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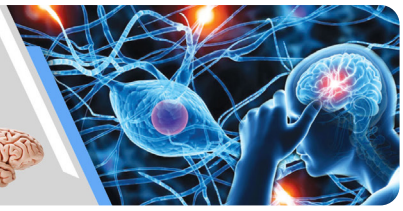

ABO Gene is Likely a Genetic Cause of Anxiety Diagnosis

Donna K. Hobgood*

Abstract

Anxiety is a common and debilitating symptom without full understanding of genetic causes. ABO B allele frequency was seen associated with lower anxiety diagnosis prevalence while ABO A allele frequency with higher anxiety diagnosis prevalence in world population studies. Genetic analysis suggests that the association is causative. Dopamine beta hydroxylase (DBH) causes conversion of dopamine to norepinephrine and is related to anxiety as well as ABO blood groups through linkage disequilibrium (LD). Linkage dysequilibrium allelic analysis is consistent with ABO B in linkage with low activity DBH. High activity DB causes high norepinephrine:dopamine ratio. Anxiety diagnosis is associated with high norepinephrine. Low activity DBH causes lower norepinephrine and thus lower anxiety. Population studies were reviewed and showed lower anxiety prevalence in areas with high ABO B frequency. Mendelian randomization inferring causation from gene and proteins and diagnoses shows that ABO gene's association with anxiety diagnosis is causative since Asian populations have markedly high ABO B frequency as well as a markedly lower ABO A with essentially no ABO A2 frequency distinguishing Asia from Europe and Africa and the Middle East as well as a markedly lower anxiety diagnosis prevalence. While population stratification confounds, mendelian randomization may clarify causation instead of just association of ABO with anxiety diagnosis since DBH low activity marker rs 1611115T causes high dopamine to norepinephrine ratio and is thus a cause of lower anxiety in LD with ABO B frequency, an association with lower anxiety in population studies.

Keywords: ABO Gene Allele Frequencies; Dopamine Beta Hydroxylase; Anxiety Diagnosis; Mendelian Randomization

Introduction

ABO being the first human gene recognized has been associated with many diagnoses most notably being thrombosis risks in ABO non-O and pancreatic cancer risks in ABO non-O. [1] Anxiety and many related diagnoses have been associated with ABO but not consistently [2-6]. Dental anxiety in children was found to be lower in Indian population in ABO A groups. ABO AB showed positive findings of Neuroticism in a Croatian study [7] and in a Pakistan study [8] and in an Iranian study. Additionally, a study done in Italy and in Boston showed ABO AB associated with Neuroticism. But most studies reviewed showed either no significant differences in personality in ABO with anxiety related traits or did not address any anxiety dimensions of personality [9-13]. Most commonly used modern personality tests such as the Cloninger traits (Novelty-Seeking, Harm Avoidance, Reward Dependence and Persistence) and The Big Five traits (Openness, Conscientiouness, Extraversion, Agreeableness, and Neuroticism) are validated as having genetic correlates

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and don't include anxiety as a personality trait. Anxiety may not be a primary and thus genetically linked personality trait like the Cloninger and the Big Five but instead may result from a combination of environmental and polygenetic multifactorial factors [14,15, 12]. While anxiety may not be a personality trait, related traits such as Neuroticism have been found in many populations to be associated with AB blood type. Using sympathetic activity prominence in anxiety related states, observations of noradrenergic pathways as well as worldwide population prevalence of anxiety diagnoses point to ABO gene as relevant to anxiety diagnoses. ABO gene perhaps through linkage disequilibrium with DBH dopamine beta hydroxylase appears to be a cause of anxiety diagnosis.

The first line of evidence for this is in ABO and DBH having shared trait research. Some research implicates genetic causes of anxiety diagnosis. Heritability is thought to be around 50%. Many genes such as serotonin transporter have been associated with anxiety related traits but without replication [16]. Dopamine beta hydroxylase (DBH) has been considered to relate to many behavioral effects. A possible link of anxiety with ABO blood groups could then relate to dopamine beta hydroxylase (DBH) genetics since ABO gene is in tight linkage disequilibrium (LD) with DBH [17,18].

Based on the literature showing anxiety related sympathetic nervous system correlates, anxiety likely is higher with higher norepinephrine and the genetic cause, higher high activity DBH. ABO A and O appear to be in LD with higher DBH, higher norepinephrine and higher anxiety, and ABO B appears in LD with lower DBH, lower norepinephrine and lower anxiety. (19,20), Studies have linked ABO A and ABO O with high DBH and high norepinephrine and adrenergic associated traits such as sensation-seeking while ABO B and low DBH and low norepinephrine are associated with traits thought to have dopamine correlates such as impulsiveness and cocaine induced psychosis, [21] Many health risks have been studied as to co-occurrence with ABO blood groups and with DBH. As examples, ABO group B has less smoking risk than ABO groups O and A, and dopamine beta hydroxylase, DBH TT (low activity) in LD with ABO B, has less smoking risk than DBH CC [22]. This is consistent with research consensus regarding the relatively higher genetic dopamine activity patterns in non-smokers. Since ABO group B marker rs8176746 is in linkage disequilibrium with DBH, rs1611115, with consistent population frequency distributions, it is likely that the ABO blood group B association with not only smoking risk but also illnesses and personality traits may be related to linkage disequilibrium with DBH [23-27]. The second line of evidence for this lies in DBH showing association with diagnoses consistent with that of ABO. DBH, the catecholamine enzyme that converts dopamine to norepinephrine, varies in individuals as a function of genetics. Low activity and high activity variants are described most studied being rs1611115, the locus having worldwide frequency distributions of high activity variant C at .79 and low activity variant T at .21. Associations include increased hypertension, diabetes, and myocardial infarction risk in high activity variants as well as post-traumatic stress disorder (PTSD), Inflammatory bowel disease, hypothyroid, and major depressive disorder [23-28]. Low activity DBH associated with bipolar disorder and schizophrenia in a Pakistani study and of Alzheimer's Disease in a Croatian population and obsessive-compulsive disorder in a Turkish study. Other associations with low DBH include migraine, autism, hyperthyroid, attention deficit hyperactivity disorder (ADHD). ABO research is consistent with DBH research with ABO A/O higher hypertension the most prevalent and the most replicated finding [1]. ABO gene with worldwide frequency distributions of O .63, A .21 and B .16 is known to be in tight linkage disequilibrium with DBH gene. Inspection of the LD pattern (D') between ABO and DBH shows that the pattern of D' numbers (higher values indicating tighter linkage) with DBH allele rs1611115 and ABO alleles are consistent with literature of linkages with DBH alleles and ABO alleles as well as world population frequencies of these alleles [29].

Table 1: ABO and DBH are in linkage disequilibrium such that ABO B is linked with DBH low activity

ABO allele	ABO blood group	D' LD with DBH
rs8176746T	ABO B	32
rs512770A	ABO O	40
rs8176704G	ABO A or O	31
rs495828G	ABO A or O	77
rs1752337T	ABO A or O	81
rs9411493A	ABO A	43
rs7025162C	ABO O	82
rs624960T	ABO O	80
rs4962043C	ABO O	37
rs8176743C	ABO O	32
rs8176693C	ABO O	32
rs8176672C	ABO O	32
rs8176668A	ABO O	33
rs 651007C	ABO O	79
rs479459G	ABO B	79
rs7030248G	ABO O	30
rs558240G	ABO O	40
rs11244065C	ABO O	83
rs532207A	ABO O	80
rs561585A	ABO O	80
rs17150319C	ABO O	66

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DBH and ABO role in anxiety is supported by personality trait research and genetic correlations. Anxiety would intuitively include such traits as Cloninger traits of Persistence trait and high Reward Dependence based on intensity of emotions present in anxiety states and would be likely associated with higher norepinephrine state and thus higher ABO A and DBH high activity. For comparison, ABO blood group B's has been found to be associated with high tough-mindedness (thought related to high unemotionality) and low Reward Dependence (thought related to level of engagement propencity) including subtraits of low attachment, low dependence, low openness to warm communication, low persistence, low pain perception [30,31]. The association of ABO B with low DBH via LD with ABO B supports ABO B's association with traits of impulsiveness, low extraversion and low sensation-seeking and low persistence [21, 32-35]. Persistence trait has been linked with dopamine transporters and receptors (36,37) so since DBH determines the ratio of dopamine to norepinephrine, DBH would be related to Persistence trait via dopamine and norepinephrine activities. Dopamine and norepinephrine activities are also implicated in Impulsiveness trait via its association with DBH. Because of the relationship of dopamine and norepinephrine activity to motivation and Aggression (38) DBH allele specificity would then stratify Impulsive action (aggression) vs Persistent action (aggression) such that low activity DBH allele would be associated with Impulsiveness of action and the high activity DBH allele would be associated with Persistence of action. The linkage with dopamine activity to Persistence has been demonstrated by studies which show that for dopamine transporter (DAT), alleles of high dopamine affinity are linked to higher Persistence trait, thus implicating decreased dopaminergic neurotransmission in Persistence trait expression. (39-41) Many studies are consistent with Persistence trait's connection with relatively low dopamine transmission either from high DBH or from high dopamine transporters and from low avidity or low numbers of dopamine receptors. A study in Japan did demonstrate Persistence trait associated with ABO A and with high DBH [42]. Review of research in PubMed and google scholar site population prevalence of anxiety diagnosis association with ABO allele frequencies. Anxiety diagnosis and ABO blood groups were compared using population studies and ABO allele frequencies from standard registries. Anxiety may be a complex state with environmental and polygenetic underpennings. So, comparing genetic associations to anxiety diagnosis among populations may be prone to confounding from population stratification. An approach to the problem of population stratification was addressed be using Mendelian Randomization, inferring causation starting from association by assessing allelic links with both an illness in a population and with a known physiologic cause of the illness. Mendelian Randomization is a standard model that has been employed to understand many genetic effects including inference that folate metabolic defects is a cause of neural tube defects.

Populations representing areas having available anxiety diagnosis frequencies with available data on ABO allele frequencies were reviewed. Compared to Western European and Middle Eastern populations, ABO A and especially ABOA2 is of lower frequency in Asia while ABO B is of high frequency. Using Mendelian Randomization model, ABO A allele is associated with both high DBH thus high norepinephrine/dopamine ratio and with higher anxiety population prevalence, supporting a conclusion that ABO A especially ABOA2 allele with highest world frequencies in Western Europe and the Middle East is a cause of higher anxiety. Also, ABO B by Mendelian Randomization is associated with both low DBH and thus low norepinephrine/dopamine ratio and with low anxiety population prevalence, supporting a conclusion that ABO B is a cause of low anxiety. Thus Asia having both high ABO B and low A especially A2 frequencies has lower anxiety population prevalence [43]. Tables 2, 3, Figure 1, 2

Table 2: Anxiety population prevalence and ABO gene table ordered by increasing Anxiety diagnosis population prevalence

Population	Anxiety/1000	ABO O	ABO A	ABO B
China	28	55	24	21
Pakistan	28	60	20	20
Hong Kong	28	60	19	21
Croatia	32	62	25	13
Sudan	44	70	15	15
Hispanic	45	75	22	3
African Amer	54	70	18	12
Kuwait	60	55	28	17
Palestine	60	60	24	16
Saudi Arabia	60	60	28	12
Spain	62	60	34	6
Netherlands	64	65	29	6
Germany	64	64	28	8
White Amer	64	65	28	7

Table 3: Anxiety diagnosis population prevalence and ABO gene table ordered by increasing frequency rs1611115C, high activity DBH

Population	Anxiety/1000	ABO O	ABO A	ABO B
Hispanic	45	75	22	3
Kuwait	60	55	28	17
Palestine	60	60	24	16
Saudi Arabia	60	60	28	12
Netherlands	64	65	29	6
Croatia	32	62	25	13
Germany	64	64	28	8
China	28	55	24	21
Pakistan	28	60	20	20

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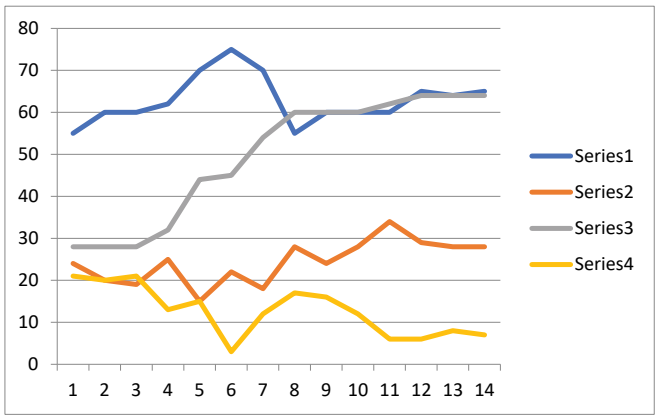
Hong Kong	28	60	19	21
White Ameri	64	65	28	7
Spain	62	60	34	6
African Ameri	54	70	18	12
Sudan	44	70	15	15

Figure 1: Series 3-Anxiety diagnosis in world populations (1-14) in order on increasing prevalence and Series 1-ABO O, Series 2-ABO A and Series 4-ABO B allele frequencies



X= populations in order of increasing anxiety prevalence per 1000

Y=1 blue ABO O, 2 red ABO A, 3 green anxiety dx prevalence per 1000 population, 4 purple ABO B

Figure 2: Series 3 Anxiety diagnosis in world populations (1-14) in order on increasing DBH high activity (rs1611115C) and Series 1-ABO O, Series 2-ABO A and Series 4-ABO B allele frequencies

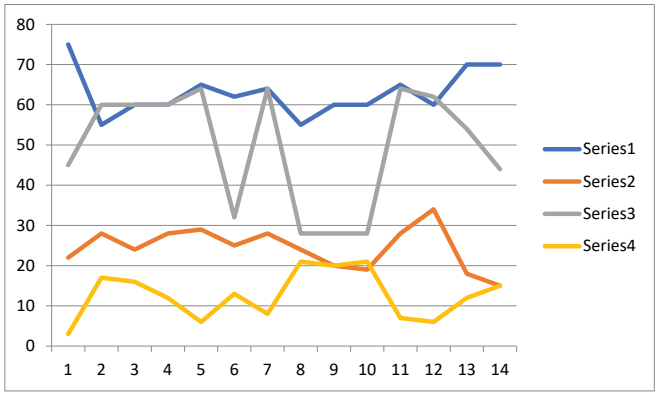


Table 2 and Figure 1 show population 1-14 in order of increasing anxiety population prevalence illustrating that ABO O shows less correlation with anxiety while ABO A shows positive correlation and ABO B shows negative correlation with anxiety diagnosis. Table 3 and Figure 2 show populations 1-14 in order of increasing frequency of rs1611115C DBH high activity thus allowing some sense of how ABO gene alleles for O, A and B vary when ordered by or controlled for linked DBH high activity allele.

Figure 2 illustrates that when DBH 1611115 C high activity is controlled for ABO A is seen as varying directly with anxiety diagnosis prevalence and ABO B is seen as varying indirectly with anxiety diagnosis prevalence. This would indicate the central relationship between ABO gene even more than DBH and anxiety diagnosis prevalence in populations worldwide. DBH 1611115 C individuals with ABO A and B and not so much ABO O seems more related to anxiety diagnosis. Additionally based on populations with high ABO A2 having much higher anxiety diagnosis than populations with high ABO A1 one suspects ABO A2 to be the driver of ABO A and anxiety diagnosis correlation.

Discussion

Understanding the related genetics leads to improved screening for anxiety diagnosis allowing targeting of interventions best suited to the individual, thus furthering personalized medicine. And since self-knowledge would further healing, this hypothesis advances that goal.

Limitations drawing inferences from population studies of anxiety diagnosis include variations in how the anxiety diagnosis is made that would impact prevalence rates in populations studied. Other relevant considerations include cultural inputs on anxiety prevalence as to what level of anxiety symptoms is considered pathological. Additionally, Resource availability and other social determinants of health vary within and between populations. Consensus seems to be that low resource availability may not increase prevalence of anxiety diagnosis as much as disparities among the population in resource availability [43]. So, advancing understanding of genetics of anxiety such as this hypothesis would be meaningful to the individual and to society.

For the individual, anxiety genetics may associate with many health-related issues. High anxiety correlates with emotional and circulatory illnesses [25] while low anxiety correlates with outcomes of low alertness and low attention such as accidents [44, 24]. At the level of society, there may be geopolitical differences that could be attributable to genetic differences in propensity to anxiety. Areas of conflict are associated with higher anxiety prevalence long-term [45]. Anxiety is a leading cause of morbidity in both males and females, but population studies show that the male: female ratio of diagnosis of anxiety disorder is 0.46 from either environmental and or genetic inputs [45]. It is associated with higher mortality rates, loss in ability to participate in the workforce, in community organizations, and in interpersonal relationships. Pharmacologic treatment and counseling are mainstays of treatment, but progress depends on elucidating physiologic and genetic causes. Understanding physiology of anxiety is work in progress. This review uses Mendelian Randomization to show that ABO blood group A is likely a cause of anxiety symptoms and that ABO B is a likely a cause of low anxiety. While we treat individuals, knowing the context of the prevalence of a diagnosis in a population has meaning. And knowing the causes of symptoms can facilitate screening strategies. In the setting of anxiety

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symptoms, ABO blood group testing being widely available in populations may prove helpful in screening for genetic etiologies of anxiety diagnosis.

Conclusion

ABO blood groups through linkage disequilibrium with dopamine beta hydroxylase appears to be a cause of anxiety diagnosis. Large-scale testing populations for correlations between ABO phenotype and anxiety diagnosis is feasible, but ABO genotype would also be necessary since ABO A subtype A2 in populations appears to be more related to anxiety diagnosis than ABO A1. Verification of this hypothesis would serve to further knowledge of genes and their effects and thus lead to better treatments for anxiety. And just as important, this hypothesis would allow better insight for the individual to understand who he is and what it is that makes him feel and think as he does.

Conflicts of interest: None

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