DOI: https://doi.org/10.2298/SARH200306026Z
UDC: 616.28-004:575

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Genetic basis of otosclerosis

Branka Zukić[1], Marina Anđelković[1], Vladimir Gašić[1], Jasmina Grubin[2], Sonja Pavlović[1], Dragoslava Đerić[3]

[1]University of Belgrade, Institute of Molecular Genetics and Genetic Engineering, Laboratory for Molecular Biomedicine, Belgrade, Serbia;
[2]Ministry of Education, Science and Technological Development of the Republic of Serbia, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Clinical Center of Serbia, Clinic for Otorhinolaryngology, Belgrade, Serbia

SUMMARY
Introduction Otosclerosis is a disorder of the bone labyrinth and stapes resulting in conductive hearing loss. The genetic basis of otosclerosis still remains unknown.
We aimed at reporting a comprehensive review of up-to-date knowledge on genetic basis of otosclerosis.
Methods Narrative literature review was undertaken to summarize the data about genetics of otosclerosis.
Results Genetics of otosclerosis has not been studied extensively and the literature on this topic is scarce. However, knowledge of genetic basis of otosclerosis is recently increasing. We have presented an overview of the knowledge of association of genetic markers with otosclerosis, gained from linkage analyses, candidate-gene studies, and modern high-throughput genomic studies.
Conclusion Due to its complex pathophysiology, otosclerosis is not a disease whose genetic base will be easily understood. Multiple omics analysis and bioinformatics will lead to elucidation of genetic basis of otosclerosis.
Keywords: otosclerosis; genetics; linkage analyses; candidate-gene studies; high-throughput genomic studies

INTRODUCTION

Otosclerosis is a disorder of the bone labyrinth and stapes known to affect only humans. Unlike all other bones in the body, the human otic capsula undergoes very little remodeling following development. Otosclerosis is a process of pathologic remodeling within a bone that is normally refractory to remodeling. The foci of otosclerotic bone are silent clinically, until the movement of stapes is impaired by invasion of the stapediovestibular articulation. Otosclerosis is a disease of inflammatory character where there is abnormal bone production in the otic capsule and around the base of the stapes. It is one of the most common causes of conductive hearing loss [1]. Its etiology is not fully understood. Some of the proposed causes are genetics, viral diseases and autoimmune reactions [2]. Among viral agents, measles are prominent.

The primary symptom produced by the otosclerotic lesions is conductive hearing loss, usually bilateral, with the onset between the age 20 and 30 years. The magnitude of the hearing loss is directly related to the degree of fixation of the stapes' footplate [3]. The patients with otosclerosis may also exhibit vestibular disturbance.

Some studies have demonstrated the effect of vitamin D deficiency and of some heavy metals, especially calcium, on the progression of otosclerosis [4]. Therefore, it is speculated that dietary regime for patients with otosclerosis could be based on fruits and vegetables containing specific nutrients [5].

Surgical treatment, such as stapedectomy, is used in the treatment of otosclerosis, but the disease can also be managed through hearing amplification with hearing aids [6].

The genetic cause underlying otosclerosis development still remains unknown. The fact that otosclerosis affects multiple members in large families indicates its strong genetic foundation. Also, sporadic forms of otosclerosis have been identified. Linkage analysis have been used to identify genetic loci/genes responsible for otosclerosis in families segregating an autosomal dominant form of the disease [7]. So far, eight genetic loci have been mapped, designated *OTSC1-5, OTSC7-8* and *OTSC10* loci [8, 9]. Although a genetic cause is evident in otosclerosis, none of the genes involved in otosclerosis development have been proven in these loci. Several genetic association studies have been conducted to determine genetic background of the sporadic forms of otosclerosis. Quite a few genes and molecular pathways have been implicated in otosclerosis development, playing roles in bone metabolism, immune system, inflammation, and endocrine system [8, 10, 11, 12]. Candidate gene studies were directed by considering physiologic processes that could be important for otosclerosis development. For that purpose, genes and proteins involved in bone remodeling were among the first to be analyzed [12–15]. Also, the "building

Received • Примљено: March 6, 2020
Revised • Ревизија: April 29, 2020
Accepted • Прихваћено: April 30, 2020
Online first: May 7, 2020

Correspondence to:
Sonja PAVLOVIĆ
Laboratory for Molecular Biomedicine
Institute of Molecular Genetics and Genetic Engineering
University of Belgrade
Vojvode Stepe 444a
11000 Belgrade, Serbia
sonya@sezampro.rs

Table 1. Candidate genes associated with otosclerosis

Gene	Full name of the gene	Protein function	Type of the study	Reference
COL1A1	Type I collagen A1	strengthens and supports many tissues in the body, including cartilage, bone, tendon, skin, and the white part of the eye (the sclera)	association study	[16]
			case control studies	[17, 18, 31, 32, 33]
COL1A2	Type I collagen A2	encodes the pro-alpha2 chain of type I collagen whose triple helix comprises two alpha1 chains and one alpha2 chain	case control study	[32]
COL2A1	Type II collagen A1	encodes the alpha-1 chain of type II collagen, a fibrillar collagen found in cartilage and the vitreous humor of the eye.	animal studies, case reports	[34, 35]
ACE	Angiotensin converting enzyme	central component of the renin–angiotensin system (RAS), which controls blood pressure by regulating the volume of fluids in the body. It converts the hormone angiotensin I to the active vasoconstrictor angiotensin II	case control studies	[36, 37]
AGT	Angiotensinogen	component of the renin-angiotensin system (RAS), a hormone system that regulates blood pressure and fluid balance	case control studies	[30, 36]
ATII	Angiotensin-II	hormone that may act on the central nervous system to regulate renal sympathetic nerve activity, renal function and blood pressure	case control study	[38]
ATIIR	Angiotensin-II receptor	receptor for angiotensin-II	case control study	[38]
RELN	Reelin	extracellular matrix protein	genome-wide association studies	[41]
			case control study	[13, 15, 29, 42, 43]
TGFB1	Transforming growing factor beta 1	multifunctional cytokine family	case control studies	[12–15, 29]
BMP2	Bone morphogenetic protein 2	multi-functional growth factors that belong to the transforming growth factor beta	case control studies	[12–15]
BMP4	Bone morphogenetic protein 4	multi-functional growth factors that belong to the transforming growth factor beta	case control study	[12–15]
SERPINF1	Serpin peptidase inhibitor, clade F	pigment epithelium-derived factor – potent inhibitor of angiogenesis	family study - whole exome sequencing	[44]
CD46	Cluster of differentiation cell surface antigen 34	measles virus receptor, transmembrane phosphoglycoprotein	case control study	[40]
HLA-B40	Human leukocyte antigen	human leukocyte antigen (HLA) proteins complex	case control study	[39]

blocks" of the skeletal system have been legitimate candidates for investigation [16, 17, 18].

We aimed at reporting a comprehensive review of up-to-date knowledge on the genetic basis of otosclerosis.

SEARCH STRATEGY

We used an approach characteristic for a narrative review, consisting of critical analysis of the literature published in electronic or paper-based journal articles. We searched the PubMed database from 1980 to December 2018 using the terms "otosclerosis" AND "gene" OR "genetic" OR "familial" [19]. Studies were identified from the titles and abstracts by the primary reviewers (BZ, JG) and the secondary reviewer (SP). The ethical norms of the Declaration of Helsinki were followed.

GENETIC BASIS OF OTOSCLEROSIS: AN OVERVIEW

Here we present an overview of the knowledge of association of genetic markers with otosclerosis, gained from the association studies of genetic markers and otosclerosis using diverse methodology, starting from linkage analyses, through candidate-gene studies, to modern high-throughput genomic studies, such as genome-wide association studies (GWAS), microarray, and next generation sequencing (NGS).

LINKAGE ANALYSES

Linkage analyses have contributed to the identification of genetic loci associated with otosclerosis. Eight genetic loci have been mapped, designated *OTSC1-5*, *OTSC7-8*, and *OTSC10* loci. *OTSC1* locus was mapped on chromosome 15q25-q26 and contains 33 genes. It was identified in large Indian and Tunisian families [20, 21]. *OTSC2* locus with 152 genes was located on chromosome 7q34-36 and found in Belgian and British families [22]. *OTSC3* locus was mapped to 6p21.3-22.3 and identified in Cypriot and Tunisian families [23]. This locus contains 488 genes and maps to the major histocompatibility complex (MHC) locus. One study revealed that the MHC locus have been associated with otosclerosis in Greek patients with otosclerosis [24].

OTSC4 locus comprising 74 genes was located on chromosome 16q21-23.2 and described in an Israeli family [25]. *OTSC5* locus with 59 genes was defined in a Dutch family and located on chromosome 3q22-24 [26]. *OTSC7* locus containing 66 genes was mapped to chromosome 6q13-16.1 and identified in a Greek family [27]. *OTSC8* locus with 24 known and 121 predicted genes was mapped in a Tunisian family to chromosome 9p13.1-9q21.11 [28]. *OTSC10* locus was identified in a Dutch family on 1q41–44 chromosome and it comprised 306 genes/predicted genes [9]. Loci *OTSC6* and *OTSC9* have been reserved by the Human Genome Organization Gene Nomenclature Committee but are still not published. Although a genetic cause is evident in otosclerosis, none of the genes involved in otosclerosis development have been proven in these loci.

CANDIDATE-GENE STUDIES

Additionally, several genes have been shown to be disease-causing/disease-related for otosclerosis. Genes influencing dysregulation of bone remodeling within the otic capsule were investigated as otosclerosis has been identified as the primary disorder of bone remodeling. Bone morphogenetic proteins (BMPs) and TGF-β1, members of the TGF-β superfamily, are critical regulators of bone turnover. These proteins work as specific growth factors and also as inflammatory cytokines. Out of 20 different BMPs identified so far, only BMPs 2–7 have a central role in the embryonic endochondral bone development and later in new bone formation and repair [13]. Elevated expression levels of BMPs contribute to the increased bone turnover in active phases of otosclerosis. A significant association between clinical otosclerosis and variants in *BMP2* and *BMP4* genes was demonstrated. However, it is concluded that rare variants in *BMP2* and *BMP4* are not a major genetic component in the otosclerosis, at least in the German otosclerosis population [14]. Nonfunctional variants influence reduced downstream *BMP* signaling, namely phosphorylation of Smad1/5/8 [14]. As for the other gene involved in the regulation of bone turnover, *TGF-β1*, a significant association between variants in *TGF-β1* and clinically and histologically confirmed otosclerosis in Hungarian and in British populations was found [15, 29].

Type I collagen *COL1A1* gene was already shown to be involved in the development of osteogenesis imperfecta, a disease similar to otosclerosis by its major characteristics, namely conductive hearing loss [30]. An American study demonstrated a significant association of otosclerosis and *COL1A1* [16]. The same group further revealed a significant association between clinical otosclerosis and the Sp1 binding site variant in the first intron of *COL1A1* [17]. A replication study on German patients with otosclerosis identified haplotypes including the Sp1 binding site variants associated with otosclerosis [18]. A significant association between otosclerosis and *COL1A1* were additionally confirmed in Egyptian, Turkish, and Tunisian studies [31]. Despite finding that in Spanish samples of 100 cases and 100 matched controls the previous findings were not replicated [32], results of a comprehensive meta-analysis are supporting the fact that *COL1A1* and otosclerosis have been strongly associated [33].

Variations in *COL1A2* gene could indirectly influence *COL1A1,* thus possibly impacting otosclerosis as well. A German study showed that some of the *COL1A1* otosclerosis-associated variants alter binding of transcription factors that regulate transcription of *COL1A2* [18]. They have confirmed that targeted deletion of *COL1A2* in the mouse model leads to a mild conductive hearing loss. However, a Spanish group found no evidence in favor of *COL1A2* genes association with otosclerosis [32]. Type II collagen, the main collagen of cartilage, is encoded by the *COL2A1* gene. Autoreactivity to COL2A1 was proposed as a cause of otosclerosis [34]; nevertheless, this finding has been revisited [35].

Association with genes in the renin-angiotensin-aldosterone system and otosclerosis was also demonstrated [36]. Variants in angiotensinogen gene (*AGT*) and angiotensinogen converting enzyme gene (*ACE*) in a French-Caucasian cohort were related to higher plasma concentrations of ACE and also associated with a higher risk of otosclerosis development. A replication study done in a larger Belgian-Dutch population was unable to confirm these findings [37]. Also, four members of the activation pathway of AGT cascade were not expressed at protein level in otosclerotic stapes footplates [38]. However, it is possible that other variants in renin-angiotensin-aldosterone system could be associated with otosclerosis.

Class I MHC has been described in otosclerosis when *OTSC3* was mapped and the frequency of HLA-B40 was significantly lower in patients with otosclerosis than in healthy blood donors [28, 39].

Additionally, an environmental factor, namely persistent measles infection, was implicated in the development of otosclerosis [2]. A novel splice variant in the *CD46* receptor gene was detected and a potential association between measles virus infection and otosclerosis was demonstrated [40].

HIGH-THROUGHPUT GENOMIC STUDIES

Genomic studies performed using high-throughput methodology are not numerous, but their contribution to the elucidation of the genetic basis of otosclerosis is significant. One of these studies represents the first successful genome-wide association study for a hearing impairment [41].

A genome-wide association study recognized a significant association of the *RELN* gene, coding for an extracellular matrix protein important in brain development and synaptic plasticity, and the pathogenesis of otosclerosis [41]. This association was observed in various European and non-European populations [29, 42, 43]. Nevertheless, variants in the *RELN* gene might be associated with a specific otosclerosis-like phenotype, clinically not distinguishable from otosclerosis [38]. The *RELN* gene is not actively expressed in adult stapes footplates and further studies are needed to determine the role of *RELN* in the pathophysiology of otosclerosis [13].

A whole-exome sequencing study in four families with inherited otosclerosis identified several rare heterozygous *SERPINF1* (serpin peptidase inhibitor, clade F) variants suggesting that it may be a common pathogenic pathway in the otosclerosis development [44]. *SERPINF1* gene encodes PEDF (pigment epithelium-derived factor), which is shown to be involved in the regulation of bone density and inhibition of angiogenesis.

The review of the literature that covers candidate genes associated with otosclerosis is presented in Table 1.

CONCLUSION

Otosclerosis is a complex genetic disorder, without a clearly defined genetic basis. Genetics of otosclerosis has not been studied extensively and the literature on this topic is scarce. High-throughput methodology, such as NGS, has transformed genetic and biomedical research, enabling genetic profiling of each patient. Nowadays, it is widely used for diagnostics, monitoring, and administering appropriate molecular-targeted and gene therapy for many diseases. As for research, NGS has become a powerful tool in GWAS. It contributes to the discovery of new disease-causing and disease-related genetic markers of complex rare diseases, which could be implemented in clinical practice [45]. Using NGS in families affected by otosclerosis, analyzing disease-affected and disease-nonaffected family members, sharing the same genetic background, can add to understanding the molecular basis of the disease [46].

However, due to its complex pathophysiology, otosclerosis is not a disease whose genetic base will be easily understood. High-throughput genotyping will provide a vast amount of data, but more effective data analysis tools are missing [47, 48]. Databases that contain genomic variant data, collected using the microattribution approach principle, could assist in elucidating the genetic basis of complex rare diseases [49, 50]. Unquestionably, bioinformatics is a bottleneck of research in finding reliable genetic associations with otosclerosis. Also, gene–gene and gene–environment interactions should be considered. Multiple omics analysis, including epigenomics, transcriptomics, proteomics and radiomics, together with powerful bioinformatics will eventually lead to implementation of the knowledge on genetic basis of otosclerosis in clinical practice.

ACKNOWLEDGMENT

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, EB: 451-03-68/2020-14/ 200042 and COST Action BM1306.

Conflict of interest: None declared.

REFERENCES

1. Donaldson J, Snyder J. Otosclerosis. In: Cummings C, Fredrickson J, Harker L, Krause C, Schuller D, eds. Otolaryngology-Head and Neck Surgery. St. Louis, MO: Mosby Yearbook Co; 2007. p. 2997–3016.
2. Karosi T, Szekanecz Z, Sziklai I. Otosclerosis: an autoimmune disease? Autoimmun Rev. 2009;9(2):95–101.
3. Djeric D. Stapes pathology in otosclerosis: scanning electron microscopic examination. Adv Otorhinolaryngol. 2007;65:59–60.
4. Wiatr A, Składzień, J, Świeży K, Wiatr MA. Biochemical Analysis of the Stapes. Med Sci Monit. 2019;25:2679–86.
5. Grubin J, Tomović G, Stevanović B, Jovanić PB. Heavy metals phytoextraction in selected plants. Fresenius Environmental Bulletin. 2012;21(9):261.
6. Gillard DM, Harris JP. Cost-effectiveness of Stapedectomy vs Hearing Aids in the Treatment of Otosclerosis. JAMA Otolaryngol Head Neck Surg. 2020;146(1):42–8.
7. Moumoulidis I, Axon P, Baguley D, Reid E. A review on the genetics of otosclerosis. Clin Otolaryngol. 2007;32(4):239–47.
8. Ealy M, Smith RJ. The genetics of otosclerosis. Hear Res. 2010;266(1–2):70–4.
9. Schrauwen I, Weegerink NJ, Fransen E, Claes C, Pennings RJ, Cremers CW, et al. A new locus for otosclerosis, OTSC10, maps to chromosome 1q41-44. Clin Genet. 2011;79(5):495–7.
10. Ealy M, Chen W, Ryu GY, Yoon JG, Welling DB, Hansen M, et al. Gene expression analysis of human otosclerotic stapedial footplates. Hear Res. 2008;240(1–2):80–6.
11. Bittermann AJ, Wegner I, Noordman BJ, Vincent R, van der Heijden GJ, Grolman W. An introduction of genetics in otosclerosis: a systematic review. Otolaryngol Head Neck Surg. 2014;150(1):34–9.
12. Schrauwen I, Thys M, Vanderstraeten K, Fransen E, Dieltjens N, Huyghe JR, et al. Association of bone morphogenetic proteins with otosclerosis. J Bone Miner Res. 2008;23(4):507–16.
13. Csomor P, Liktor B, Liktor B, Szekanecz Z, Sziklai I, Karosi T. Expression of bone morphogenetic protein 2, 4, 5, and 7 correlates with histological activity of otosclerotic foci. Acta Otolaryngol. 2012;132(6):624–31.
14. Ealy M, Meyer NC, Corchado JC, Schrauwen I, Bress A, Pfister M, et al. Rare variants in BMP2 and BMP4 found in otosclerosis patients reduce Smad signaling. Otol Neurotol. 2014;35(3):395–400.
15. Sommen M, Van Camp G, Liktor B, Csomor P, Fransen E, Sziklai I, et al. Genetic association analysis in a clinically and histologically confirmed otosclerosis population confirms association with the TGFB1 gene but suggests an association of the RELN gene with a clinically indistinguishable otosclerosis-like phenotype. Otol Neurotol. 2014;35(6):1058–64.
16. McKenna MJ, Kristiansen AG, Bartley ML, Rogus JJ, Haines JL. Association of COL1A1 and otosclerosis: evidence for a shared genetic etiology with mild osteogenesis imperfect. Am J Otol. 1998;19(5):604–10.
17. McKenna MJ, Nguyen-Huynth AT, Kristiansen AG. Association of otosclerosis with Sp1 binding site polymorphism in COL1A1 gene: evidence for shared genetic etiology with osteoporosis. Otol Neurotol. 2004;25(4):447–50.
18. Chen W, Meyer NC, McKenna MJ, Pfister M, McBride DJ, Jr., Fukushima K, et al. Single-nucleotide polymorphisms in the COL1A1 regulatory regions are associated with otosclerosis. Clin Genet. 2007;71(5):406–14.
19. National Center for Biotechnology Information, U.S. National Library of Medicine. Available online: https://pubmed.ncbi.nlm.nih.gov [Accessed: 01. 03. 2020]
20. Tomek MS, Brown MR, Mani SR, Ramesh A, Srisailapathy CR, Coucke P, et al. Localization of a gene for otosclerosis to chromosome 15q25-q26. Hum Mol Genet. 1998;7(2):285–90.
21. Babcock TA, Liu XZ. Otosclerosis: From Genetics to Molecular Biology. Otolaryngol Clin North Am. 2018;51(2):305–18.
22. Van Den Bogaert K, Govaerts PJ, Schatteman I, Brown MR, Caethoven G, Offeciers FE, et al. A second gene for otosclerosis, OTSC2, maps to chromosome 7q34-36. Am J Hum Genet. 2001;68(2):495–500.

23. Chen W, Campbell CA, Green GE, Van Den Bogaert K, Komodikis C, Manolidis LS, et al. Linkage of otosclerosis to a third locus (OTSC3) on human chromosome 6p21.3-22.3. J Med Genet. 2002;39(7):473–7.
24. Gregoriadis S, Zervas J, Varletzidis E, Toubis M, Pantazopoulos P, Fessas P. HLA antigens and otosclerosis. A possible new genetic factor. Arch Otolaryngol. 1982;108(12):769–71.
25. Brownstein Z, Goldfarb A, Levi H, Frydman M, Avraham KB. Chromosomal mapping and phenotypic characterization of hereditary otosclerosis linked to the OTSC4 locus. Arch Otolaryngol Head Neck Surg. 2006;132(4):416–24.
26. Van Den Bogaert K, De Leenheer EM, Chen W, Lee Y, Nurnberg P, Pennings RJ, et al. A fifth locus for otosclerosis, OTSC5, maps to chromosome 3q22-24. J Med Genet. 2004;41(6):450–3.
27. Thys M, Van Den Bogaert K, Iliadou V, Vanderstraeten K, Dieltjens N, Schrauwen I, et al. A seventh locus for otosclerosis, OTSC7, maps to chromosome 6q13-16.1. Eur J Hum Genet. 2007;15(3):362–8.
28. Bel Hadj Ali I, Thys M, Beltaief N, Schrauwen I, Hilgert N, Vanderstraeten K, et al. A new locus for otosclerosis, OTSC8, maps to the pericentromeric region of chromosome 9. Hum Genet. 2008;123(3):267–72.
29. Mowat AJ, Crompton M, Ziff JL, Aldren CP, Lavy JA, Saeedet SR, et al. Evidence of distinct RELN and TGFB1 genetic associations in familial and non-familial otosclerosis in a British population. Hum Genet. 2018;137(5):357–63.
30. Nager GT. Osteogenesis imperfecta of the temporal bone and its relation to otosclerosis. Ann Otol Rhinol Laryngol. 1998;97(6 Pt 1):585–93.
31. Ertugay OC, Ata P, Kalaycik Ertugay C, Kaya KS, Tatlipinar A, Kulekci S. Association of COL1A1 polymorphism in Turkish patients with otosclerosis. Am J Otolaryngol. 2013;34(5):403–6.
32. Rodríguez L, Rodríguez S, Hermida J, Frade C, Sande E, Visedo G, et al. Proposed association between the COL1A1 and COL1A2 genes and otosclerosis is not supported by a case-control study in Spain. Am J Med Genet A. 2004;128A(1):19–22.
33. Schrauwen I, Khalfallah A, Ealy M, Fransen E, Claes C, Huber A, et al. COL1A1 association and otosclerosis: a meta-analysis. Am J Med Genet A. 2012;158A(5):1066–70.
34. Yoo TJ. Etiopathogenesis of otosclerosis: a hypothesis. Ann Otol Rhinol Laryngol. 1984;93(1 Pt 1):28–33.
35. Sølvsten Sørensen M, Nielsen LP, Bretlau P, Jørgensen MB. The role of type II collagen autoimmunity in otosclerosis revisited. Acta Otolaryngol. 1988;105(3–4):242–7.
36. Imauchi Y, Jeunemaitre X, Boussion M, Ferrary E, Sterkers O, Grayeli AB. Relation between renin-angiotensin-aldosterone system and otosclerosis: a genetic association and in vitro study. Otol Neurotol. 2008;29(3):295–301.
37. Schrauwen I, Thys M, Vanderstraeten K, Fransen E, Ealy M, Cremers CW, et al. No evidence for association between the renin-angiotensin-aldosterone system and otosclerosis in a large Belgian-Dutch population. Otol Neurotol. 2009;30(8):1079–83.
38. Liktor B, Csomor P, Szász CS, Sziklai I, Karosi T. No evidence for the expression of renin-angiotensin-aldosterone system in otosclerotic stapes footplates. Otol Neurotol. 2013;34(5):808–15.
39. Dahlqvist A, Diamant H, Dahlqvist SR, Cedergren B. HLA antigens in patients with otosclerosis. Acta Otolaryngol. 1985;100(1–2):33–5.
40. Karosi T, Szalmás A, Csomor P, Kónya J, Petkó M, Sziklai I. Disease-associated novel CD46 splicing variants and pathologic bone remodeling in otosclerosis. Laryngoscope. 2008;118(9):1669–79.
41. Schrauwen I, Ealy M, Huentelman MJ, Thys M, Homer N, Vanderstraeten K, et al. A genome-wide analysis identifies genetic variants in the RELN gene associated with otosclerosis. Am J Hum Genet. 2009;84(3):328–38.
42. Schrauwen I, Ealy M, Fransen E, Vanderstraeten K, Thys M, Meyer NC, et al. Genetic variants in the RELN gene are associated with otosclerosis in multiple European populations. Hum Genet. 2010;127(2):155–62.
43. Khalfallah A, Schrauwen I, Mnaja M, Fransen E, Lahmar I, Ealy M, et al. Genetic variants in RELN are associated with otosclerosis in a non-European population from Tunisia. Ann Hum Genet. 2010;74(5):399–405.
44. Ziff JL, Crompton M, Powell HR, Lavy JA, Aldren CP, Steel KP, et al. Mutations and altered expression of SERPINF1 in patients with familial otosclerosis. Hum Mol Genet. 2016;25(12):2393–403.
45. Milosevic G, Kotur N, Krstovski N, Lazic J, Zukic B, Stankovic B, et al. Variants in TPMT, ITPA, ABCC4 and ABCB1 Genes As Predictors of 6-mercaptopurine Induced Toxicity in Children with Acute Lymphoblastic Leukemia. J Med Biochem. 2018;37(3):320–7.
46. Anđelković M, Spasovski V, Vreća M, Sovtić A, Rodić M, Komazec J, et al. The importance of genomic profiling for differential diagnosis of pediatric lung disease patients with suspected ciliopathies. Srp Arh Celok Lek. 2019;147(3–4):160–6.
47. Pavlovic S, Kotur N, Stankovic B, Zukic B, Gasic V, Dokmanovic L. Pharmacogenomic and Pharmacotranscriptomic Profiling of Childhood Acute Lymphoblastic Leukemia: Paving the Way to Personalized Treatment. Genes (Basel). 2019;10(3):191.
48. Pavlovic S, Klaassen K, Stankovic B, Stojiljkovic M, Zukic B. Next-Generation Sequencing: The Enabler and the Way Ahead. In: Kambouris ME and Velegraki A (eds). Microbiomics: Dimensions, Applications, and Translational Implications of Human and Environmental Microbiome Research. San Diego: Elsevier/ Academic Press; 2020. p. 175–94.
49. Giardine B, Borg J, Higgs D, Peterson K, Philipsen S, Maglott D, et al. Systematic documentation and analysis of human genetic variation in hemoglobinopathies using the microattribution approach. Nat Genet. 2011;43(4):295–301.
50. Viennas E, Komianou A, Mizzi C, Stojiljkovic M, Mitropoulou C, Muilu J, et al. Expanded national database collection and data coverage in the FINDbase database worldwide database for clinically relevant genomic variation allele frequencies. Nucleic Acids Res. 2017;45(D1):D846–D853.

Генетичка основа отосклерозе

Бранка Зукић[1], Марина Анђелковић[1], Владимир Гашић[1], Јасмина Грубин[2], Соња Павловић[1], Драгослава Ђерић[3]

[1]Универзитет у Београду, Институт за молекуларну генетику и генетичко инжењерство, Лабораторија за молекуларну биомедицину, Београд, Србија;

[2]Министарство просвете, науке и технолошког развоја Републике Србије, Београд, Србија;

[3]Универзитет у Београду, Медицински факултет, Клинички центар Србије, Клиника за оториноларингологију, Београд, Србија

САЖЕТАК

Увод Отосклероза је поремећај коштане капсуле лавиринта и слушних кошчица ува, који доводи до губитка слуха због немогућности провођења звука. Генетички узрок отосклерозе је непознат.

Циљ овог рада је био да се сачини свеобухватни преглед савремених сазнања о генетичкој основи отосклерозе.

Методе За приказ података о генетици отосклерозе коришћен је наративни преглед литературе.

Резултати Генетика отосклерозе није много изучавана и литературни подаци о генетичкој основи отосклерозе су оскудни. Међутим, у новије време, проширују се знања о генетичкој основи отосклерозе. Овде је приказан преглед знања о асоцијацији генетичких маркера и отосклерозе, која су резултат анализа генетичке повезаности, као и асоцијативних студија гена кандидата и свеобухватних анализа генома.

Закључак Отосклероза због своје комплексности није болест чија ће генетичка основа бити лако расветљена. Анализе омика и биоинформатика ће допринети разумевању генетичке основе отосклерозе.

Кључне речи: отосклероза; генетика; анализа генетичке повезаности; студија гена кандидата; свеобухватна анализа генома