



SIRT1 rs7895833 and SOD1-50bp ins/del Gene Variations in Age-Related Cataract Patients: A Case-Control Study

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<p>Submitted: 2023-12-10 Accepted: 2024-02-18</p> <p>Keywords: Oxidative stress SOD1 SIRT1 Polymorphism Cataract</p> <p>How to Cite this Article: L. Kohan, S. Sharghi, A. Karimi. "SIRT1 rs7895833 and SOD1-50bp ins/del Gene Variations in Age-Related Cataract Patients: A Case-Control Study " Personalized Medicine Journal, Vol. 9, no. 32, pp. 16- 22.</p>	<p>Abstract:</p> <p>Aim: Oxidative stress is one of the main factors has been implicated in pathophysiology of cataracts. Superoxide dismutase (SOD) can prepare the first line of defense versus detrimental reactive oxygen species (ROS) and Sirtuin (SIRT) confers protection against oxidative stress and retinal degeneration. Correlation of SOD1-50bp ins/del and SIRT1-rs7895833 polymorphisms with risk of cataracts is not studied currently. Therefore, we aimed to explore possible relationship between SOD1 (50bp ins/del) and SIRT1 (rs7895833) polymorphisms with the risk of cataracts in Iranian population.</p> <p>Methods: Our study design consisted of 200 patients with age-related cataracts and 200 healthy individuals as a control group. After DNA extraction, the identification of polymorphisms was conducted using PCR-based methods and data analysis was done by SPSS software.</p> <p>Results: A significant difference in <i>SOD1</i> DD genotype distribution was observed between studied groups (OR: 3.42, P:0.037), the D allele was more frequent in patients in comparison with controls (OR: 1.68, P:0.009). Also, in the dominant genetic model for the D allele (comparison between ID+DD vs. II), ID+DD genotypes increased the risk of cataracts (OR: 1.62, P: 034). The association between <i>SIRT1</i>-rs7895833 polymorphism and cataract was significant in the AG genotype (OR: 2.37, P<0.001) and G allele (OR: 1.97, P<0.001). The <i>SIRT1</i>-1 polymorphism increased the risk of cataracts in the dominant tested inheritance model (OR: 2.34, P<0.001). In the combined analysis of two polymorphisms, there is an additive effect of the high-risk putative alleles about the risk of cataracts. Risk estimation according to the number of high-risk alleles showed that χ^2 for linear trend for 0, 1, 2, 3 and 4 putative high-risk alleles is equal to 20.10 (P<0.001).</p> <p>Conclusion: The results showed that for the first time, <i>SIRT1</i> rs7895833 and <i>SOD1</i>-50bp ins/del gene variations had additive effects on the risk of cataracts.</p>
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INTRODUCTION

Cataracts have been recognized as the opacification of the eye lens with the breakdown of the lens protein microarchitecture that can harmfully influence the light transmission on the retina (1). The WHO estimates that over 94 million people suffer visual impairment due to cataracts worldwide (2). Oxidative stress is currently known as an initiating parameter in the pathogenesis of cataracts. An imbalance between oxidative stress processes, antioxidant protection and repair, promotes cataracts (3). Superoxide dismutase (SOD) is the main enzymatic antioxidant in the lens. SOD prepares the first line of defence versus detrimental reactive oxygen species (ROS) (4). In the lens, SOD1 was determined

as the main isoform for about 90% of the whole SOD activity. It is determined that specific SOD1 activity can be reduced as a function of age in the cataract patient's blood (3, 5) as well as in human lenses (6). Previous investigations determined that the decreased activities of the SOD1 isoform in cataractous lenses are commonly associated with protein expression and reduced levels of mRNA transcripts (7). The overexpression of SOD1 is demonstrated to prevent ROS-induced oxidative loss for lenses together with regulating cataract formation (8). In cataractous lenses, impaired activity of SOD1 can be caused by genetic polymorphisms in coding regions along with noncoding regions of the SOD1 gene (9). Several

studies showed an association of SOD1 gene variants with diseases like cancer (10), type 2 diabetes (11), and cardiovascular disease (12).

Sirtuin 1 (SIRT1) is another protein which can protect cells against oxidative stress, regulates glucose or lipid metabolism, and enhances the stability of DNA by binding and deacetylating many substrates (13). The protein of SIRT1 has been reported as a member of the Silent Information Regulator 2 (Sir2) protein family (i.e., a group of nicotinamide adenine dinucleotide (NAD⁺)-dependent histone deacetylases) (14). This protein can enhance cell survival using the inhabitation of cellular senescence or may apoptosis due to stress, consisting of DNA damage as well as oxidative stress (15). It is richly divided into different tissues together with organs and is determined in the cytoplasm and nucleus of cells from whole the ocular structures consisting of the retina, iris, lens, cornea and ciliary body (16). SIRT1 polymorphisms are associated with many diseases consisting diabetes (17), cancers (18), cardiovascular (19) and neurodegenerative (20) diseases.

Genetic polymorphisms are introduced as rather affecting the genetic risk elements for cataracts and enhancing efforts were focused on detecting the associations among cataract susceptibility and genetic polymorphisms (21). Based on the previous reports, we hypothesized that polymorphisms in the genes of SOD1 and SIRT1 can be associated with susceptibility to cataracts. A number of polymorphisms are specified in SOD1 and SIRT1 genes, which affect gene regulatory regions consisting of promoter. Therefore, in this study for the first time, we selected two common promoter polymorphisms, SOD1 50bp ins/del and SIRT1 rs7895833, to assess their association and genotype combination with age-related cataract in an Iranian population and calculate the additive effect of these two polymorphisms about the susceptibility to age-related cataract.

MATERIAL AND METHODS

Sample collection

This study was conducted following approval from the Ethics Committee of Arsanjan Islamic Azad University (approval ID number: IR.IAU.SHIRAZ.REC.1402.274). In this research, 200 age-related cataract patients and 200 age and sex-matched-healthy individuals are recruited. The control group consisted of subjects without any ocular disorders. Informed written consents are achieved from all participants. Blood samples are collected from cataract patients at Mirhosseini Hospital of Shiraz city (Fars province-Iran). Cataract status was confirmed through a slit lamp examination by a specialist. With the inclusion criteria of: (I) patients aged ≥ 60 years old; (II) patients diagnosed with age-related cataracts; (III) clinical

data of patients was complete and true. Subjects were excluded from the study if they suffered from any metabolic disorder or secondary cataracts due to diabetes or trauma. Also, patients with corneal, fundus, or other diseases that affect vision, i.e., other than cataracts, were excluded.

DNA extraction and Genotyping

DNA was isolated from whole blood by utilizing the salting out method as described in the previous study (22). Analysis of SIRT1 polymorphism was carried out by the Tetra-ARMS PCR method. The polymerase chain reaction is done in a total reaction volume equal to 12.5 μ l including 6.25 μ l PCR master mix, DNA template of 1 μ l (400 ng/ml), 1 μ l of each forward and reverse internal primers (10 pm/ μ l), 0.25 μ l of each forward and reverse outer primers (2.5 pm/ μ l), and 2.75 μ l H₂O. For detection of SOD1 polymorphism, polymerase chain reaction was performed in a total reaction of 12.5 μ l volume consisting of 6.25 μ l PCR master mix, 1 μ l DNA template (400 ng/ml), 0.5 μ l of each forward and reverse primers (5 pm/ μ l), and 3.25 μ l H₂O. The details of primer sequences are shown in Table 1.

STATISTICAL ANALYSIS

SPSS software version 18.0 was utilized to analyse data. Demographic characteristics and Hardy-Weinberg equilibrium were assessed using the Pearson χ^2 test. Odds ratios with a 95% confidence interval were calculated to examine the relationship between gene polymorphisms and cataract risk. P values less than 0.05 were attended as significant.

RESULTS

The comparison of general data between cataract patients and controls is shown in Table 2. The average age of patients and controls was 64.18 \pm 8.83 years. and 63.98 \pm 9.03 yrs, respectively. There was no significant difference in mean age between case and control groups (P=0.82).

The distribution of SOD1 50bp ins/del and SIRT1-rs7895833 polymorphisms in cataract patients and healthy individuals is shown in Table 3 and Table 4, respectively. No significant deviations from Hardy-Weinberg equilibrium were found for SOD1 50bp ins/del ($\chi^2=0.33$, df=1, P=0.56) and SIRT1 rs7895833 ($\chi^2=0.15$, df=1, P=0.70) in control group.

Our results showed that there was a significant association between SOD1-DD genotype and cataract susceptibility (OR: 3.42, 95%CI: 1.1-10.8, P: 0.037). Also, in the dominant genetic effect of the D allele (comparison between ID+DD vs. II), ID+DD genotypes increased the risk of cataracts and the D allele, as a putative high-risk allele, was associated with increased risk of cataract (OR: 1.68, 95%CI: 1.14-2.48, P: 0.009).

Table1.Details of primers using for genotyping SIRT1 and SOD1 polymorphisms.

Polymorphism	Primers	Sequence (5' to 3')	Annealing Temp (°C)
<i>SIRT-1</i> rs7895833	FI	GTGGTAAAAGGCCTACAGGCAA	57
	RI	CTTGCTTCCTAATCTCCATTACGTTTAC	
	FO	CCTAGCTGGTCTATCTCCCTTACCTC	
	RO	GCACATCTGTGTATCCCCTAGAAAG	
<i>SOD1</i> 50bp ins/del	F	AATTCCTTACCCCTGTTCTA	60
	R	GGCAGATTTTCAGTTCATTGT	

F: forward; R: Reverse; I: Inner; O: Outer; Temp: Temperature

Table2. Comparison of basic data between patient and control groups.

Variables	Controls (%) N=200	Cases (%) N=200	P-value
Gender			
Female	118 (59)	118 (59)	NS
Male	82 (41)	82 (41)	
Family History			
No	177 (88.5)	149 (74.5)	<0.001
Yes	23 (11.5)	51 (25.5)	
Smoking			
No	164 (82)	168 (84)	0.59
Yes	36 (18)	32 (16)	

NS: not significant

According to SIRT1-rs7895833 genotype distribution, the AG genotype was associated with cataract susceptibility (OR: 2.37, 95%CI: 1.52-3.69, $P < 0.001$). Moreover, the frequency of the rs7895833G allele was significantly higher in cases compared to controls and this high putative allele was associated with an enhanced risk of cataracts (OR: 1.97, 95%CI: 1.36-2.86, $P < 0.0001$).

To investigate whether the high-risk alleles of SOD1 and SIRT1 had an additive effect on the risk of age-related cataracts, we considered the association between the combination of alleles and the risk of cataracts. The reference group consisted of individuals with the double low-risk alleles of SOD1 and SIRT1. Data analysis showed that there were significant associations between combined alleles and the risk of

Table 3. SOD1-50bp ins/del polymorphism in cataract patients and Controls.

Polymorphism	Cases (%)	Controls (%)	OR (95% CI)	P-Value
<i>Genotypes</i>				
II	136 (68)	155 (77.5)	1	
ID	52 (26)	41 (20.5)	1.44 (0.9-2.31)	0.124
DD	12 (6)	4(2)	3.42 (1.1-10.8)	0.037
<i>Alleles</i>				
I	324 (81)	351 (88)	1	
D	76 (19)	49 (12)	1.68 (1.14-2.48)	0.009
<i>Dominant model</i>				
II	136 (68)	155 (77.5)	1	
ID+DD	64 (32)	45 (22.5)	1.62 (1.04-2.53)	0.034
<i>Recessive model</i>				
II+ID	188 (94)	196 (98)	1	
DD	12 (6)	4 (2)	3.13 (0.99-9.86)	0.052

cataracts (Table 5). Also, there was a linear trend in risk associated with 0, 1, 2, 3 & 4, alleles (χ^2 : 20.10, $P < 0.001$).

DISCUSSION

The genetic variations are one of the important intrinsic factors can potentially affect many aspects of disease management and its medical treatment. Initially, our research focused on investigating the correlation between genetic variations in the promoter regions of SOD1 and SIRT1 genes and the susceptibility to cataracts. Our findings suggest that these genetic alterations may act as risk factors influencing the development of age-related cataracts in the Iranian population. We found that the G allele of SIRT1-rs7895833 and the D allele of SOD1 50bp ins/del, as high-risk alleles, were associated with an increased risk of cataracts. However, a combination study showed that there were significant associations between combined high-risk alleles and the risk of cataracts; it means that the high-risk alleles of these two polymorphisms had additive effects about the risk of

cataracts. According to these results, we reported that individuals with the high risk alleles in these studied genetic variations and specially who had combination of these high risk alleles, are marked for personalized medicine; and these polymorphisms may help in decision to the prevention, diagnosis, and treatment of cataracts in future.

There have been several reports studying the association between various genes as well as several SNPs with cataracts (23, 24). Previous evidence demonstrated that the generation of ROS leads to cross-linking, and aggregation of lens proteins as well as abnormal degradation and was consisted in cataractogenesis (25). The oxidative damage during cataractogenesis can be reduced by cellular defence mechanisms in the eye; SOD1 and SIRT1 proteins play important roles in this situation. As yet there are no studies on the effect of SOD1 50bp ins/del and SIRT1 rs7895833 polymorphisms and the additive effect of these polymorphisms on cataract susceptibility. It has been shown that polymorphisms in promoter regions could affect gene expression and enzyme activity (26,

Table 4. SIRT1-rs7895833 polymorphism in cataract patients and Controls

Polymorphism	Cases (%)	Controls (%)	OR (95% CI)	P-Value
<i>Genotypes</i>				
AA	115 (57.5)	152 (76)	1	
AG	79 (39.5)	44 (22)	2.37 (1.52-3.69)	<0.001
GG	6 (3)	4 (2)	1.98 (0.55-7.20)	0.3
<i>Alleles</i>				
A	309 (77)	348 (87)	1	
G	91 (23)	52 (13)	1.97 (1.36-2.86)	<0.001
<i>Dominant model</i>				
AA	115 (57.5)	152 (76)	1	
AG+GG	79 (39.5)	44 (22)	2.34 (1.52-3.59)	<0.001
<i>Recessive model</i>				
AA+AG	309 (77)	348 (87)	1	
GG	91 (23)	52 (13)	1.51 (0.42-5.45)	0.52

Table 5. Risk estimation according to number of high risk allele

N of high risk allele	Case (%)	Control (%)	OR (95% CI)	P
0	72 (36)	120 (60)	Reference	-
1	94 (47)	63 (31.5)	2.48 (1.61-3.83)	<0.001
2	29 (14.5)	14 (7)	3.45 (1.71-6.96)	0.001
3 & 4	5 (2.5)	3 (1.5)	2.78 (0.64-11.97)	0.17

X^2 for linear trend: 20.10, $P < 0.001$

27). A 50bp ins/del polymorphism (rs36232792) has been recognized in the SOD1 promoter region (1684 bp upstream of the start codon of ATG). Its role is demonstrated with reduced promoter activity together with low mRNA levels in cells can be caused due to the loss of two Sp1 binding sites (28). Attending that the Del allele causes to reduction of the promoter activity of the SOD1. It may change the enzymes' antioxidant

capacity which leads to synergistic effects with cataracts induced by oxidative damage subsequently. The results of the present case-control study demonstrate that the risk of cataracts was associated with the Ins/Del polymorphism of SOD1. Although there is no published study regarding the effects of the SOD1 50bp ins/del variant on cataract susceptibility, the role of another genetic variant in the SOD1 gene has already

been studied in the pathogenesis of cataracts. Zhang et al. suggested that the SOD1-251A/G polymorphism may be associated with an increased risk of cataracts (9), also, Celojevic et al. found no correlation between SOD1 intron variants (rs17881180, rs2234694) and age-related cataract (29). Recently, Mahmood et al., reported that there was a significant association between SOD1 rs2070424 polymorphism and the development of cataracts in patients of Karachi, Pakistan (30).

It has been reported that up-regulation of SIRT1 in retinal cells protects cells from apoptotic death induced by anti-retinal antibodies, while down-regulation of SIRT1 causes retinal damage through multiple mechanisms and proposed that SIRT1 may play a role in the retina and optic nerve protections versus degeneration (31). In previous reports, Kilic et al. observed that the oxidative stress index and SIRT1 protein level enhanced in older people [19]. Also, it has been shown that SIRT1 plays crucial roles in regulating longevity, ageing, or in the pathogenesis of age-corresponded metabolic diseases (32). In addition, the explanation of SIRT1 is observed in the lens epithelium of patients along with age-related cataracts, adult retinas, and corneal epithelium (33). Therefore, SIRT1 can protect the retinal cells from apoptotic retinal death and oxidative stress-related retinal damage as well as anti-inflammation (16).

The outcomes of the current investigation demonstrated that the G allele of SIRT1-rs7895833 was associated with an enhanced risk of cataracts. Chen et al. previously reported that SIRT1-rs12778366 could be implicated in the pathophysiology of age-related macular degeneration (34). Furthermore, a recent study by Kaikaryte et al. revealed that the SIRT1 polymorphisms rs7895833 and rs3818292 and also, rs3818292-rs3758391-rs7895833 haplotype G-T-G could be associated with the development of exudative age-related macular degeneration (35). The correlation of SIRT1-rs7895833 polymorphism with diabetes (36), and neurodegenerative diseases, such as primary open-angle glaucoma (37), metabolic syndrome (38), and cardiovascular disease (39) have already been reported.

The results of the present research were influenced by the limited number of controls and cases, which represents a fundamental constraint in our study. Therefore, further efforts, including expanding the sample size and conducting functional experiments, are necessary to elucidate the precise impact of SOD1 and SIRT1 polymorphisms on cataract development.

CONCLUSION

This study represents the initial evidence proposing a potential link between the SIRT1-rs7895833 and SOD1-50bp ins/del polymorphisms with the cataract risk. To validate our findings, additional studies involving larger sample sizes across diverse ethnic

groups are warranted.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Author contributions

LK Supervision, Methodology, Reviewing and Editing, SSh and AK Investigations, Statistical analysis, Original draft preparation and Data collection

REFERENCES

- Sun W, Su L, Sheng Y, Shen Y, Chen G. Is there association between Glutathione S Transferases polymorphisms and cataract risk: a meta-analysis? *BMC. Ophthalmology*. 2015;15,84.
- Mackenbrock LHB, Labuz G, Baur ID, Yildirim TM, Auffarth GU, Khoramnia R. Cataract Classification Systems: A Review. *Klin. Monbl. Augenheilkd*. 2024; 241(1),75-83.
- Lee B, Afshari NA, Shaw PX. Oxidative stress and antioxidants in cataract development. *Curr. Opin. Ophthalmol* 2023.
- Younus H. Therapeutic potentials of superoxide dismutase. *Int. J. Health. Sci*. 2018; 12(3),88.
- Elmazar HM, Elmadbouh I, Mandour SS, Al Ariny GM, Ibrahim AM. Association between cataract progression and ischemia-modified albumin in relation to oxidant-antioxidant profiles in the serum, aqueous humor, and lens. *J. Cataract. Refract. Surg*. 2018; 44,134-139 (2018).
- Rong X, Qiu X, Jiang Y, Li D, Xu J, Zhang Y, et al. Effects of histone acetylation on superoxide dismutase 1 gene expression in the pathogenesis of senile cataract. *Sci. Rep*. 2016; 6,34704.
- Rajkumar S, Vasavada AR, Praveen MR, Ananthan R, Reddy GB, Tripathi H, et al. Exploration of molecular factors impairing superoxide dismutase isoforms activity in human senile cataractous lenses. *Invest. Ophthalmol. Vis. Sci*. 2013; 54(9),6224-33.
- Lin D, Barnett M, Grauer L, Robben J, Jewell A, Takemoto L, et al. Expression of superoxide dismutase in whole lens prevents cataract formation. *Mol. Vis*. 2005; 11(11),853-8.
- Zhang Y, Zhang L, Sun D, Li Z, Wang L, Liu P. Genetic polymorphisms of superoxide dismutases, catalase, and glutathione peroxidase in age-related cataract. *Mol. Vis*. 2011; 17,2325.
- Kopp TI, Vogel U, Dragsted LO, Tjonneland A, Ravn-Haren G. Association between single nucleotide polymorphisms in the antioxidant genes CAT, GR and SOD1, erythrocyte enzyme activities, dietary and life style factors and breast cancer risk in a Danish, prospective cohort study. *Oncotarget*. 2017; 8(38),62984.

11. Neves AL, Mohammadi K, Emery N, Roussel R, Fumeron F, Marre M, et al. Allelic variations in superoxide dismutase-1 (SOD1) gene and renal and cardiovascular morbidity and mortality in type 2 diabetic subjects. *Mol. Genet. Metab.* 2012;106(3),359-65.
12. Eskandari-Nasab E, Kharazi-Nejad E, Nakhaee A, Afzali M, Tabatabaei SP, Tirgar-Fakheri K, et al. 50-bp Ins/Del polymorphism of SOD1 is associated with increased risk of cardiovascular disease. *Acta. Med. Iran.* 2014; 52(8),591-5.
13. Cheng Y, Takeuchi H, Sonobe Y, Jin S, Wang Y, Horiuchi H, et al. Sirtuin 1 attenuates oxidative stress via upregulation of superoxide dismutase 2 and catalase in astrocytes. *J. Neuroimmunol.* 2014; 269(1-2),38-43.
14. Elibol B, Kilic U. High levels of SIRT1 expression as a protective mechanism against disease-related conditions. *Front. Endocrinol.* 2018; 9,614.
15. He J, Zhang A, Song Z, Guo S, Chen Y, Liu Z, Zhang J, Xu X, Liu J, Chu L. The resistant effect of SIRT1 in oxidative stress-induced senescence of rat nucleus pulposus cell is regulated by Akt-FoxO1 pathway. *Biosci. Rep.* 2019; 39(5),BSR20190112.
16. Mimura T, Kaji Y, Noma H, Funatsu H, Okamoto S. The role of SIRT1 in ocular aging. *Exp. Eye. Res.* 2013; 116,17-26.
17. Zhao Y, Wei J, Hou X, Liu H, Guo F, Zhou Y, Zhang Y, Qu Y, Gu J, Zhou Y, Jia X, Qin G, Feng L. SIRT1 rs10823108 and FOXO1 rs17446614 responsible for genetic susceptibility to diabetic nephropathy. *Sci. Rep.* 2017; 7(1),10285.
18. Lv Y, Lin S, Peng F. SIRT1 gene polymorphisms and risk of lung cancer. *Cancer. Manag. Res.* 2017; 9,381-386 9.
19. Kilic U, Gok O, Bacaksiz A, Izmirli M, Elibol-Can B, Uysal O. SIRT1 gene polymorphisms affect the protein expression in cardiovascular diseases. *PLoS One.* 2014; 9(2),e90428.
20. Zhang A, Wang H, Qin X, Pang S, Yan B. Genetic analysis of SIRT1 gene promoter in sporadic Parkinson's disease. *Biochem. Biophys. Res. Commun.* 2012; 422(4),693-6.
21. Wu X, Lai W, Lin H, Liu Y. Association of OGG1 and MTHFR polymorphisms with age-related cataract: A systematic review and meta-analysis. *PloS one.* 2017; 12(3),e0172092.
22. Kohan L, Mirhosseini M, Mortazavizadeh SM. The risk of relapse in breast cancer patients is associated with MMP-9 gene polymorphism: a prospective study in a sample of the Iranian population. *Nucleosides Nucleotides Nucleic Acids.* 2022; 41(10),1012-1023.
23. Kafeel S, Bizenjo N, Shivji SS, Keran A, Hashim Z, Nawab SN. DNA Repair Enzyme XRCC4 30 bp Indel Intron 3 Locus Significant Association with Predisposition of Cataract in Senility. *Appl Biochem Biotechnol.* 2024; 196(1),99-112.
24. Zafar S, Khurram H, Kamran M, Fatima M, Parvaiz A, Shaikh RS. Potential of GJA8 gene variants in predicting age-related cataract: A comparison of supervised machine learning methods. *PLoS One.* 2023; 18(8),e0286243.
25. Berthoud VM, Beyer EC. Oxidative stress, lens gap junctions, and cataracts. *Antioxid. Redox. Signal.* 2009; 11(2),339-53.
26. Harati-Sadegh M, Kohan L, Teimoori B, Mehrabani M, Salimi S. The effects of placental long noncoding RNA H19 polymorphisms and promoter methylation on H19 expression in association with preeclampsia susceptibility. *Iubmb Life.* 2020; 72(3),413-25.
27. Harati-Sadegh M, Kohan L, Teimoori B, Mehrabani M, Salimi S. Analysis of polymorphisms, promoter methylation, and mRNA expression profile of maternal and placental P53 and P21 genes in preeclamptic and normotensive pregnant women. *J. Biomed. Sci.* 2019; 26(1),92.
28. Saify K, Saadat M. Influence of a 50bp Ins/Del polymorphism at promoter of the superoxide dismutase-1 on gene expression and risk of heroin dependency. *Environ. Health. Prev. Med.* 2017; 22(1),4.
29. Celojevic D, Nilsson S, Behndig A, Tasa G, Juronen E, Karlsson JO, Zetterberg H, Petersen A, Zetterberg M. Superoxide dismutase gene polymorphisms in patients with age-related cataract. *Ophthalmic Genet.* 2013; 34(3),140-5.
30. Mahmood A, Aziz Q, Nangrejo R, Ahmed I, Soomro S, Ara I. Superoxide Dismutase (SOD1) Gene Polymorphism in Cataract Patients of Karachi, Pakistan. *Journal of the Dow University of Health Sciences (JDUHS).* 2022; 16(1),22-6.
31. Kubota S, Kurihara T, Ebinuma M, Kubota M, Yuki K, Sasaki M, Noda K, Ozawa Y, Oike Y, Ishida S, Tsubota K. Resveratrol prevents light-induced retinal degeneration via suppressing activator protein-1 activation. *Am. J. Pathol.* 2010; 177(4),1725-31.
32. Maeda S, Koya D, Araki SI, Babazono T, Umezono T, Toyoda M, et al. Association between single nucleotide polymorphisms within genes encoding sirtuin families and diabetic nephropathy in Japanese subjects with type 2 diabetes. *Clin. Exp. Nephrol.* 2011; 15(3),381-390.
33. Zheng T, Lu Y. Changes in SIRT1 expression and its downstream pathways in age-related cataract in humans. *Curr. Eye. Res.* 2011; 36(5),449-55.
34. Chen Z, Zhai Y, Zhang W, Teng Y, Yao K. Single Nucleotide Polymorphisms of the Sirtuin 1 (SIRT1) Gene are Associated With age-Related Macular Degeneration in Chinese Han Individuals: A Case-Control Pilot Study. *Medicine (Baltimore).* 2015; 94(49):e2238.
35. Kaikaryte K, Gedvilaite G, Vilkeviciute A, Kriauciuniene L, Mockute R, Cebatoriene D, Zemaitiene R, Balciuniene VJ, Liutkeviciene R. SIRT1: Genetic Variants and Serum Levels in Age-Related Macular Degeneration. *Life.* 2022; 12(5),753.
36. Botden IP, Zillikens MC, De Rooij SR, Langendonk JG, Danser AJ, Sijbrands EJ, et al. Variants in the SIRT1 gene may affect diabetes risk in interaction with prenatal exposure to famine. *Diabetes Care.* 2012; 35(2),424-6.
37. Siwak M, Maślankiewicz M, Nowak-Zduńczyk A, Filipek B, Wojtczak R, Radek M, Kucharska E, Szafflik J, Szafflik JP, Majsterek IJ. Analysis of rs7895833 polymorphism of SIRT1 gene and its influence on the risk occurrence and progression of neurodegenerative disease, such as primary open-angle glaucoma in a Polish population. *Journal of Pre-Clinical and Clinical Research.* 2022.
38. Tao TT, Lin XH, Tang SJ, Gui WW, Zhu WF, Li H. Association of genetic variants in the Sirt1 and Nrf2 genes with the risk of metabolic syndrome in a Chinese Han population. *BMC. Endocrine Disorders.* 2022; 22(1),1-8.
39. Yamac AH, Uysal O, Ismailoglu Z, Ertürk M, Celikten M, Bacaksiz A, Kilic U. Premature Myocardial Infarction: Genetic Variations in SIRT1 Affect Disease Susceptibility. *Cardiol. Res. Pract.* 2019; 8921806.