The Mn-superoxide dismutase single nucleotide polymorphism rs4880 and the glutathione peroxidase 1 single nucleotide polymorphism rs1050450 are associated with aging and longevity in the oldest old

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Abstract

The free radical theory of aging states that reactive oxygen species (ROS) play a key role in age-related accumulation of cellular damage, and consequently influence aging and longevity. Therefore, variation in genes encoding proteins protecting against ROS could be expected to influence variation in aging and life span. The rs4880 and rs1050450 SNPs in the manganese superoxide dismutase (MnSOD) and glutathione peroxidase 1 (GPX1) genes, respectively, are associated with age-related diseases and appear to affect the activities of the encoded variant proteins.

In this study we genotyped these SNPs in 1650 individuals from the Danish 1905 cohort (follow-up time: 1998–2008, age at intake: 92–93 years, number of deaths: 1589 (96.3%)) and investigated the association with aging and longevity. We found decreased mortality of individuals holding either the MnSOD rs4880 C or the GPX1 rs1050450 T alleles (HR (MnSOD(CC/CT)) = 0.91, \(p = 0.001\)) and investigated the association with aging and longevity. We found decreased mortality of individuals holding either the MnSOD rs4880 C or the GPX1 rs1050450 T alleles (HR (MnSOD(CC/CT)) = 0.91, \(p = 0.001\)) and investigated the association with aging and longevity. We found decreased mortality of individuals holding either the MnSOD rs4880 C or the GPX1 rs1050450 T alleles (HR (MnSOD(CC/CT)) = 0.91, \(p = 0.001\)). Finally, moderate positive associations with good self rated health, decreased disability and increased cognitive capacity were observed. Our results thus indicate that genetic variation in MnSOD and GPX1 may be associated with aging and longevity.

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1. Introduction

Genetic factors contribute to the variation in life span by approximately 25\% (Herskind et al., 1996), a contribution believed to be minimal before age 60 years and most profound from age 85 years and onwards (Hjelmborg et al., 2006). The candidate genes encode proteins involved in several biological processes including the protection against oxidative stress (Christensen et al., 2006). Reactive oxygen species (ROS) are produced because approximately 2–3\% of the oxygen atoms taken up by the mitochondria are reduced insufficiently (Valko et al., 2004). ROS can oxidize and damage nucleic acids, proteins and lipids hereby altering their stability and function. Thus, protein modifications (such as protein carbonylation and nitration) and the formation of lipid peroxida-

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localizes both to the mitochondria and in the cytoplasm (Esworthy et al., 1997).

An influence of MnSOD on aging and life span has been observed in several model organisms. Over expression of Sod2 (the MnSOD homologue) leads to increased life span in Drosophila melanogaster (Sun et al., 2002) and in Mus musculus (Hu et al., 2007), while Saccharomyces cerevisiae and D. melanogaster Sod2 null mutants show a decreased life span (Duttaroy et al., 2003; Fabrizio et al., 2003). Sod2 knock out mice display neonatal lethality (Lebovitz et al., 1996; Huang et al., 2002), while mice expressing 50% of the normal Sod2 level have increased susceptibility to oxidative stress, severe mitochondrial dysfunction, cardiomyopathy and degeneration of central nervous system neurons (Van Remmen et al., 2003; Hinerfeld et al., 2004). Gpx1 (the GPX1 mouse homologue) knock out mice on the other hand develop normally, yet show increased sensitivity to oxidative stress-inducing agents and have increased lethality when exposed to high doses (de Haan et al., 1998). In addition, mouse Gpx1−/− cells in culture show senescence-like changes (such as reduced proliferation and DNA synthesis) as compared to Gpx1+/+ cells (de Haan et al., 2004).

The human gene encoding MnSOD is designated SOD2 (http://www.genenames.org/data/hgnic_data.php?hgnc_id=11180) and contains a c.477T-C single nucleotide polymorphism (SNP) (also referred to as rs4880 (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4880)). The SNP results in an alanine substitution and is located within the mitochondrial targeting sequence, correspondingly at position 16 of the precursor protein and position -9 of the processed mature (active) protein (Rosenblum et al., 1996). Hence, the SNP is in the literature also referred to as p.V16A and p.-9V/-9A. The SNP possibly poses an effect on the localization and activity of the variant proteins (Shimoda-Matsubayashi et al., 1996; Sutton et al., 2003). In this paper we will refer to the SNP as the rs4880 MnSOD SNP. The rs4880 MnSOD SNP has been found to be associated with several diseases: the T allele with cardiomyopathy (Hiroi et al., 1999), atherosclerosis (Kakko et al., 2003), and lung cancer (Wang et al., 2001), while the C allele has been associated with breast, prostate and colorectal cancers (Ambrosonne et al., 1999; Stoehlmacher et al., 2002; Woodson et al., 2003), hypertension (Hsueh et al., 2005), sporadic motor neuron disease (Van LanDEgeh et al., 1999), Parkinson's disease (Shimoda-Matsubayashi et al., 1996), and Alzheimer's disease (Wiener et al., 2007).

The human gene encoding GPX1 is designated GPX1 (http://www.genenames.org/data/hgnic_data.php?hgnc_id=4553). GPX1 contains a c.599C>T SNP (previously referred to as c.593C>T), which is also referred to as rs1050450 (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1050450)). The SNP leads to a proline > leucine substitution, hence the SNP is also referred to as p.P200L (however, previously it was referred to as Pro198Leu (see e.g. Moscow et al., 1994)). The SNP likely affects the activity of the variant proteins (Ravn-Hener et al., 2006). In this paper we will refer to the SNP as the rs1050450 GPX1 SNP. The T allele of the rs1050450 GPX1 SNP has been associated with bladder, lung and colorectal cancers (Ambrosone et al., 1999; Van LanDEgeh et al., 1999; Ravn-Hener et al., 2006). The p-values for Hardy–Weinberg disequilibrium were 0.88 for the rs4880 MnSOD SNP and 0.005 for the rs1050450 GPX1 SNP. Compared to a previous study of the rs1050450 GPX1 SNP genotype frequencies in 798 middle-aged Danes, the association of the rs1050450 GPX1 SNP with human survival yet with inconsistent results (De Benedictis et al., 1998; Steßman et al., 2005; Taufet et al., 2005).

The genotype frequencies of the rs4880 MnSOD SNP and of the rs1050450 GPX1 SNP in the Danish 1905 cohort are summarized in Table 1. The allele frequencies for the rs4880 MnSOD SNP were 49.9% for C and 50.1% for T, while for the rs1050450 GPX1 SNP they were 69.1% for C and 30.9% for T, which correspond with previous reports in Caucasians (Ambrosonne et al., 1999; Van LanDEgeh et al., 1999; Ravn-Hener et al., 2006). The p-values for Hardy–Weinberg disequilibrium were 0.08 for the rs4880 MnSOD SNP and 0.005 for the rs1050450 GPX1 SNP. Compared to a previous study of the rs1050450 GPX1 SNP genotype frequencies in 798 middle-aged Danes, the association of the rs1050450 GPX1 SNP with human survival yet with inconsistent results (De Benedictis et al., 1998; Steßman et al., 2005; Taufet et al., 2005).
aged Danes (Raaschou-Nielsen et al., 2007), the frequencies of CC and CT individuals in our 1905 cohort were not significantly different ($p$-value, $P = 0.66$), yet we did observe a slightly lower frequency of TT individuals. Genotype frequencies were not different between males and females ($P(rs4880) = 0.15$, $P(rs1050450) = 0.23$), therefore the combined frequencies were used for the subsequent survival analyses and association studies of the age-related phenotypes.

### 3.2. Longevity

In the 10-year follow-up 1589 individuals out of the 1650 initial individuals died.

The sex adjusted mortality risks were calculated using the Cox proportional hazard model with the most frequent homozygote genotype as the reference group (TT for the rs4880 MnSOD SNP and CC for the rs1050450 GPX1 SNP). The sex adjusted mortality risks according to the rs4880 MnSOD SNP showed a significantly decreased mortality of CT and CC genotype individuals (Hazard ratio, HR (CT) = 0.82; HR (CC) = 0.87), while the sex adjusted mortality risks according to the rs1050450 GPX1 SNP showed decreased mortality of CT and TT individuals (HR (CT) = 0.87; HR (TT) = 0.88, not being statistical significant for TT individuals).

The estimates for the rs4880 MnSOD SNP suggest a dominant effect of the C allele (a survival advantage of CC and CT individuals). Combining the CC and CT genotypes (and comparing to the TT genotype) shows a HR of 0.91 ($P = 0.002$).

With respect to the rs1050450 GPX1 SNP, there seems to be a heterozygote advantage, since there are less homozygotes (both CC and TT individuals) in the 1905 cohort than expected from the allele frequencies (using the Hardy–Weinberg equation). However, deviations from expected frequencies have been reported before for the oldest old (Bathum et al., 1998; Geesaman et al., 2003). In addition, the survival estimates obtained here have the same effect size and indicate a survival advantage of CT and TT individuals in old age, although not significant for the TT genotype. Combining the CC and TT individuals shows a HR of 0.93 ($P = 0.008$). The survival data is summarized in Table 2.

When fitting these sex adjusted mortality risk estimates to their respective Kaplan-Meier Survival estimates, there was good correspondence (data not shown), validating the use of the Cox proportional hazard model. The Kaplan-Meier Survival estimates when combining carriers of the minor allele are shown in Fig. 1.

These survival data indicate that both the rs4880 MnSOD SNP and the rs1050450 GPX1 SNP may be mortality risk factors.

### Table 1

The rs4880 MnSOD SNP and rs1050450 GPX1 SNP genotype frequencies in the Danish 1905 cohort. 1905 cohort: the Danish 1905 cohort.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>284</td>
<td>128</td>
<td>412</td>
<td>539</td>
<td>207</td>
<td>746</td>
</tr>
<tr>
<td>CT</td>
<td>589</td>
<td>233</td>
<td>822</td>
<td>536</td>
<td>201</td>
<td>737</td>
</tr>
<tr>
<td>TT</td>
<td>312</td>
<td>104</td>
<td>416</td>
<td>85</td>
<td>45</td>
<td>130</td>
</tr>
</tbody>
</table>

### Table 2

Mortality risk according to the rs4880 MnSOD SNP genotypes or to the rs1050450 GPX1 SNP genotypes. 1905 cohort: the Danish 1905 cohort. HR: hazard ratio. CI: confidence interval.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>HR</th>
<th>95%CI</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CT</td>
<td>0.82</td>
<td>0.756–0.998</td>
<td>0.048</td>
</tr>
<tr>
<td>CC</td>
<td>0.87</td>
<td>0.727–0.925</td>
<td>0.001</td>
</tr>
<tr>
<td>CC/CT</td>
<td>0.91</td>
<td>0.864–0.967</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype</th>
<th>HR</th>
<th>95%CI</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CT</td>
<td>0.87</td>
<td>0.787–0.968</td>
<td>0.010</td>
</tr>
<tr>
<td>TT</td>
<td>0.88</td>
<td>0.729–1.068</td>
<td>0.202</td>
</tr>
<tr>
<td>TT/CT</td>
<td>0.93</td>
<td>0.889–0.982</td>
<td>0.008</td>
</tr>
</tbody>
</table>

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Fig. 1. Kaplan-Meier Survival estimates for the 1905 cohort by (A) rs4880 MnSOD SNP genotype or by (B) rs1050450 GPX1 SNP genotype. $N$ (MnSOD) = 1650, $N$ (GPX1) = 1613.
3.3. Gender related difference in survival

When looking at males and females separately, it was observed that the effect of the advantageous rs4880 MnSOD and of the rs1050450 GPX1 SNP genotypes on mortality seemed to be most pronounced for males (data not shown). Fig. 2 shows an example of this difference in survival: the Kaplan-Meier Survival estimates for the rs4880 MnSOD SNP CC/CT and TT genotypes for females (Fig. 2A) and males (Fig. 2B) separately. When calculating the HR for the CC/CT genotype it was 0.86 for males ($P = 0.011$, 95% confidence interval (CI): [0.775–0.967], $N = 465$), while it was 0.93 for females ($P = 0.045$, 95% CI: [0.875–0.998], $N = 1185$).

3.4. Synergetic effect of the MnSOD and GPX1 SNPs

Since the MnSOD and GPX1 proteins are involved in the same biological pathway we wanted to investigate a possible synergetic effect of the two SNPs. Hence, the association of the combinations of the rs4880 MnSOD and rs1050450 GPX1 SNP genotypes with survival was investigated. Individuals holding at least one minor allele in both SNPs had a significantly decreased mortality as compared to individuals being homozygous for both the major alleles. The HR was 0.76 ($P = 0.001$, 95% CI: [0.647–0.894], $N = 1613$), indicating that there might be a more than additive effect of holding both the “best survival” alleles as compared to holding both the “worst survival” alleles.

3.5. Moderate effects on aging related phenotypes

The possible associations of the two SNPs to the functional ability and to the cognitive function of the elderly were also investigated.

With respect to self reported health, a lower frequency of CC/CT rs4880 MnSOD individuals reported a “poor/very poor” health (9.02% (CC/CT) versus 13.75% (TT), $N = 1586$, $P = 0.007$). For the rs1050450 GPX1 SNP genotype 11.31% (CC), 9.31% (CT) and 11.11% (TT) (combined CT/TT: 9.58%) reported a “poor/very poor” health ($N = 1551$, $P = 0.446$) When applying the Activity of Daily Living (ADL) strength score, the rs4880 MnSOD SNP CC/CT genotype showed a positive (although not statistical significant) sex adjusted coefficient of 0.0359 ($P = 0.296$, 95%CI = [−0.0189–0.0622], $N = 1633$). With respect to the rs1050450 GPX SNP, a positive statistical significant sex adjusted coefficient of 0.0783 ($P = 0.039$, 95%CI = [0.0039–0.1528], $N = 726$) was found for the CT genotype, while a positive but non-significant coefficient of 0.0359 ($P = 0.605$, 95% CI = [−0.1001–0.1719], $N = 129$) was found for the TT genotype. The combined CT/TT group showed a statistical significant coefficient of 0.0216 ($P = 0.049$, 95%CI = [0.0002–0.0717], $N = 1596$). Still, a moderate increased ADL score may indicate that the individuals holding the genotypes associated with decreased mortality tended to be less disabled, which corresponds well with a tendency of a better self reported health.

Finally, the MMSE criteria showed a positive coefficient for the rs4880 MnSOD SNP CC/CT group; sex adjusted coefficient CC/CT = 0.404 ($P = 0.015$, 95% CI = [0.079–0.729], $N = 1582$). With respect to the rs1050450 GPX1 SNP, a coefficient of 0.307 ($P = 0.309$, 95%CI = [−0.2855–0.9001], $N = 708$) for the CT genotype and a coefficient of −0.267 ($P = 0.627$, 95%CI = [−1.3484–0.8131], $N = 126$) for the TT genotype were found. Nevertheless, a moderate increased MMSE for the rs4880 MnSOD SNP genotype individuals indicates a moderate increased cognitive function of the individuals holding the genotypes associated with decreased mortality.

4. Discussion

In this paper we show associations of the rs4880 MnSOD SNP and of the rs1050450 GPX1 SNP with longevity, indicating that variation in the genes encoding MnSOD and GPX1 may influence the variation in human life span. Due to minimal immigration into the Danish 1905 cohort, population stratification is minimized, hence, the cohort must be considered to be genetically homogenous.

Previously, three cross sectional studies have been published on the role of the rs4880 MnSOD SNP in human survival or longevity. Tauerf et al. (2005) did not find an association with survival from newborn ($N = 65$), to age 21–79 years ($N = 296$) or to age 80–105 years ($N = 75$) in individuals of mixed European Caucasian and native South American origin. De Benedictis et al. (1998) did not find an association with survival from newborn to age 90 years ($N = 455$) while they found a positive association with the rs4880 MnSOD SNP CT genotype in centenarians and controls split according to their geographical origin (northern or southern Italy) the results were not statistically significant. However, based on their geographical origin (northern or southern Italy) the hypothesis that the rs4880 MnSOD SNP CT genotype may be associated with longevity was supported.
mitochondrial DNA lineage studies previously showed homo-
genous miscenagenation (Parra et al., 2003). Finally, since the two
studies are cross sectional, it cannot be excluded that cohort
specific variation in environment may introduce bias.

One study indicated an association of the T allele with survival
from age 22 (N = 441) to age 75 (N = 224) (Stessman et al., 2005).
An increase in T allele frequency from 33% to 51% and an increase
of TT homozygotes (from 25% to 45.5%) were here observed in an
Israeli (Ashkenazi) population. These results are somehow contra-
dictory to our results, yet there are several possible explanations
for this inconsistency. Firstly, an association of the rs4880 MnSOD
SNP with survival may differ between populations (Israeli versus
Danes); secondly, the role of rs4880 MnSOD genotype (and hence
possibly activity (see below)) may be of different importance at
different ages (22–75 years versus 92–100+) and finally, the
difference in study design (cross sectional versus longitudinal)
may be of importance.

When looking at the possible functional basis of the observed
association of the rs4880 MnSOD SNP genotype with longevity,
several experiments support such an association. The SNP is
located in the mitochondrial targeting signal leading to disruption
of its helical structure in the 16Valine(T) variant protein (Shimoda-
Matsubayashi et al., 1996). By using purified rat liver mitochondria,
Sutton et al. (2003) showed that this disruption hampers the
transport of the protein into the mitochondrial matrix; about 35% of
(recombinant) 16Valine(T) proteins are arrested in the inner
mitochondrial membrane, as compared to only 8% of the
16Alanine(C) proteins. In the matrix the mitochondrial targeting
signal is cleaved off generating the active protein (Matsuda et al.,
1990). This processing is hampered for the 16Valine(T) variant,
since it generates 29% less processed protein than the 16Alanine(C)
variant and the activity of the 16Valine(T) variant is 23% less than
the 16Alanine(C) variant (Sutton et al., 2003). A hampered
processing of the 16Valine(T) variant has also been found by
Hiroi et al. (1999). Sutton et al. later confirmed their data in a
human in vivo system (hepatoma cells transfected with construct
carrying either genotype); in 16Alanine(C) variant cells the levels
of processed protein and the activity were four fold higher than in
16Valine(T) variant cells. Also, the $O_2^\cdot$ level in 16Alanine(C) cells
was 60% lower than in 16Valine(T) cells (Sutton et al., 2005).

These results indicate that the genetic variation in the rs4880
MnSOD SNP might lead to difference in MnSOD activity in the
matrix and hence to difference in oxidant–antioxidant balance. CC
(alanine–alanine) and CT (alanine–valine) individuals would likely
hold a higher MnSOD activity (than TT (valine–valine) individuals)
and hence to difference in oxidant–antioxidant balance. CC
MnSOD SNP might lead to difference in MnSOD activity in the
mitochondrial extracts (Bastaki et al.: 102 males and 129 females and
Elsakka et al.: 20 individuals). Moreover, when measuring the MnSOD
activity in mitochondrial extracts the genetic background of the
individuals can influence the activity; hence the difference in results may
simply be due to difference in genetic background of the study
populations. In any case does the study by Bastaki et al. show the
opposite as Sutton et al. However, Sutton et al. did use a cellular
system only differing in the rs4880 MnSOD SNP, excluding
influence from difference in genetic background. Yet, the in vivo
data obtained by Sutton et al. remains to be confirmed in a separate
study.

We report for the first time an association of the rs1050450
GPX1 SNP with longevity. The rs1050450 GPX1 SNP genotype
frequencies in the 1905 cohort deviate from the once expected
from the observed allele frequencies. However, as previously
mentioned, such deviations have been reported before for SNP
genotype frequencies in populations of the oldest old (Bathum
et al., 1998; Geesaman et al., 2003). A deviation might indicate that
there is a selection with respect to the rs1050450 GPX1 SNP
genotypes up until old age (the 1905 cohort members were age 92–
93 when they entered the survey, an age at which individuals can
be said to be cases of extreme survival). Furthermore, the survival
estimates obtained here have the same effect size and indicate a
survival advantage of CT and TT individuals in old age, although not
significant for the TT genotype.

Compared to a cohort of middle aged Danes (Raaschou-Nielsen
et al., 2007), we find a slightly lower frequency of TT individuals.
This might indicate an antagonistic pleiotropic effect of the SNP in
Danes; TT individuals might have an increased mortality from
middle age to very old age (as compared to CC and CT individuals),
whereas in very old age TT individuals have a survival advantage.
On the other hand, the deviation in TT individuals may simply be a
chance observation.

Three studies measuring the GPX1 activity (with respect to the
rs1050450 GPX1 SNP) in human erythrocyte extracts have been
reported; the activity of CT/TT extracts was found to be 9% lower
than the activity of CC extracts (Ravn-Haren et al., 2006) and the
activity was 13% lower in TT males as compared to CT/CC males
(Bastaki et al., 2006), while Forsberg et al. (2000) detected no
difference. Hence, it might be that the rs1050450 GPX1 SNP
genotypes (CT and TT) we find to be associated with decreased
mortality in the oldest old may be the variant holding slightly
lower activity. This seems somehow contradictory to the idea that
efficient antioxidant enzyme activity contributes to reduced
mortality. However, oxidative stress is believed also to have
beneficial effects; moderate levels of ROS or a temporary increase
in ROS levels have positive effects on cellular homeostasis (Droge,
2002; Radak et al., 2008). Hence, there is probably a delicate
balance between the advantageous and disadvantageous effects of
ROS, and the relation between ROS and life span is probably not as
straight forward as low ROS levels (possibly ensured by efficient
antioxidant enzymes) equaling increased life span. Finally, a
slightly more active GPX1 could lead to increased OH$^-$ levels due to
decreased levels of reduced glutathione. Therefore, it can not be
excluded that a slight decrease in GPX1 activity (in the TT and CT
rs1050450 GPX1 SNP genotypes) could have a positive effect on
longevity.

We observe a difference between genders in the effects of
genotypes on mortality; the effects are apparently more pro-
nounced in males. Bastaki et al. (2006) observed a 16% decreased
MnSOD activity in males as compared to females. Since the
proposed hampering of the T variant is only partial and if women in
general hold a slightly higher MnSOD activity, it can be speculated
that the MnSOD activity in female TT individuals could reach a
threshold of activity enabling them to overcome (at least in part) the
oxidative stress, perhaps resulting in a less severe effect of the
increased mortality in TT genotype individuals observed in our
study. For GPX1 the activity in males also appear to be lower than
in females; Bastaki et al. (2006) reported it to be 7.7% lower,
whereas Blankenberg measured a 5% difference (Blankenberg et al.,
such a difference may explain the less severe effect of the CC rs1050450 GPX1 genotype in females.

We observe a synergy effect in individuals holding both the CC or CT or rs4880 MnSOD genotypes and the TT or CT rs1050450 GPX1 genotypes, indicating that this genetic combination may influence human longevity in a positive direction. A synergy effect of the rs4880 MnSOD and rs1050450 GPX1 SNP genotypes has been reported once before; Cox et al. (2006) observed no association on Aging (P01 AG08761-18). The Danish Aging Research Center is supported by a grant from the VELUX Foundation (95-103-11419).


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