Manganese-superoxide dismutase (MnSOD) polymorphisms

[Özelter: Mangan süperoksit dismutaz (MnSOD) polimorfizmi]

Yavuz Silig, Ayca Tas, Hatice Pinarbasi

ABSTRACT

Objective: Manganese superoxide dismutase (MnSOD, SOD2), the only known superoxide scavenger in mitochondria, may be particularly important for antioxidant defense because mitochondria are the major sites for cellular metabolism and hence production of reactive oxygen species.

Methods: In this study, 440 Turkish individuals were genotyped for polymorphisms of SOD2 gene. The distribution of these polymorphisms in this population was examined using a PCR-RFLP method.

Results: In the present study, a total of 440 (females: 201, 46% and males: 239, 54%) healthy individuals were studied. The mean age of the study population was 54.41±5.76 years (males, 55.34±5.76; females, 53.12±7.16). The observed genotype frequencies of SOD2 were 17.5, 50.5 and 32.0% for CC, CT and TT, respectively.

Conclusion: This study provides basic information about the allele and genotype frequency distributions of polymorphisms of rs4880 in the SOD2 gene studied. These frequencies may be useful parameters as a reference for future studies on genetic basis of various diseases and cancer susceptibility.

Key Words: Manganese-superoxide dismutase, SOD2, polymorphisms

Conflict of Interest: The authors have no conflict of interest.

ÖZET

Amaç: Mangan süperoksit dismutaz (MnSOD, SOD2) hücresel metabolizmada reaktif oksijen türlerinin en çok oluşturduğu mitokondride bilinen tek süperoksit süpürcü ve antioksidan savunma siteminin önemli bir enzimidir.

Metod: Bu çalışmadan, toplam 440 Türk sağlıklı bireyler incelendi. Türk toplumunda bu polymorfizmin dağılımı bir PCR-RFLP yöntemi kullanılarak incelemiştir.

Bulgular: Bu çalışmada, toplam 440 (kadın: 201, 46% ve erkek: 239, 54%) Türk sağlıklı bireyler incelendi. Çalışma grubunun yaş ortalaması 54,41±5,76 yıl (erkek, 55,34±5,76; kadın, 53,12±7,16) idi. Mangan süperoksit dismutaz gözlenen genotip frekansları sırasıyla CC: %17,5, CT: %50,5 ve TT için %32,0 olarak tespit edildi.

Sonuç: Bu çalışma, Türk toplumunda SOD2 geninde rs4880 polymorfizmlerinin allele ve genotip frekans dağılımları hakkında temel bilgiler sağlamıştır. Bu frekanslar gelecekte çeşitli hastalıklar ve kanser yakıklılığı çalışmalarında yararlı referans parametreler olabilir.

Anahtar Kelimeler: Mangan süperoksit dismutaz, SOD2, polymorfizm, Türk popülasyonu

Çıkar Çatışması: Yazarların çıkar çatışması yoktur.

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**Introduction**

Oxidative stress has been linked to the progression of many diseases ranging from cancers [1], diabetes [2], cardiovascular [3] and chronic kidney disease [4], to neurodegenerative diseases such as Alzheimer’s [5]. Reactive oxygen species (ROS) are unstable and cause damage by oxidizing macromolecules. Oxidative stress can occur due to an increased concentration of ROS and/or a reduction in antioxidant capacity. Exogenous antioxidants are consumed in the diet and consist mainly of carotenoids such as β-carotene, tocopherols such as vitamin E, and ascorbic acid (vitamin C). Endogenous antioxidants include thiols such as glutathione and the enzymes, superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase [6]. SOD is the key antioxidant enzyme involved in the detoxication of superoxide radicals [7]. SOD contains an active site that has transition metals for rapid electron exchange, converting the superoxide free radical (O2•) to hydrogen peroxide (H2O2) [8]. Three isoforms of SOD have been identified. SOD1 contains copper (Cu) and zinc (Zn) within the active site (also known as CuZn SOD), and is mainly found in cell cytoplasm. SOD2 or manganese (Mn) SOD has an active site that contains manganese and is located in mitochondria. SOD3 or extracellular (EC) SOD also has Cu and Zn within the active site and is the least studied of the three SOD isoforms. SOD2 is the only antioxidant enzyme known to present within the mitochondria and this has important implications because this is a major site for the production of ROS during normal cellular metabolism [9,10]. There are several polymorphisms located in distinct regions of the SOD2 gene. These polymorphisms have been associated with different diseases. The SOD2 gene structure consists of five exons interrupted by four introns and the promoter, which control SOD2 expression [11]. From the polymorphisms located in the coding sequence, the one called rs4880 polymorphism, forward primer 5’-ACC AGC AGG CAG CTG GCG CCG G-3’ and reverse primer 5’- GCG TAT GGA TTA GAT GGA-3’ were used. PCR reactions contained 0.75 µL (25 pmol/µL) of each primer, 2µL dNTPs (1mmol/L), 1.5µL of 25 mmol/L MgCl2, 1.5 Units of Taq DNA polymerase and 16,2µL sterile deionized water. DNA 50-100 ng is in a total volume of 50 µL. The distribution of these polymorphisms was examined using a PCR-RFLP method. For amplifying the SOD2 rs4880 polymorphism, forward primer 5’-ACC AGC AGG CAG CTG GCG CCG G-3’ and reverse primer 5’- GCG TTG ATG TGA GGT TCC AC-3’ were used. PCR reactions contained 0.75 µL (25 pmol/µL) of each primer, 2µL dNTPs (1mmol/L), 1,5µL of 25 mmol/L MgCl2, 1.5 Units of Taq DNA polymerase and 16,2µL sterile deionized water. DNA 50-100 ng is in a total volume of 50 µL. The PCR program was initial denaturation at 95°C for 5 minutes followed by 35 cycles of 95°C for 1 minute, 61°C for 1 minute (annealing), and 72°C for 2 minutes (extension). The PCR was completed by a final extension cycle at 72°C for 7 minutes. Amplified product was digested overnight with Pdi restriction enzyme at 37°C and electrophoresed on 3% agarose gel stained with ethidium bromide. Genotypes were determined for the polymorphism as TT (107 bp), CT (107, 89, 18 bp), or CC (89, 18 bp) [20].

**Genotyping**

The distribution of these polymorphisms was examined using a PCR-RFLP method. For amplifying the SOD2 rs4880 polymorphism, forward primer 5’-ACC AGC AGG CAG CTG GCG CCG G-3’ and reverse primer 5’- GCG TTG ATG TGA GGT TCC AC-3’ were used. PCR reactions contained 0.75 µL (25 pmol/µL) of each primer, 2µL dNTPs (1mmol/L), 1,5µL of 25 mmol/L MgCl2, 1.5 Units of Taq DNA polymerase and 16,2µL sterile deionized water. DNA 50-100 ng is in a total volume of 50 µL. The PCR program was initial denaturation at 95°C for 5 minutes followed by 35 cycles of 95°C for 1 minute, 61°C for 1 minute (annealing), and 72°C for 2 minutes (extension). The PCR was completed by a final extension cycle at 72°C for 7 minutes. Amplified product was digested overnight with Pdi restriction enzyme at 37°C and electrophoresed on 3% agarose gel stained with ethidium bromide. Genotypes were determined for the polymorphism as TT (107 bp), CT (107, 89, 18 bp), or CC (89, 18 bp) [20].

**Statistical analysis**

All statistical analyses were performed using the Statistical Package for Social Sciences Program (SPSS, version 11). The Chi-square ($\chi^2$) test was used to evaluate the association between healthy individuals and SOD genotypes. Genotype, allele frequencies was estimated by counting. Hardy–Weinberg equilibrium between expected and observed genotype distributions was assessed using the $\chi^2$ test. Also, statistical evaluation of allele frequencies was

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**Table 1. Characteristics of the study population**

| Sample size | Healthy individuals |
|-------------|---------------------|
| Gender      |                     |
| Males       | 239 (54%)           |
| Females     | 201 (46%)           |
| Age (year)  |                     |
| Range       | 14–80               |
| Means±SD    |                     |
| Males       | 54.41±5.76          |
| Females     | 55.34±5.76          |

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The study protocol was approved by both scientific and ethics committees (Cumhuriyet University) and written informed consent was obtained from all participants. The study population included 440 (females: 201, 46% and males: 239, 54%) unrelated healthy volunteers from central Anatolia. There was no age and sex restriction for selection of the healthy volunteers, who were free of any chronic diseases, living in the same geographic area, and having no history of any cancer. We attempted to include all the control studies published to data on the SOD2 rs4880 polymorphism.

**DNA isolation**

Two milliliters peripheral blood samples were collected in to citrate containing tubes from all subjects. DNA was extracted from whole blood by salting out procedure as soon as the samples reached to laboratory [19].

**MATERIALS AND METHODS**

**Subject selection**

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**Statistical analysis**

All statistical analyses were performed using the Statistical Package for Social Sciences Program (SPSS, version 11). The Chi-square ($\chi^2$) test was used to evaluate the association between healthy individuals and SOD genotypes. Genotype, allele frequencies was estimated by counting. Hardy–Weinberg equilibrium between expected and observed genotype distributions was assessed using the $\chi^2$ test. Also, statistical evaluation of allele frequencies was
Discussion
Antioxidant enzymes constitute one of the major cellular protective mechanisms against oxidative stress in the human body. Many of the antioxidant genes are known to be polymorphic, which can lead to altered enzyme activity [21]. \( \text{SOD2} \) is a mitochondrial enzyme that catalyzes the formation of \( \text{H}_2\text{O}_2 \) from superoxide radicals. The variant allele of \( \text{SOD2} \) has been associated with elevated risk of breast [22], prostate [23], lung [24] and ovarian [25] cancers and non-Hodgkin’s lymphoma [26].

There is a polymorphic site identified in the mitochondria targeting sequence of human \( \text{SOD2} \) gene. This C to T substitution results in an amino acid change from valine (Val) to alanine (Ala) at codon 16, which is predicted to form amphiphilic helix with higher enzyme activity [7]. These polymorphisms have variable allele and genotype frequencies among ethnic groups [7,27]. Our study aimed to determine the allelic and genotypic frequency distribution of polymorphisms of rs4880 in the \( \text{SOD2} \) gene and to compare findings with other ethnic groups. The frequencies of C and T alleles were 43% and 57% respectively, whereas the frequencies of the CC, CT and TT genotypes were 17.5%, 50.5%, and 32.0% respectively in the controls respectively. The frequency distributions of C and T alleles were found to be respectively 43% and 57% in the controls (\( \chi^2=18.04, p=0.001 \)) in Table 2. As shown in Figure 1, the analysis of the polymorphisms located at \( \text{SOD2} \) chromosome 6 (6q25) in the controls showed that TT (107 bp), CT (107, 89, 18 bp), CC (89,18 bp) genotypes.

Results
We confirmed the presence of the rs4880 single nucleotide polymorphism in human subjects. The distribution of these polymorphisms was examined using a \( \text{PdiI} \)-RFLP method. In this study, 440 (239 men and 201 women) Turkish individuals were genotyped for polymorphisms of \( \text{SOD2} \) gene. The demographic characteristics of the study population are listed in Table 1. The mean age of the study population was 54.41±5.76 years (males, 55.34±5.76; females, 53.12±7.16) in Table 1. Allele and genotype frequencies of the subjects for rs4880 polymorphism in the \( \text{SOD2} \) gene are shown in Table 2.

All genotypes and alleles in the healthy controls were in Hardy-Weinberg equilibrium (p>0.05). The frequencies of TT, CT, CC genotypes were found to be 32.5%, 50.5% and 17.5% in the controls respectively. The frequency distributions of C and T alleles were found to be

![Figure 1](https://example.com/f1.jpg)

**Figure 1.** PCR-RFLP patterns of polymorphisms of \( \text{SOD2} \) rs4880

M: pUC19/Msp I DNA ladder (501, 489, 404, 331, 242, 190, 147, 111, 110bp); 1, CC (89, 18 bp); 2, CT (107, 89, 18 bp); 3, TT (107 bp); 4, \( \text{SOD2} \) PCR product, 107 bp.

Table 2. Genotype frequencies for \( \text{SOD2} \) rs4880 polymorphism

| SOD2     | Sample size | Percentage | p   | \( \chi^2 \) |
|----------|-------------|------------|-----|-------------|
| Allele frequency |             |            |     |            |
| C allele | 377         | 0.43       | 0.001 | 18.04*      |
| T allele | 503         | 0.57       | 0.465 | 0.534*      |
| Genotype frequency |         |            |     |            |
| CC       | 77          | 17.5       | 0.465 | 0.534*      |
| CT       | 223         | 50.5       | 0.465 | 0.534*      |
| TT       | 140         | 32.0       | 0.465 | 0.534*      |
| CT+TT    | 363         | 82.5       | 0.465 | 0.534*      |
| Total    | 440         | 100        | 0.465 | 0.534*      |

*For one-sample Chi-square \( (\chi^2) \) test with a critical alpha of 0.05 (i.e., \( p<0.05 \)); *For Hardy-Weinberg equilibrium; (1 degree of freedom, \( p<0.05 \) if \( \chi^2 > 3.84 \)).

Sutton et al. found that the C allele (Ala) form of \( \text{SOD2} \)
is targeted into the mitochondria, whereas the T allele (Val) form is partially arrested in the inner mitochondrial membrane. Their study exposed that Ala form of \(SOD2\) was 30% to 40% more efficiently localized to the mitochondria than the Val form. Based on these findings, it is expected that the Val form is likely to be associated with higher levels of ROS and thus predisposes to a greater risk of cancer. On the other hand, various experiments aiming to study association between this polymorphism and different carcinoma reveal a controversial picture. Although few reports find associations between Val form and higher cancer risk, major studies have shown the Ala form to be associated with the risk of different types of cancer (7). Our study, T allele (Val) frequency found more than C allele (Ala) frequency (\(\chi^2=18.04, P=0.001\)) (Table 2). In view of this finding, \(SOD2\) rs4880 polymorphism in Turkish population may pose a risk for some diseases such as cancer. We compared the distribution of three genotypes in different ethnic groups in the world in Table 4. Data presented here show that the Turkish population has the similar CC genotype frequency as seen in African-American [35], Finn [36], and Italian populations [37]. We detected considerably lower CC genotype frequency than those found in Korean [38], Japan [39], Chinese [40] and Taiwan [41] populations and higher frequencies than those found in American [23], Polish [42], Danish [43], German [44] and Russian [45] populations. Eventually, CC genotype frequency in populations of the eastern countries, were lower (between 0-17%) found than the western countries (between 42-67%) (Table 4). CC genotype frequency found in the present study was consistent with the above mentioned situation that the value (17.7%) was between the values of eastern and western populations. CC genotype frequency is between west and east in the Turkish population (17.5%) were identified. Geographical situation confirms this result.

This study provides basic information about the allele and genotype frequency distributions of polymorphisms of rs4880 in the \(SOD2\) gene studied. Our sample size was much larger than those of other studies (in Turkey), which

| Table 3. Distribution of polymorphisms of \(SOD2\) rs4880 genotype frequencies in Turkish population |
|-------------------------------------------------------|-----------------|-----------------|-----------------|-------------------|
| Turkish population | Year | Sample size | \(CC\) (%) | \(CT\) (%) | \(TT\) (%) |
|---------------------|------|-------------|-------------|-------------|-------------|
| Dalan et al.        | 2008 | 51          | 11.7        | 33.3        | 54.9        |
| Atilgan et al.      | 2014 | 50          | 16.0        | 38.0        | 46.0        |
| Gurel et al.        | 2004 | 105         | 16.2        | 43.8        | 40.0        |
| Kadioolu et al.     | 2010 | 40          | 20.0        | 57.5        | 22.5        |
| Akyol et al.        | 2005 | 196         | 23.5        | 42.8        | 34.2        |
| Erbil et al.        | 2008 | 35          | 25.7        | 51.4        | 22.9        |
| Kocabas et al.      | 2005 | 103         | 36.9        | 38.3        | 24.3        |
| This study          | 2014 | 440         | 17.5        | 50.5        | 32.0        |

| Table 4. Distribution of polymorphisms of \(SOD2\) rs4880 genotype frequencies in different populations |
|-------------------------------------------------------|-----------------|-----------------|-----------------|-------------------|
| Country         | Year | Sample size | \(CC\) (%) | \(CT\) (%) | \(TT\) (%) |
|-----------------|------|-------------|-------------|-------------|-------------|
| African, American | 2008 | 331         | 25.2        | 53.7        | 21.1        |
| Finn            | 2002 | 63          | 14.7        | 57.9        | 27.4        |
| Italian         | 2006 | 275         | 24.2        | 48.8        | 27.0        |
| Korean          | 2006 | 106         | 20.3        | 47.9        | 31.7        |
| Japan           | 2007 | 107         | 0.0         | 35.8        | 64.2        |
| Chinese         | 2010 | 1065        | 24.6        | 50.8        | 24.7        |
| Taiwan          | 2007 | 115         | 14.4        | 62.8        | 22.9        |
| American        | 2007 | 395         | 20.0        | 49.1        | 30.9        |
| Polish          | 2005 | 361         | 32.0        | 50.0        | 18.0        |
| Danish          | 2009 | 1650        | 19.0        | 57.1        | 23.9        |
| German          | 2009 | 603         | 17.9        | 60.4        | 21.7        |
| Russian         | 2001 | 88          | 1.9         | 42.4        | 73.9        |
| This study      | 2014 | 440         | 25.0        | 49.8        | 25.2        |
is very important for the making of more precise estimations in epidemiological studies. The results of the present study, in conjunction with the results regarding SOD2 polymorphisms in a Turkish population, provide a framework for further studies concerning the role of this enzyme as a susceptibility many diseases, including certain cancers.

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Conflict of Interest
There are no conflicts of interest among the authors.

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