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ABO group B is associated with personality traits through linkage disequilibrium with low activity dopamine beta hydroxylase

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Abstract

ABO blood groups have been studied for associations with personality traits with no scientific consensus of positive findings. Because of previously known variations in population frequency distributions of ABO blood groups and newly discovered single nucleotide polymorphisms in ABO gene in the human genome project, associations of personality traits and health risks with ABO blood groups continue to be delineated with increasing specificity. One of the catecholamine enzymes, DBH, dopamine beta hydroxylase, is in tight linkage disequilibrium with the ABO locus. Because personality traits as well as illnesses have been linked to the catecholamine genes, the DBH/ABO linkage may contribute to stratification of ABO blood groups in personality traits as well as in illnesses.

Hapmap population frequency distributions are similar for ABO blood group B and for low activity of the major allelic marker contributing to variation in DBH activity, rs1611115. And linkage disequilibrium within the ABO locus is consistent with this. Further, review of the publically available genomes of two individuals, Craig Venter and James Watson, and their biographical information is also supportive of this association. Both Venter and Watson appear to have both non-B ABO blood group and high activity DBH and to have dopamine genotypes consistent with Persistence personality trait research as well as to evidence this trait in publically available biographical information. This hypothesis can be verified by comparing genotypes of ABO and DBH and personality traits in large populations.

The Cloninger trait of Persistence has been associated with dopamine neurotransmission and is likely related to the ABO/DBH linkage via the role of DBH in determining the dopamine:norepinephrine ratio. Low DBH is known to be associated with trait Impulsiveness so it would appear that impulsiveness may be related to a higher dopamine to norepinephrine ratio, and based on research demonstrating the role of dopamine neurotransmission in the expression of motivation as well as trait Persistence, the likely situation is that lower tonic dopaminergic transmission produces Persistent action and higher tonic dopaminergic transmission produces Impulsive action.

If large population genetic studies confirm this hypothesis, given the widespread availability of data on ABO blood groups in virtually every population, new light could be shed on the biochemical underpinnings of human behavior both at the level of the individual and at the level of societies and cultures.

Background

ABO blood groups demonstrate stratification in not only medical illnesses but also personality traits. Since the discovery of ABO blood groups by Landsteiner in 1901, many researchers have noted personality trait tendancies in ABO blood groups. The first linkage in modern research was the finding of a spectrum of tough-mindedness vs tender-mindedness (similar to Cloninger's low Reward

Dependence vs high Reward Dependence) in AB, B, O, and A, in that order [1]. A similar order of ABO blood groups has been described in the spectrum of high Anger vs low Anger (except that in Anger, O moves to the highest position in the list). More recently, obsessive-compulsive disorder having a genetic linkage with ABO blood group A has been a hypothesis supported by some but not all researchers [2,3]. Japan and Korea have a long tradition of popular interest in ABO blood groups' linkage with personality with some research refuting and some supporting but with scientific consensus refuting [4,5].

In medical illness stratification of ABO blood groups, risks of myocardial infarction, pancreatic, breast, ovarian, lung and gastric cancers, smoking

prevalence, poorer lung function, H. pylori infection and other illnesses follow the spectrum of ABO blood group order in the low Anger vs high Anger spectrum in populations having mostly ABO groups A and O and in the high Reward Dependence vs low Reward Dependence spectrum in populations having equal frequencies of ABO groups A, O, and B with lower Anger/ higher Reward Dependence having the most risks [6-25].

Hypothesis

Linkage disequilibrium may help explain these relationships. For example, ABO group B has less smoking risk than ABO groups O and A [26], and dopamine beta hydroxylase, DBH TT (low activity), has less smoking risk than DBH CC [27]. 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 hapmap population distributions, it is likely that the ABO blood group B association with not only smoking risk but also illnesses may be related to linkage disequilibrium with DBH. 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 [28-30] as well as their respective associations with diseases of mind and body including increased hypertension, diabetes, neurologic disease, and myocardial infarction risk in high activity variants [31-35] and increased risk of dementia in low activity variants [36-38]. And, considering the known effects of catecholamines on behavior, it is likely that linkage disequilibrium between DBH and ABO also explains personality trait associations with ABO blood groups.

Evaluation

ABO gene is known to be in tight linkage disequilibrium with DBH gene [28]. Inspection of the LD pattern between ABO and DBH shows that of all ABO single nucleotide polymorphisms, snps, ABO blood group markers for non-B show the highest LD (D' numbers) with DBH allele rs1611115 (Table 2) with hapmap population frequency distributions a good fit between high activity DBH alleles and ABO blood groups non-B. And the two individuals whose genomes are publically available demonstrate a consistency with this linkage. CraigVenter and James Watson have genotypes consistent with ABO blood groups non-B. The human genome reference sequence represents non-B (actually O) [39], and the reference snps' genotypes are quite similar to the ABO snp genotypes of Watson (probable ABO O) and somewhat less so to Venter's (probable ABO A) (Table 2). Both Venter and Watson have DBH, 1611115CC, high activity variant (Table 1).

Findings of personality trait research for ABO blood groups and for DBH activity are compatible. In populations such as India and China where ABO group B has high frequency, DBH low activity allele also has high frequency, and in these populations these two genes are in concert associated with both the same diagnoses and with personality trait of toughmindedness (low Reward Dependence). ABO blood group B's association with high tough-mindedness and low Reward Dependence includes subtraits of low attachment, low dependence, low openness to warm communication, low persistence, low pain perception [1,40,41] while low DBH is associated with impulsiveness, low extraversion and low sensation-seeking [42-46]. The translation of these two sets of traits into one of the Cloninger traits could be the Persistence trait spectrum [47-48] with ABO group B/DBHTT (rs1611115T(low)) associated with low Persistence trait via low attachment (ABO), low sensation-seeking (DBH) and like traits and ABO groups A and O/DBHCC (high) with high Persistence via high attachment (ABO), high sensation-seeking (DBH) and like traits. Persistence trait has been linked in association studies with dopamine transporters and receptors [49-55] so since DBH determines the ratio of dopamine to norepinephrine, DBH would be theoretically related to Persistence trait via dopamine and norepinephrine activities. Dopamine and norepinephrine activities are also implicated in Impulsiveness trait via its association with DBH. Also, because of the relationship of dopamine and norepinephrine activity to motivation and Aggression [56], 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 DAT, dopamine transporter, allelles of high dopamine affinity are linked to higher Persistence trait, thus implicating decreased dopaminergic activity in Persistence trait expression. 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. One exception may be the case of DRD4 7R, a low affinity receptor which has been linked to

low Persistence trait in a subset of ADHD patients. This exception may be one which supports the rule however. Evolutionary history of DRD4 7R [57] can be seen to be overlapping with ABO blood group O's distribution frequency, less common in Asia than in the Americas, group O being linked with high activity DBH with consistent hapmap frequency distribution and with Persistence trait according to this hypothesis. Given that BO heterozygotes would allow, through crossover in meiosis, a small proportion of future ABO group OO (and AO) individuals to carry DBH TT (low activity), one can see how the hapmap population MEX(M), Mexican ancestry in Los Angeles, California, through founder effects of haplogroup Q3 (M3) , for example, could have both a very high frequency (.337) DBH TT and a very high frequency ABO blood group O (.73) and yet not refute this hypothesis.

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Table 1: Some personality genotypes of Venter and Watson

GENE	*snp*	*Venter*	*Watson*
COMT	rs4680	low	low
DBH	rs1611115	high	high
DRD2	rs1800497	high	heterozygous
DRD3	rs6280	high	heterozygous
DRD4	rs752306	high	het?/low variant
SLC6A3 (DAT)	rs27072	high	heterozygous
5HT2A	rs6311	High/hetero	low
5HT2A	rs7997012	heterozygous	low
SERT	rs25531	heterozygous	high
MAOA	See table 3	high	?low
ABO	See table 2	Non-B/?A	Non-B/?O

[66-70]

Enhanced reward would seem then to be experienced by the individual when dopamine transmission is delayed instead of immediately achieved, thus yielding Persistence of behaviors in the same way that intermittent instead of constant reward motivates persistence of behaviors in reinforcement theory research [58]. Persistence trait thus seems to be a manifestation of a perception of high impending though delayed reward attached to an impending action. Low Persistence trait would be a manifestation of the individual's perception of low impending reward attached to an impending action.

Examining the genotypes of Venter and Watson for these dopamine genes shows that they are both homozygous for DBH rs1611115C while Venter is homozygous and Watson is heterozygous for high activity dopamine transporter, both genotypes supporting expression of Persistence trait. Though no studies have addressed the role of all the different dopamine receptors in Persistence trait, if the trends in dopamine transmission and their relationships to Persistence trait expression are consistent, some mitigation of their Persistence trait, however, may attach to the homozygosity in Venter and heterozygosity in Watson (except possibly in the case of DRD4) for high activity dopamine receptors. Further possible mitigation of dopamine reward effects are found in the presence in both Venter and Watson of the low activity COMT gene, allowing somewhat slower catabolism of dopamine (Table 1). This may help prevent their Persistence trait from being in extreme forms such as substance abuse and antisocial personality, and, according to several lines of evidence, helps give them Perfectionism personality trait. Also relevant to antisocial personality traits, while Watson's MAOA genotype may be low activity with some tendancy toward trait Aggression and antisocial personality, Venter's MAOA genotype would appear to be of high activity variant.

Though only one study has been reported showing MAO related to ABO blood group, their finding was that ABO blood group O is associated with decreased MAO activity [59] as may be the case for Watson. Publically available biographical information supports the conclusion that Venter is Persistent and non-Aggressive and Perfectionistic, and Watson is Persistent and Aggressive and Perfectionistic. Further, their serotonin genes show heterozygosity for Venter and low receptors and high/hetero

Table 2: Some snps in ABO gene: genotypes of Venter and Watson

Snp in ABO	**reference**	**Venter**	**Watson**	**D'/rs1611115**
rs10793959	G	AA	AA	
rs11999677	G	Ref	Reference?	
rs4379511	T	GG	GG	
rs4507838	T	GG	GG	
rs6597612	C	?	Ref	
rs7036324	G	Ref	Ref	
rs7469576	G	AG	Ref	
rs9919007	C	CT	Ref	
rs4363269	A	AG	Ref	
rs8176749C	C	Ref	Ref	
rs8176746T-B	G	G	Ref	32
rs2073824	A	Ref	GG	
rs512770	A	GG	AG	40
rs8176704	G	Ref	Ref	31
rs574347	C	TT	Ref	
rs2073828	G	AG	Ref	
rs8176694	T	Ref	GG	
rs657152	C	Ref	Ref	
rs500498	T	CT	Ref	
rs505922C-A	T	CT	Ref	
rs630014	A	CC	Ref	
rs568203	A	CC	Ref	
rs495828	G	Ref	Ref	77
rs13298002	G	AA	Ref	
rs500428	A	GG	Ref	
rs1752337	T	Ref	Ref	81
rs9411493	A	GG	Ref	43
rs7025162	C	CT	Ref	82
rs624960	T	CC	CT	80
rs4962043	G	AG	Ref	37
rs554710	C	TT	Ref	
rs11244079	G	Ref	Ref	
rs493014	G	TT	Ref	
rs507666A-A1	G	?	Ref	
rs8176743	C	Ref	Ref	32
rs8176693	C	Ref	Ref	32
rs8176672	C	?	Ref	32
rs8176668	A	Ref	Ref	33
rs651007	C	Ref	Ref	79
rs579459 B	T	Ref	Ref	79
rs7030248	G	AG	Ref	30
rs558240	G	?	Ref	40
rs11244065	C	Ref	Ref	83
rs532207	A	GG	Ref	80
rs561585	A	CC	Ref	80
rs17150319	C	?	Ref	66

[66-70]

Table 3: Some markers, MAOA gene: genotypes of Venter and Watson

MAOA marker	**Venter**	**Watson**
rs6323G high	TT low	G ref high
rs 5953210A high	AA high	G ref low
rs2283725G high	GG high	A ref low
rs2205718T	CC	T ref
rs979606C	AA	C ref
rs3027407A	GG	A ref
rs1799835T	?	T ref
rs1465108A	GG	A ref
rs1181252A high	GG low	GG low
rs979605C high	CC high	AA ref low
rs766117G high	GG high	GG high
rs1137070C high	CC high	T ref low
VNTR 3/half repeat	4-repeat high	?3/half ref high

[66-70]

transporter for Watson, yielding perhaps, in general, more dopaminergic activity instead of serotonergic activity in the case of Watson (Table 1).

Both individuals appear to have non-B blood group and high DBH as well as Persistence personality trait so their phenotypes are consistent with their personality genotypes and of the linked ABO blood group genes consistent with this hypothesis.

Discussion

If replicated in large genetic association studies, these findings may not only reveal much about the link between emotions and illness but also may arouse speculations about the evolutionary meaning of these links and therefore about our deep ancestry. DBH allelic hapmap population frequencies vary with ethnicity and geography but show that C allele has a much higher frequency worldwide with the ancestral allele being C. The only primate to have a level of DBH even close to humans is the gorilla, the chimpanzee being quite low. And the gorilla is also the only primate to be almost exclusively of ABO blood group B while the chimpanzee has only types A and O. This complete reversal in non-human primates of the linkage of ABO phenotype to DBH phenotype doesn't affect human stratification and linkage of DBH/ABO because the DBH alleles as well as A and B alleles have evolutionary histories in the non-human primates unrelated to that of humans [60,61].

To understand the ABO genomic locus and its stratification as to personality traits and illness, one must understand the manner in which the ABO system evolved in humans: type A blood was hypothetically selected against by an advantage conferred to type O blood in severity of malaria susceptibility in sub-Saharan Africa [62] in humans living in as well as those migrating out of Africa over 50,000 years ago. The geneTLR4 is in linkage disequilibrium with the ABO locus and affects the susceptibility to severity of malaria. ABO distributions of both aboriginal people the world over and of modern populations as they reflect migration patterns of deep ancestry help tell the story of where the African immigrants with varying blood group distributions headed when they left Africa. Modern geographic areas with highest ratios of O,A:B blood seem to have been initially settled by immigrants from Africa some 50,000 or more years ago going into the Mediterranean area as well as into Central Asia (and later into the area of present day Europe and the Americas). ABO group B, following somewhat the geographic pattern of the Mongolian invasions of the twelfth century [63], probably evolved later than ABO group O. From a setting of universal ABO blood group A in the earliest known humans in Africa over 50,000 years ago to the current world wide distribution of a majority of ABO blood group O, moderate A, and very little B reflects both new mutations and possibly environmental selection of type O blood over type A blood in part related to the health risks of ABO blood group A relative to those of O.

The evolutionary effects of DBH stratification putatively with predominantly ABO group B having higher frequency DBH low activity alleles may not be related as much to selection as to founder effects. If a major single evolutionary event yielding DBH low activity occurred in an ABO blood group B individual, the spread of ABO blood group B as the Genghis Khan culture spread may help explain both the modern hapmap frequency distribution of ABO blood group B as a common finding in India and Asia, for example, as well as

a higher hapmap distribution of DBH low activity alleles in those same areas. Any possible selection events around the mutation that caused ABO group B are not as clear because B (as well as AB which has been found to express mostly B antigen effects [64]) may be the less prevalent ABO group merely because it is the newest group to evolve and not because of its putative linkage with low Persistence personality trait and low DBH activity.

ABO blood types and traits of personality have been studied by mainstream scientists as well as by some pseudoscientific groups, such as in the Nazi era when type B, for example, was considered as a mark of the lower instincts, thought commonly present, according to the Nazis, in the Asian as well as in the Jewish people, this being part of the propaganda of racism and pseudo-science that marked the regime. But, when much more data are gathered, ratios of various personality traits linked to the ABO blood groups as they may reflect themselves in the structure of a society are possible future candidates for analysis of a social structure and their relationships to other societies. This future truly scientific study of ABO blood group antigens will, no doubt, reveal the complexity of these patterns. Besides population stratification based on founder effects and migration patterns and besides intrinsic effects of the presence or absence of the A and B antigens' effects on the cell membrane and of linkage disequilibrium with the catecholamine gene DBH, other genes near the ABO locus could relate to the ABO linkages with personality and illnesses. DYT1 encoding for torsin-A, an ATPase was found to be associated with dystonia and attention deficit disorder [65] as have neighboring DBH alleles. Other candidate genes near the ABO locus include genes for PAPPA (a pregnancy associated protein used for fetal screening), microcephaly, thrombotic thrombocytopenic purpura, acute hepatic porphyria and susceptibility to lead poisoning, amyloidosis, juvenile amylotrophic lateral sclerosis, hypophosphatemic rickets, COX deficiency, tuberous sclerosis, lymphangioleiomyomatosis, muscular dystrophy, Ehlers-Danlos connective tissue disease, aortic valve disease, susceptibility to colorectal cancer, and longevity [66].

Conflicts of Interests

There are no conflicts of interests to report

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