number of interactions with other genes.

These polymorphisms form the main intergenic interactions, which account for 50% of all interactions in the gene network.

= CONCLUTION =

The construction of gene networks of transcriptional regulation and their topological analysis makes it possible to build and study the structural and functional organization of gene-gene interactions in relation to the study of the pathogenesis of primary open-angle glaucoma for the subsequent development of approaches to personalized prevention and therapy.