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Are the Catalase Gene Mutations Responsible for the Decreased Blood Catalase Activity?

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1. INTRODUCTION

The enzyme catalase (EC 1.11.1.6) decomposes the toxic concentration of hydrogen peroxide. It is in excessive concentration may cause damages to proteins, DNA, RNA and lipids while its low concentration is required in signaling processes.

Acatalasemia, the inherited deficiency of catalase enzyme seems to be a factor in various age related disorders such as diabetes mellitus, arteriosclerosis, schizophrenia, and vitiligo [1].

Erythrocytes are responsible for more than 98 per cent of blood catalase. Blood catalase activity could be measured with a simple photometric assay. Its reference range is 82-144 MU/L (n:1756). Due to the high activity of catalase in erythrocytes its activity is given in M (Mega: 10^6) Units/L of blood [2].

A previous study of 25 252 hospitalized patients yielded decreased (bellow the reference range) blood catalase activities in 2 884 (11.4 %) anemic patients, in 130 (0.5%) patients with different tumors, in 1 237 (4,9%) patients with atherosclerosis, and in 275 (1.1%) patients with schizophrenia. The decreased blood catalase could be attributed to the low number of erythrocytes in the anemic patients and partly in those with tumors. Genetic or regulatory factors could be responsible for the other 1642 (36.3%) cases [3].

Table1. *Blood catalase activities and catalase gene mutations in diseases with decreased blood catalase activities[4,5]*

Disease	n	Blood	catalase	activity	MU/l
		Mean±SD	<reference range	< 50 %	Mutation(n)
beta-thalassemia	43	85±13	19 (44.2%)	9 (20.9%)	
Microcytic anemia	58	90±31	25 (43.1%)	8 (13.8%)	G1(1), H1(1)
Type 1 diabetes	115	101±21	16 (13.9 %)	1 (0.8%)	
Type 2 diabetes	225	90±24	36 (16.0%)	11 (4.9%)	G1(1), H1(1), H2(1),H3(1)
Presbycusis	136	78±31	40 (31.7%)	21(16.7%)	
Vitiligo	78	98±18	8 (10.3%)	2 (2.6%)	E(1)
Control	245	104±15	1 (0.3%)	0 (0.0%)	
All patients	655		145	52	
G1:c.106.107insC					
H1: 379C□ T, H2:390C□ T					
H3:431A□ T,E:c.37C□ T					

In another study including 295 controls and 655 hospitalized patients (type 1 diabetes mellitus: 115, type 2 diabetes mellitus: 225, beta-thalassemia: 43, microcytic anemia: 58, presbycusis: 136, vitiligo: 78) were examined for blood catalase activity [4,5]. Of 144 (22.1%) patients and 1(0.3%) control had their blood catalase activities bellow the reference range. Furthermore, 52 (7.9%) patients yielded their blood catalase activity less than 50 % of the reference mean. For these patients all exons and partly of the exon-intron boundaries of the catalase gene were examined for catalase gene mutations. Their genomic DNA were screened with PCR-SSCP (Single Strand Conformational Polymorphism) and PCR-heteroduplex analyses and the polymorphisms detected were identified with nucleotide sequencing method. Finally, when the effect of this polymorphisms on the catalase activity was verified it was registered as an acatalasemic mutation. This study resulted four novel catalase exon

mutations (Table 1). These mutations were detected in seven patients (13.7%) of 52 patients that had less than 50% of blood catalase [4].

For detection of acatalasemia different methods of blood catalase activity were used for screening. These screening methods yielded 125 cases of acatalasemia in 61 families from 11 countries. Contrary, only 14 acatalasemic mutations (eleven in exons, three in introns) were reported. The genetically identified acatalasemic mutation were detected in Japan (A and B forms), in North America and from Hungary as A,B,C,D,E,F,G,G1,H,H1,H2,H3 forms [1,4]. The blood catalase activities of acatalasemic (homozygote) patients were less than 10 % and it was about 50 % for the heterozygotes. The frequency of actalasemia is about 0.04/1000 in Switzerland, 0.08/1000 in Japan and 0.05/1000 in Hungary [6].

These findings challenge further questions to be answered or to initiate further research.

a. The low (0-10%) blood catalase activity of the acatalasemic homozygotes.

For its explanation it may be supposed that the blood components which could be oxidized and peroxide removal enzymes (peroxiredoxin, glutathion peroxidase) that may use hydrogen peroxide also consume the catalase substrate [7]. Thus, the decrease in hydrogen peroxide could be higher than those which was consumed by catalase and used for calculation of catalase activity.

b. The low (14, 11.2%) rate of the known acatalasemic mutations for the 125 acatalasemic patients. Furtermore, the low (13.7%) ratio of exonic/intronic mutations in patients with less than half of the normal blood catalase activities.

Apart from the known acatalasemic mutations the decrease in blood catalase activity might be due to further acatalasemic mutations, DNA polymorphisms in the non coding regions (introns, 5' UTR and 3' UTR) of the catalase gene. Furthermore, other regulatory mechanism such as epigenetic modifications (DNA methylation, histone acethylation/methylation, micro RNAs) could also contribute to the decrease in blood catalase activity.

Two recent papers may predict the ongoing research for solving of these problems.

Glorieux C. et al. in their review reported that the core promoter of the catalase gene has binding sites for transcription factors like NF-Y, Sp1, FoxO3a, and PPARγ, Oct-1. They may play an essential role in the regulation of catalase expression [8].

Dawson NJ. and Storey KB. found that wood frog catalase could be activated by phosphorylation of serine and thyrosine of the catalase protein. They are suggesting that researchers should explore the activation of catalase enzyme by phosphorylation in other catalases especially in human catalase enzyme [9].

2. CONCLUSION

The known catalase gene mutations could explain less than 20 % of the cases of the decreased blood catalase activities. Further research could concentrate on the examination of the non coding regions of catalase gene and its regulatory mechanisms.

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AUTHORS' BIOGRAPHY

Laszlo Goth, received master degree from University of Veszprem in 1967, PhD from Veszprem University in 1971, Candidate of Science in 1985, and Doctor of Science in 2006 from Hungarian Academy of Science. He worked as professor for University of Debrecen, Hungary. He thought clinical chemistry in training programs for clinical laboratory scientists. He is serving as an expert reviewer and editorial member of several reputed journals. He has authored more than 109 research articles including Clinical Chemistry (9) and Clinica Chimica Acta (8).

His research is focused on the clinical chemistry and molecular biology of enzyme catalase special regards on its inherited deficiency (acatalasemia), and diabetes mellitus.

Teréz Nagy, graduated as a clinical laboratory scientist (BSc) in 2008 at University of Debrecen. This year, she started the research on catalase with Prof. Dr. László Góth and his research group. She received master degree (MS) in molecular biology from University of Debrecen in 2013. From 2014, she pursues PhD studies at the University of Debrecen. She is co-author of several research papers on catalase gene polymorphisms. She is actively involved in the training of clinical laboratory scientists at the Faculty of Medicine of the University of Debrecen. Her main interest fields are clinical chemistry, molecular biology, gene mutations, polymorphisms of catalase gene, and examination of blood catalase decrease in various diseases.