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Association of *CAT* polymorphisms with catalase activity and exposure to environmental oxidative stimuli

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Abstract

We tested the hypotheses that catalase activity is modified by *CAT* single nucleotide polymorphisms (SNPs) (-262;-844), and by their interactions with oxidant exposures (coal dusts, smoking), lymphotoxin alpha (*LTA*, *Nco* I) and tumor necrosis factor (*TNF*, -308) in 196 miners. Erythrocyte catalase, superoxide dismutase, and glutathione peroxidase activities were measured. The *CAT*-262 SNP was related to lower catalase activity (104, 87 and 72 k/g hemoglobin for CC, CT and TT, respectively, $p < 0.0001$). Regardless of *CAT* SNPs, the *LTA Nco* I but not the *TNF*-308 SNP was associated with catalase activity ($p = 0.04$ and $p = 0.8$). *CAT* -262 T carriers were less frequent in highly exposed miners (OR = 0.39 [0.20–0.78], $p = 0.007$). In *CAT*-262 T carriers only, catalase activity decreased with high dust exposure ($p = 0.01$). Haplotype analyses (combined *CAT* SNPs) confirm these results. Results show that *CAT*-262 and *LTA Nco* I SNPs, and interaction with coal dust exposure, influenced catalase activity.

Keywords: *Catalase, polymorphism, coal dust, lymphotoxin, tumor necrosis factor, catalase by environment interaction*

Introduction

Interest in potential genetic variants in antioxidant pathways and disease progression has increased [1–7]. The first line of cellular defense against reactive oxygen species (ROS) is through superoxide dismutase (E.C.1.15.1.1, superoxide dismutase [Cu–Zn]) which produces hydrogen peroxide (H_2O_2) [4], and through catalase (E.C.1.11.1.6, catalase) and glutathione peroxidase (E.C.1.11.1.9, cellular glutathione peroxidase) which metabolize H_2O_2 [8]. It has been demonstrated that erythrocyte catalase has an almost exclusive role in the removal of H_2O_2 [9]. Associations with diabetes [10] and arsenic-induced hyperkeratosis [11] are consistent with a potential important role of *CAT* polymorphisms for late-onset diseases, in which direct (from environment) or indirect (from inflammatory cells) sources of oxidants could play a role. Studies on changes in homocysteine, lipid peroxidation and carbohydrate metabolism in families of catalase deficient patients [12,13] further support the potential role of *CAT* polymorphisms and catalase activity in the development of oxidative stress-mediated diseases. However, few studies have specifically investigated associations of *CAT* polymorphisms with diseases [14]; only one study has attempted to assign functional relevance of a *CAT* polymorphism with enzyme levels [15], and none of the studies considered simultaneously exposure to environmental oxidative stimuli.

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Common environmental oxidative stimuli include air pollutants (i.e. ozone and particles) and tobacco smoke. Chronic inhalation of coal dusts produces ROS, indirectly from activated inflammatory cells such as macrophages and polymorphonuclear leucocytes, and directly from coal dusts themselves [16]. Exposure to coal mine dust particles also produces H_2O_2 [16], and activity of erythrocyte catalase was increased in relation to coal dust exposure [17,18]. In a conceptual temporal sequence [19] from environment and genetic background towards disease, catalase activity may be an early pathological sign and low-level intermediate phenotype [20] of biological importance in the response to environmental oxidative stimuli. Oxidative stress is implicated in the aetiology of environmental and occupational chronic lung diseases in association with inflammation through upregulation of redox-sensitive transcription factors, and proinflammatory and antioxidant genes [21].

We previously found associations of single nucleotide polymorphism (SNP) in pro-inflammatory genes tumor necrosis factor (*TNF*) and lymphotoxin alpha (*LTA*) with erythrocyte catalase activity, and with disease prevalence in miners with low catalase activity, respectively [22]. In the present study, we tested the hypothesis that erythrocyte catalase activity is influenced by *CAT* SNPs (T-844C and C-262T) and by their interactions with oxidant exposures (coal dust and tobacco smoke). We also tested whether catalase activity is modified by interaction of *CAT* -844 and -262 with *TNF* and *LTA* SNPs. Strengths of the study were the contrasted exposure to oxidants by design in the study sample, the availability of objective measurements of coal dust exposure, and quantitative phenotypes to assess response to oxidative stimuli with one being the activity of the product of the gene studied.

Methods

Study sample

The population studied consisted of 240 unrelated coal miners recruited through a standardized protocol in a French coal mine (Houillères du Bassin de Lorraine, in north eastern France) based on a selection contrasted by exposure and disease status [22]. Miners (aged 34–50 years in 1990) were re-examined in 1994 and 1999.

Our study sample was composed of the 196 miners examined in 1994 for whom genetic, biological and environmental data were available. Comparison of the 196 miners with those not included in the analyses ($n = 44$) did not show differences regarding genotype, exposure, and biology. The appropriate ethical committee approved the study and written consent was obtained from all subjects.

Environment

Smoking history and detailed information on current and life-long coal dust exposure were recorded. Low or high current dust exposure based on job description, and cumulative personal exposure estimated from each person's job history and from dust measurements at various sites of the mine were recorded. High current exposure refers to miners working at the coal face, mining, stope or drift advance; low exposure refers to those working at ventilation maintenance, pumping, haulage, shaft, stock equipment, or safety. Cumulative personal exposure to dust was expressed as mg/m^3 for the respective time spent in each job (x year) [23].

Biological responses to oxidative stimuli

Erythrocyte catalase, Cu^{++}/Zn^{++} superoxide dismutase, and glutathione peroxidase activities were determined at the 1994 survey as previously described [18]. Briefly, blood samples were collected into 5 ml Vacutainer tubes containing lithium heparinate (Becton Dickinson, USA). On the same day, corresponding plasma and hemolysates were prepared and stored at $-35°C$, and analyzed in the two weeks following storage.

Catalase activity was determined at 25°C according to the method of Aebi [24], and activity of 1 K was defined as the rate constant of the first order reaction. The Cu^{++}/Zn^{++} superoxide dismutase activity was measured as previously described [18], and adapted for a Cobas-Mira S analyser (Hoffman-La Roche, Basle, Switzerland). Human erythrocyte superoxide dismutase was used as a standard. Glutathione peroxidase activity was measured as previously described [18] using a Cobas-Mira S analyser.

Activities were expressed as U/g hemoglobin (Hb) (Cu^{++}/Zn^{++} superoxide dismutase, glutathione peroxidase) or k/g Hb (catalase). Samples were analyzed in duplicate or triplicate and the precision (coefficient of variation) was $<10\%$ for each enzymatic assay. The accuracy was checked by analyzing external reference samples together with the test samples.

Genotyping procedures

Genomic DNA was isolated as previously described [22]. *CAT* C-262T was amplified utilizing the Fail-safe PCR system (Epicentre, Madison, WI) with buffer D and primers designed by Forsberg et al. [15]. PCR products were digested with *Sma*I at 25°C for 2 h, electrophoresed on 2% agarose gels stained with ethidium bromide and visualized on a GelDoc 2000 (BioRad, Hercules, CA). The *CAT* T-844C SNP reported by Jiang et al. [25] was genotyped by allelic discrimination using TaqMan probes (Applied Biosystems, Foster City, CA). Reactions consisted of 900 nM primer F (tactcttcaacatagctttttaaagacaca),

900 nM primer R (aattggcttctttaaacactggagaa), 200 nM Vic-labeled probe C (aaattttacCcccaggtaa), 200 nM 6Fam-labeled probe T (caaattttacTcccaggtaa), 1x Universal PCR Mastermix, no AmpErase UNG (Applied Biosystems), and 20 ng genomic DNA. Amplification was performed in a GeneAmp 9700 PCR machine (Applied Biosystems) with conditions consisting of 95°C for 10 min and 50 cycles of 95°C for 15 s and 60°C for 1 min. Fluorescence was captured by post-amplification plate read in the Prism 7000 sequence detection system (Applied Biosystems) and genotypes were determined by manual clustering. The A to G polymorphism at position -308 within *TNF* and the *Nco*I RFLP within the first intron of *LTA* were analyzed as previously described [22].

Statistical methods

Analyses of qualitative variables were performed with χ^2 (or Fisher exact test when appropriate). Analyses of variance, and multiple regression analyses were performed for quantitative variables using SAS statistical software. Significance was assessed at the 5% two-sided level. All analyses were conducted considering each *CAT* SNP separately and combined (haplotypes). Haplotype analysis was performed using a maximum likelihood method for haplotype-phenotype association as implemented in the THESIAS program (http://www.genecanvas.ecgene.net/) [26]. The most frequent haplotype was used as the referent.

Results

CAT genotype distributions

The main characteristics of the miners are presented in Table I. Genotype distributions for *CAT* -262 and -844 SNPs fit predictions for Hardy-Weinberg equilibrium ($p = 0.07$ and 0.8, respectively). *CAT* -262 and -844 genotypes were in complete linkage disequilibrium, and 3 haplotypes were found: *CAT* -262C/-844T (43.1%), *CAT* -262C/-844C (33.7%) and *CAT*-262T/-844T (23.2%).

CAT genotypes and catalase activity

The *CAT*-262 SNP was significantly associated with erythrocyte catalase activity; the lowest activity was found in miners with the *CAT* -262 TT genotype (Table II). Among miners with the *CAT* -262 CC genotype, we also found a significant association of the *CAT* -844 genotype with low catalase activity (114 ± 38, 104 ± 22 and 91 ± 22 k/g Hb in miners with *CAT* -844 TT, TC and CC, respectively; $p = 0.01$). Analysis with a multivariate linear regression model confirmed that *CAT* -262 and *CAT* -844 SNPs were significantly associated with catalase activity ($p < 0.0001$ and 0.04, respectively).

Table I. Characteristics of the 196 coal miners in 1994.

	Value*
Age (years, mean (SD))	46.7 (3.5)
Smoking habits	
Non-smokers	39 (19.9)
Ex-smokers	60 (30.6)
Current smokers	97 (49.5)
Pack-years (mean (SD))	17.1 (15.1)
Coal dust exposure	
None (retirement) or low	142 (72.5)
High	54 (27.5)
Cumulative dust exposure (mg/m^3 *x* year, mean (SD))	57.8 (42.4)
Geographical origin	
France	134 (68.4)
Other European countries	59 (30.1)
North Africa	3 (1.5)
TNF -308 genotype	
AA	144 (74.6)†
AG	48 (24.9)
GG	1 (0.5)
*LTA Nco*I genotype	
B1B1	16 (8.2)‡
B1B2	87 (44.4)
B2B2	93 (47.4)
Chest *x* ray grade	
0/0	146 (74.5)
0/1 or 1/0	44 (22.4)
1/1 or over	6 (3.1)

*Unless otherwise stated, values are frequency (%). †Hardy-Weinberg equilibrium $p = 0.15$. ‡Hardy-Weinberg equilibrium $p = 0.7$.

Haplotype analyses showed that mean [95% confidence interval] catalase activity was significantly decreased in *CAT* -262T/-844T (−19.98 k/g Hb, [−27.90; − 12.05], $p = 10^{-6}$) and *CAT*-262C/-844C (−6.71 k/g Hb, [−13.21; − 0.20], $p = 0.04$) haplotypes as compared to the referent *CAT*-262C/-844T. *CAT* -262 and -844 genotypes, and *CAT* haplotypes were not related to superoxide dismutase or glutathione peroxidase activities.

Change in catalase activity according to TNF, LTA and CAT genotypes

The *LTA Nco*I but not the *TNF* -308 SNP was significantly associated with catalase activity in a multivariate linear regression model including the *CAT* SNPs (Table III). No interaction of *CAT* SNPs with *LTA Nco*I or *TNF* -308 SNPs on catalase activity was found (data not shown).

Association of catalase activity with coal mine dust and smoking exposures according to CAT genotype

The *CAT*-262 CT or TT genotype was associated with a lower frequency of miners with high current exposure as compared to the *CAT*-262 CC genotype

Table II. Associations of *CAT*-262 and *CAT*-844 polymorphisms with erythrocyte antioxidant enzyme activities.

		CAT-262				*CAT*-844			
	All	CC	CT	TT	*P* Value	TT	TC	CC	*P* Value
n	196	111	79	6		87	86	23	
Catalase (k/g Hb)	97 ± 30	104 ± 29	87 ± 30	72 ± 11	<0.0001	96 ± 33	99 ± 29	91 ± 22	0.5
Cu^{++}/Zn^{++} superoxide dismutase (U/g Hb)	146 ± 32	147 ± 33	145 ± 32	140 ± 19	0.8	145 ± 28	148 ± 36	144 ± 32	0.8
Glutathione peroxidase (U/g Hb)	40.5 ± 13.4	40.2 ± 14.4	41.0 ± 11.9	40.3 ± 14.6	0.9	39.4 ± 13.6	41.2 ± 11.9	41.9 ± 17.7	0.6

Results are expressed as mean ± SD.

(27.8 vs. 49.3% $p = 0.007$, OR = 0.39 [0.20–0.78]). No association of *CAT* genotypes or haplotypes with cumulative dust exposure was found. No association of *CAT*-844 genotype with current or cumulative coal dust exposure was found. Age and smoking expressed as current or pack-years were unrelated to *CAT* genotypes or haplotypes (data not shown).

In miners with the *CAT*-262 CT or TT genotype (those with the lowest catalase activity), catalase activity was significantly lower in those with high exposure to coal mine dusts (Figure 1). By contrast, in miners with CC genotype, no difference was found in catalase activity between miners with high exposure and those with no or low exposure. No association was found between *CAT* -262 genotype and catalase activity according to smoking habits (data not shown). No interaction of *CAT* -844 genotype with coal dust or smoking exposure on catalase activity was found (data not shown).

Results were unchanged when: (1) considering each *CAT* SNP separately and combined (haplotypes); (2) when excluding 6 miners who developed pneumoconiosis between 1990 and 1994; (3) when excluding miners with outlier values for catalase activity (303 and 254 k/g Hb); and (4) when excluding 3 miners born in North Africa.

Discussion

Our study found associations of *CAT* -262 and to a lesser extent -844 SNPs, *CAT* -262C/-844C, and *CAT* -262T/-844T haplotypes, with low catalase activity. The -844 C allele was not associated with higher catalase activity although it is in complete linkage disequilibrium with the -262 C allele. A possible explanation for this finding is that regulation of enzyme activity depends on interaction between these promoter sites (i.e. the -844 promoter site is dependent on -262). However, further research is necessary to confirm this possibility. In contrast to our findings, the *CAT* C-262T polymorphism was previously shown to confer higher enzyme levels in erythrocytes of 29 Swedish men [15]. The reason for this discrepancy needs further study, but one difference is that catalase activity was measured in the present study whereas, immunoreactive protein was determined in the study of Forsberg et al. [15]. Catalase that is immunologically reactive but enzymatically inactive may partly account for this difference, as it was previously reported in normal, hypocatalasic and acatalasemic human erythrocytes by Shibata et al. [27]. It is also possible that, in addition to enzymatically active tetramers, immunologically reactive, but enzymatically inactive dimers and monomers of catalase found in normal erythrocytes may explain the difference between studies [28].

We previously found, with the same study sample (i.e. including the outliers), that *TNF* -308 and *LTA Nco* I SNPs were associated with catalase activity [22]. In the present study, regardless of the *CAT*-262 SNP, we found that the *LTA Nco* I polymorphism was always associated with catalase activity, whereas the *TNF*-308 SNP was not. Association between *CAT*-262 CC and *TNF* -308 genotypes was found and could explain the previous association. Frequencies of the *CAT*-262 CC genotype (the highest catalase activity) with respect to *TNF* -308 genotype were 53.1, 66.0 and 100.0% in AA, AG and GG, respectively. A similar association was not found among *LTA* NcoI genotype, where the frequency of *CAT*-262 CC genotype was around 60% (from 56.0 to 62.5%). We speculate that the mechanism of regulation of catalase by *LTA* could be through the activation of specific pathways involving the nuclear factor-κB [29], and subsequently through the initiation of transcription in the catalase gene [30]. Further studies are needed to confirm the association of *LTA Nco* I with catalase activity, but the present investigation suggests that genes other than *CAT* may be involved in catalase regulation.

We found that *CAT* -262 CT or TT genotype and *CAT*-262T/*CAT*-844T haplotype associated with a low frequency of miners with high coal dust exposure. This association did not change when analyses were done without miners born in North Africa. Genotype and allele frequencies reported in our study were similar to those reported previously in Bangladesh, Caucasian or Chinese populations [11,15,25,32–34], suggesting that results are not due to a particular characteristic of our population.

Table III. Multiple linear regression of catalase activity on *CAT*-262, *CAT*-844, *LTA Nco*I and *TNF*-308 polymorphisms.

Genotypes	N	Catalase activity (k/g Hb)*	Coefficient	(95% Confidence Interval)	*P* Value
CAT-262			19.33	10.78–27.88	<0.0001
CC	111	105			
CT or TT	85	86			
CAT-844			3.72	−4.75–12.19	0.4
TT	87	96			
TC or CC	109	97			
*LTA Nco*I			10.11	0.52–19.69	0.04
B1B1 or B1B2	103	101			
B2B2	93	91			
TNF-308			1.33	−9.66–12.32	0.8
AA	145	95			
AG or GG	51	102			

* Adjusted means.

The age at retirement and respiratory symptoms or lung function, which could influence the change in exposure during the follow-up, did not explain further the association of *CAT*-262 SNP with current coal dust exposure. We suggest that health consequence of low catalase activity, which is *a priori* less protective, may have led miners to leave a high exposure work place, but this must be confirmed. The present study also found that high dust exposure was associated with decreased catalase activity in miners with at least one *CAT*-262 T allele (i.e. genetically low catalase activity). We hypothesized that high production of H_2O_2 may overwhelm the capacity of the enzyme and may reversibly inhibit or irreversibly inactivate it as previously found [31]. Unfortunatly, due to the relatively small sample size, our study precludes detailed analyses to address simultaneously all environmental and genetic factors.

Results from association studies between *CAT*-262 SNP and disease outcomes are discordant. In a study of arsenic-induced hyperkeratosis [11], a significantly increased risk was found for *CAT*-262 T carriers with high exposure to arsenic as compared to miners with the *CAT*-262 CC genotype and low arsenic exposure. A higher frequency of diabetes was reported in Hungarian catalase deficient patients than in unaffected first-degree relatives and the general population [10]. No association was found between the *CAT*-262 SNP and Alzheimer's disease [32], or other oxidative stress-mediated disorders [33]. In a case-control and family study, Christiakov et al. found that the *CAT*-262 CC genotype was significantly associated with increased risk of the development of type 1 diabetes in a Russian population [34]. Distinct biological pathways during disease pathogenesis or differences in the magnitude or window of exposure may partly explain these discrepancies.

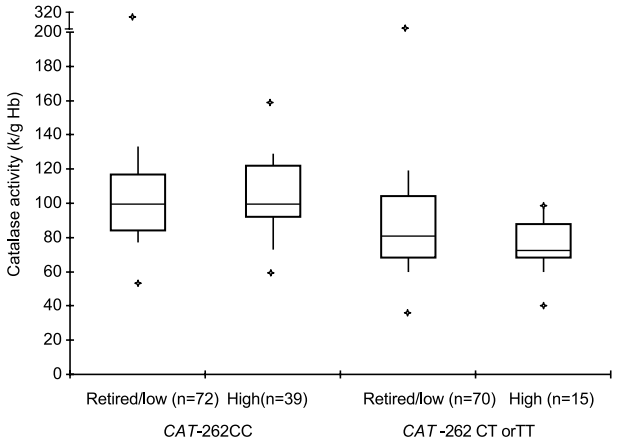

Figure 1. Box plots of catalase activity according to current exposure to dusts and to *CAT*-262 genotype. Box plots show the median (bar), the first and third quartile (box), the first and last decile (fences) and the minimum and maximum (stars) for each category. Numbers of miners in each group are shown below each bar. Means of catalase activities are 104 vs. 105 k/g Hb for *CAT* CC ($p = 0.8$), and 89 vs. 75 k/g Hb for *CAT* CT/TT ($p = 0.01$, interaction test $p = 0.13$).

In summary, we found that the *CAT*-262 and *LTA Nco*I SNPs, and interaction of the *CAT*-262 SNP with coal dust exposure, significantly influenced erythrocyte catalase activity. While results need to be confirmed in larger samples and further studies conducted to assess the role of the *CAT*-262 SNP as a functional variant, this study indicates the importance of considering measurement of enzyme activity when attempting to determine the role of SNPs in antioxidant enzyme genes.

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