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Mini Review

## ABO Blood Group Association with DBH, COMT, MAOA, and ACE: Additive Effects, Diversity & Stability in Human Populations

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### Abstract

ABO blood groups have distinctive population frequency distributions that show stratification of health risks and behavioral traits. Further, this Mendelian trait can be a useful tool to study how additive effects with many other Mendelian traits produce stratification of populations as to risks of disease and of personality traits. For example, via linkage disequilibrium at the ABO/DBH loci at chromosome 9q34, ABO blood group A can be seen to be associated with high activity dopamine beta hydroxylase (DBH). ABO blood group A may also be associated with high activity catechol-O-methyl transferase (COMT). Hapmap population frequencies for these related gene alleles are congruent with this association of behavior and health.

And ABO O association with MAOA low activity is seen from analysis of hapmap population frequencies and associated health risks. Also ACE has shown association with ABO blood groups with ABO A showing low levels ACE, ABO O showing moderate levels of ACE and ABO B showing high levels of ACE, the mechanism thought to be related to differential degradation of ACE enzyme from various ABO antigens that the ACE enzyme expresses. Based on population frequencies of the ACE alleles and population frequencies of the ABO alleles, it appears that individuals with high activity ACE alleles may have ABO alleles that lower activity of ACE so additive effects in this case may counterbalance against extreme ACE enzyme levels.

But the end result is that instead of being fairly uniform as to health and personality effects of dopamine levels and activities, populations are stratified as to levels of and activities of dopamine and all the stratification effects on health and behavior produced by that stratification.

ABO blood groups were the first genetically based traits studied in the laboratory for association with other traits and genes. This body of work exemplifies the lack of randomness in the association of genes and urges further efforts to understand the evolutionary forces behind this. But at the present time, since ABO phenotype is clinically readily available, these associations can be used to clinically assess the activities of the neurotransmitter enzymes and thus shed light on the individual patient's health risks as well as on evolutionary implications of these risks.

**Keywords:** Dopamine Beta Hydroxylase; Catechol-O-Methyl Transferase; ABO Blood Groups, Angiotensin Converting Enzyme, Monoamine Oxidase A

### Abbreviations:

DBH: Dopamine Beta Hydroxylase;

COMT: Catechol-O-Methyl Transferase;

MAO: Monoamine Oxidase A;

ACE: Angiotensin Converting Enzyme

## Introduction

ABO gene codes for whether antigens A and/or B are present on red blood cells as well as a wide variety of other types of cells. DBH gene codes for dopamine beta hydroxylase, an enzyme which converts dopamine to norepinephrine. MAOA codes for monoamine oxidase A, an enzyme degrading catecholamines. ACE gene codes for angiotensin converting enzyme, converting renin to angiotensin, a pivotal control of circulation that is regulated centrally by dopamine receptors. COMT gene codes for an enzyme that catalyzes the degradation of catecholamines such as dopamine. The roles of dopamine are highly varied and are crucial in stratifying health risks so efforts to assess dopamine tone in the individual clinically should be relevant to health status. Since ABO status of the individual is readily available information, understanding any linkage relationship of ABO blood groups to dopamine tone would add to this effort.

## Discussion

DBH catalyzes the formation of norepinephrine from dopamine substrate and varies its activity as a function of genetics. Low DBH may be associated with ABO group B based on the congruence of population frequency distributions and health risks. The health risks associated with high DBH as well as ABO blood group A are quite congruent and extensive. And high DBH has been found to be associated with ABO blood group A [1]. DBH and COMT both use dopamine as a substrate so it is no surprise that an effect from near the DBH site on 9q34 to the COMT gene on chromosome 22 has been noted [2]. CACNA1B rs 936249C on chromosome 9q34 appearing to be in LD with both DBH 161115C and with ABO blood groups A and O has been noted to elevate COMT activity while rs936249T in LD with ABO blood group B decreases COMT activity. The population frequency distributions and associated health risks for these respective alleles are compatible [3]. So this site at chromosome 9q34 near the DBH/ABO genes regulates COMT expression and helps explain how activities of DBH and activities of COMT could be associated. And it would appear from the population frequency distributions of DBH rs161115 and of COMT rs4680 as well as CACNA1B rs 936249 that low activity DBH populations also are the low COMT activity populations [4]. There are many examples of probable clinical correlations of low activity COMT with ABO blood group B and thus low activity DBH. Their respective known risks of illness are compatible. Decreased COMT activity with resultant higher dopamine is associated with lower risks of hypertension and myocardial infarction as is ABO blood group B [5-15]. As expected, given ABO group B's increased risk of pancreatic cancer, low expression of COMT is associated with pancreatic cancer [16-20]. And consistent with ABO group B increased risk of deep venous thrombosis, low COMT has increased risk of deep venous thrombosis [21-24]. Endometrial cancer is lower in ABO group B and in decreased COMT [25,26]. And colorectal cancer is lower in ABO group B and in low COMT [27,28]. Given the role of mutagenesis in cancer, it isn't surprising to find that

mutagenicity is lower with decreased COMT and that ABO group B cancer risk is lower in general compared to group A [29]. Small cell cancer of the lung is lower in ABO group B, and COMT is higher in expression in that cancer [30, 31]. And gastric cancer and esophageal cancer are lower in ABO group B and in lower COMT. [32-36] Ovulatory dysfunction is higher in high COMT and ovulation dysfunction is a cause of ovarian cancer which is high in ABO blood group A [37,38]. Breast cancer has been linked in some studies with higher COMT and with ABO group A [39]. ACE, angiotensin converting enzyme, among its many pleiotropic effects, controls blood pressure and interacts with sympathetic nervous system. ABO blood groups have been found to be associated with ACE activity with ABO A showing lower activity than other blood groups. The cause of this effect is currently thought to be related to the effects of blood groups antigens having differential effects on slowing or speeding up the degradation of the enzyme [40]. However, hapmap populations with high frequency low activity ACE tend to have high frequency of ABO frequencies which tend to elevate ACE enzyme levels. Those populations with medium activity frequencies of ACE tend to have medium acting alleles of ABO frequencies modulating ACE, and populations with high activity alleles of ACE tend to have low frequency of those ABO alleles that would elevate ACE. So, unlike the case of ABO association with DBH, COMT, and MAOA, additive effects of ACE and ABO may be acting to create moderate ACE enzyme levels, an evolutionary state of obvious salutary effect on stability of basal circulation of blood, a physiologic function not benefiting from any but a narrow window of diversity among human populations.

MAOA has association with ABO blood groups. Because of the health risks associated with ABO group A relative to ABO group O and of the health risks associated with elevated MAOA [41-44], there is reason to think that ABO group A could be differentiated from ABO group O in catecholamine genetics by an association with higher MAOA than is ABO group O [45]. Further, inspecting hapmap population frequency distributions for alleles of MAOA would allow a surmise that MAOA activity is higher with not only ABO group A but also of ABO group B. Essentially all health risks in areas from carcinogenesis to cardiovascular and cerebrovascular disease associated with higher COMT and higher DBH show up as associated with higher MAOA [44]. So, given the associations of the ABO blood groups with DBH, COMT, ACE, and MAOA, an insight to effects of combinations of the catecholamine enzymes in large populations may be possible by using ABO blood group population frequency distributions. ABO blood group B appears to be associated with lower DBH and lower COMT and higher ACE levels. ABO blood groups A and/or O appear to be associated with higher DBH and higher COMT as well as lower and moderate ACE levels respectively.

So, a look at the broad picture of catecholamine enzymes in populations yields a summary that ABO group B is associated

with lower DBH, lower COMT, higher MAOA, and highest ACE. ABO group A appears to trend toward higher DBH, higher COMT, higher MAOA, and lowest ACE activity. ABO group O appears to trend toward higher DBH, higher COMT, lower MAOA and moderate ACE activity.

## Conclusion

Additive effects of genes ABO, DBH, COMT, MAOA, and ACE would produce dopamine levels trending from high to low, for ABO groups B, O, and A respectively. The health risk correlations of these combinations seem consistent with the broader higher health risks known to be associated with ABO blood group A relative to ABO group O and to ABO group B. One of the many pleiotropic effects of ABO includes a stratification of ACE activity with a resultant cascade of pleiotropic effects from ACE. And through the effect of dopamine activity on renin angiotensin system, all the dopamine catabolism genes such as DBH, COMT, and MAOA in turn are affected by each other and affect ACE levels via lower dopamine activity's dis-inhibition of the renin angiotensin system. Although the complexity of these associations is obvious, there is, at the same time, a comprehensible direction with clinical effects that are discernibly manifested in the individual's behavior pattern or personality, given the dopamine behavioral links [46,47], and in his general health function. Effects of ABO, DBH, COMT, and MAOA seem to stratify additively while ACE links with these genes seem more attune to negative feedback mechanisms with a trend toward homogenization of populations. Looking at the evolutionary reason for non-randomness in the association of these genes may yield some worthwhile conclusions in understanding our behavior. If there were randomness, human health would be truly universally uniform in any given environment. We wouldn't evidence variation in propensity to illness, or, given the pleiotropy yielding behavioral differences, we wouldn't evidence behaviors being recognized as virtue or vice since genes with pleiotropic effects affecting the same traits would act randomly and tend to balance each other's effects with uniformity for all individuals. So why would evolutionary forces favor variations in humans? The answer of course is that variation arises randomly and undergoes selection by environmental forces. So this non-randomness found in additive effects of these genes represents a higher fitness for survival. Variation in illness propensity, personality and other phenotypes must be a winning construct in human existence because environment is constantly changing and a repertoire of propensities promotes ongoing survival of the species. And, from a clinical perspective, until the new age of medical care is reached where whole genomic information is available for all individuals, ABO blood groups are a readily available phenotype giving some information about many genes that may allow better informed patient assessment.

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