

Correlation of the COMT Val158Met polymorphism with latitude and a hunter-gather lifestyle suggests culture–gene coevolution and selective pressure on cognition genes due to climate

Davide PIFFER¹*

¹*Ulster Institute for Social Research, London, UK*

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Abstract Dual-inheritance theory posits that the genotype has an impact on the evolution of human behavior and that cultural traits can be constrained by genetic imperatives. A large body of studies provides evidence that the functional catechol-O-methyltransferase (COMT) Val158Met polymorphism is associated with executive function, working memory (WM), and intelligence. A survey of the population genetics database provides evidence that COMT gene frequencies vary across populations. The aim of the present study was to test the hypothesis that the COMT gene has an impact on cultural evolution, specifically on the adoption of an agricultural vs. a hunter-gatherer lifestyle. Statistically significant differences in COMT allele frequencies between hunter-gatherer and agricultural societies were found. Ethnic groups whose economy is based on farming have higher frequencies of the Met allele (symbol: A), whereas societies based on a hunter-gatherer economy have very low frequencies of the Met allele and a disproportionate predominance of the Val allele. Moreover, the frequency of the Met allele was positively correlated to the populations' IQ ($r = 0.57$). The FBNP1L gene (rs236330) is associated with childhood and adult intelligence and it varies in frequency across populations. Frequency of rs236330 was also significantly correlated with the populations' IQ ($r = 0.81$). COMT and FBNP1L had fairly similar geographical distributions ($r = 0.44$) although the result did not reach statistical significance. The results suggest that the genotype of a population influences its cultural development in fairly specific and predictable ways. Met allele frequency was positively correlated with latitude ($r = 0.56$), suggesting selective pressure due to climate.

Key words: intelligence, evolution, working memory, COMT

Introduction

Human civilizations are markedly different in their levels and types of cultural and technical achievement. Sometime in the Upper Paleolithic, humans started switching from a system of 'maintainable' to one of 'reliable' weapons. The former require comparably less effort to produce but are easier to fix (maintain) when necessary, e.g. when damaged through use. Most stone tools belong to this category (Coolidge et al., 2013). Reliable weapons, on the other hand, are not so easy to maintain (because of their more complex design, consisting of many interrelated parts) but are designed to ensure function, i.e. "to reduce as far as possible the chances for failure" (Coolidge et al., 2013). Complex projectile technology belongs to this category of weapons. Shea and Sisk (2010: 101) have argued that this development is a good marker of technical prowess: "we use the term 'complex projectile technology' to refer to weapon systems that use energy stored exosomatically to propel rela-

tively low mass projectiles at delivery speeds that are high enough to allow their user to afflict a lethal puncture wound on a target from a 'safe' distance."

The most compelling earliest evidence for this technology dates to 14000–18000 ago, with slightly simpler systems extending back to 30000 ago (Coolidge et al., 2013) in Europe. Less compelling evidence goes as far back as 70000 ago in Africa.

Managed foraging is another behavior that requires planning and intelligent behavior. Again, the earliest convincing evidence dates to 18000 ago in south-western Europe, with the late Upper Paleolithic reindeer hunters. There is evidence that these hunters followed a "tightly scheduled hunting system in which herds were intercepted and slaughtered in the fall at specific locations during migrations, but at other times of the year they were hunted individually using a different set of tactics" (Coolidge et al., 2013: 50). A review of the archeological evidence suggests that "about 50000 to 30000 years ago, the pace of culture change accelerated dramatically, beyond what seems explainable as the vagaries or biases of artifactual preservation, or as responses to the late Pleistocene climatic change" (Coolidge et al., 2013: 56). The authors argued that the mutation enhancing working memory (WM) and executive functions "evolved late in a human population that was already anatomically modern," enabling

* Correspondence to: Davide Piffer, Via Molina 15, 54033 Avenza (MS), Italy.
E-mail: davidepiffer@libero.it

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the “cognitive leap” that gave rise to an “explosion in behavioral changes” that took place between 50000 and 30000 years ago.

According to the out-of-Africa model, modern humans left Africa between 50000 and 90000 years ago (the date is still uncertain, see Henn et al., 2012) to colonize first the Middle East, then from there the rest of the world. If the hypothesis that the mutation responsible for the cognitive leap emerged in the human genome no earlier than 50000 years ago is correct, then the logical consequence is that this mutation emerged after the various human groups had split from their African ancestors. By 50000 years ago, the ancestors of today’s Australian Aboriginals, Europeans, and Chinese had all settled in their respective continents. Thus, it is not impossible that these ethnic groups have different frequencies of this mutation.

If higher WM and fluid intelligence are responsible for technological progress, then it is possible that the technological status of a civilization predicts its levels of intelligence, and conversely, its levels of WM/fluid intelligence predict its technological status.

However, human cognition is a complex system and consists of many different elements. Fluid intelligence and WM are two of the most important aspects of human cognition, but other features may be as important. Divergent thinking and cognitive flexibility contribute as much as WM and fluid intelligence to creativity. Whilst WM may be more important for technical and scientific creativity, divergent thinking plays a crucial role in artistic creativity (Piffer, 2012).

Molecular genetics studies suggest that executive function is modulated by dopamine levels in the prefrontal cortex and that different alleles of the catechol-O-methyl transferase (COMT) gene are responsible for different cognitive profiles. The COMT gene encodes a catabolic enzyme involved in the degradation of dopamine (Axelrod and Tomchick, 1958). A polymorphism that results in a Val/Met substitution at codon 158 (SNP Id: rs4680) results in a reduced activity level of COMT, with Met/Met homozygotes having a 3- to 4-fold reduction in enzyme activity relative to Val/Val homozygotes (Chen et al., 2004).

According to a prominent model, “predominant activation of dopamine D1 versus D2 receptors in prefrontal cortex (D1 state vs D2 state) is associated with a high energy barrier among different network patterns favoring robust maintenance of information in WM, whereas predominant D2 versus D1 activation is associated with a low energy barrier favoring flexible and fast switching among representations” (Durstewitz and Seamans, 2008). A D2 state is associated with either very high or very low dopamine concentrations, whereas at medium concentrations D1-mediated effects dominate. In other words, prefrontal dopamine concentration and D2/D1 receptor activation follow an inverted-U relationship. Thus, it follows that WM and dopamine levels are also linked by an inverted U-shaped function, with optimal performance at medium dopamine levels, where the ratio of D1 relative to D2 receptor activation is at its peak (Durstewitz and Seamans, 2008).

Val/Val carriers have lower (suboptimal) basal prefrontal cortex dopamine levels relative to Met/Met carriers (Jacobs and D’Esposito, 2011).

Another study found that the Val/Val genotype is associated with predominant D2 (versus D1) receptor activation, a state favouring flexible switching among representations (Wacker et al., 2012). This allele was also positively associated with verbal fluency and higher scores in the agency facet of the extraversion dimension. Conversely, the Met/Met genotype was positively correlated to fluid intelligence.

Stable and flexible cognition depend in part on different alleles of the COMT gene. Carriers of the Met allele are disadvantaged in tasks requiring cognitive flexibility, due to the opposite effects of dopamine levels on WM and cognitive flexibility (Witte and Flöel, 2012). Whilst Met carriers show better performance on the Wisconsin Card Sorting Test (WCST) and other tasks of WM or executive functions (Egan et al., 2001; Bruder et al., 2005; Caldù et al., 2007; Enoch et al., 2009), they also show larger switching costs when performing a task-switching paradigm (Colzato et al., 2010). Conversely, Val carriers are better at expressing their emotions in verbal form (Swart et al., 2011) and show lower switching costs, which translate into a higher index of cognitive flexibility (Colzato et al., 2010). In a recent study, the COMT gene locus explained 5.8% of the variance in donation behaviour, with Val carriers donating about twice as much money as individuals without a Val allele. This suggests that the Val allele favors prosocial/altruistic behavior (Reuter et al., 2011). Male Met carriers are more likely to be affected with obsessive-compulsive disorder, suggesting that the relative inflexibility of neural processing associated with met-COMT can become excessive, rendering the individual vulnerable to obsessions and compulsions (Pooley et al., 2007). Val-COMT individuals also show a greater amygdala-orbitofrontal connectivity in response to negative emotional stimuli that indicates inflexible emotional processing (Drabant et al., 2006). Goldberg et al. (2003) also showed a positive effect of COMT on a WM paradigm (N-back), with Val/Val and Met/Met individuals showing the lowest and highest performance, respectively.

If the frequencies of these alleles vary across population, they may result in different types of genotypical abilities and behavioral predispositions. Indeed, the COMT*L (the site-present allele, Met, that encodes the low-activity enzyme) and COMT*H (the site-absent allele, Val, that encodes the high-activity enzyme) alleles show significant world-wide variation, as reported by a study surveying allele frequencies of this polymorphism in a global sample of populations (Palmatier et al., 1999). Palmatier and colleagues showed that Europeans have the highest frequency of the COMT*L allele, while the COMT*H allele is much more common in populations in all other parts of the world. Their study also established that the COMT*L allele is a derived allele unique to humans. A derived allele is an allele that arises during evolution due to a mutation. In contrast, all seven nonhuman primates (gorilla, two species of chimpanzee, bonobo, and orangutan) have the G nucleotide at the variable position in the COMT gene. “The presence of the G nucleotide at this site indicates that the ancestral allele of the COMT gene in humans is the restriction site absent, Valine 158, high activity COMT*H allele” (Palmatier et al., 1999, p. 562).

Further evidence that the activity of the COMT enzyme

progressively diminished during evolution is provided by Chen et al. (2004). Comparison of the human and mouse DNA reveals that the mouse has Leucine (Leu) at the Val/Met position of the human COMT protein. The researchers found that, after synthesizing the soluble form of human and mouse COMT proteins, the mouse COMT-Leu had much higher activity than the human COMTs, and the human COMT-Val had greater activity than COMT-Met. In addition, they introduced human Val and Met mutations into the mouse and the results indicated that these mutations at the Leu site dramatically decreased the activity of the COMT proteins.

The authors concluded that “these various observations suggest that mutations from Leu to Val to Met at this polymorphic site in the COMT gene resulted in progressively lower COMT activity” (Chen et al., 2004: 814).

This provides another key to understanding the evolution of human intelligence, which so far has been correlated mostly with brain size. However, it is clear from the archeological data reviewed above that human behavior and culture became increasingly complex long after brain size had stopped increasing. Since higher COMT activity leads to impaired prefrontal cortical function (Chen et al., 2004), it is likely that highly intelligent behavior was produced by more efficient prefrontal function, which in turn was modulated by lower COMT enzyme activity, resulting in a higher dopaminergic state in the neocortex.

The point of human evolution at which the mutation responsible for the Met allele arose is not known. However, given the archeological evidence briefly reviewed above (see Coolidge et al., 2013 for a lengthier review), it is not impossible that this mutation arose around 50000 years ago when an evolutionary leap in human behavior can be inferred from the artifacts (even if this mutation predates human expansion out of Africa, it is still possible that differences in the frequencies of this mutation between populations exist). The earliest evidence for technological complexity suggestive of higher WM is found in Europe and this, accompanied by the finding that the Met allele is more frequent in European populations, suggests that the singular type of civilization achieved by Europeans may have a genetic basis. By contrast, the lowest levels of this allele are found among the Biaka (a pygmy tribe) of Africa and the Karitiana of South America, with 7% and 1% respectively, compared to an average frequency of 50% for the same allele among Europeans (Palmatier et al., 1999). The frequency of Met among Sub-Saharan Africans in general is lower than among Europeans, but much higher than among pygmies. Most Sub-Saharan Africans have made the transition from hunter-gatherers to settled farmers at one or another time during the last 4000 years, many millennia after the beginnings of agriculture in the Middle East and Egypt (Neumann, 2003), while most of the pygmies retain a primitive hunter-gatherer existence. Diamond (1997: 380) notes that the hunter-gatherer pygmies are “without crops or livestock.” Furthermore, the pygmies “were formally widespread through the equatorial forests until displaced and isolated by the arrival of black farmers” (Diamond, 1997: 380). On the other hand, the artistic achievements of the pygmies seem to be as high or higher as those of other Afri-

can populations. For example, pygmy music is characterized by a polyphonic style of singing and an extremely developed yodeling technique. Music plays an integral role in Baka society and, along with dance, is an important part of rituals, group games and tales, and pure entertainment. The Baka use traditional instruments of their own creation such as the flute, floor-standing bow, and musical bow but also instruments obtained from the Bantu, such as cylindrical drums and the harp-zither (Devin, 2012).

In turn, pygmy music was copied by their non-pygmy neighbors. This suggests that the pygmies’ greater artistic talent was balanced by less-developed technical skills.

Hunter-gatherer societies are characterized by an egalitarian social system, without power hierarchy, where resources and responsibilities are shared equally and the political structure is organized through kinship relations.

The San, the Biaka, and the Mbuti are the most numerous hunter-gatherer groups still living today in Africa.

The San are an ethnic group comprising different tribes of hunter-gatherers living in the Kalahari Desert of Namibia, Botswana, and the adjoining area of Angola. The San groups speak many dialects of Khoisan languages. They are characterized by an egalitarian social system. The Biaka (Bayaka) are one of Africa’s major ‘pygmy’ groups, sometimes referred to as the ‘western pygmies.’ They live in nomadic bands and subsist through hunting and gathering. The Mbuti live in the Ituri Forest in the Democratic Republic of the Congo (formerly Zaire). They speak several Nilo-Saharan and Niger-Kordofanian languages usually using the language of the farmers nearest to their band’s territory. Each group is composed of a number of territorially defined nomadic bands that exist without formal political structure, basing decisions upon the consensus of respected elders. Although many people have settled in villages, some Mbuti still live a traditional existence based on hunting and gathering supplemented by trading meat and labor with nearby farmers in exchange for tobacco and manufactured goods (Turnbull, 1965).

With regards to the relationship between genes and culture/society, a plausible scenario can be derived from a mechanism of gene-culture interaction (based on dual-inheritance theory) which is a mechanism whereby “culturally transmitted information, expressed in behaviour and artefacts, spreads through populations, modifying selection acting back on populations” (Laland, 2008). The best-studied example of gene-culture interaction is that regarding the evolution of lactose tolerance. Beja-Pereira et al. (2003) after finding substantial geographic coincidence between high diversity in cattle milk genes, locations of the European Neolithic cattle farming sites, and present-day lactose tolerance in Europeans, concluded that natural selection modulated by culture favored lactase-persistent individuals in cultures in which dairy products were available as a food source.

The hypothesis of the present study is that ethnic groups start as hunter-gatherers in their respective geographical locations. The populations with a higher genotypic level of WM or fluid intelligence (thanks to a high frequency of the Met allele) were initially advantaged in their quest for technological progress and the adoption of a sedentary lifestyle

requiring planning, such as that of agriculturalism. The behavioral inflexibility and lower emotional intelligence/altruism associated with Met allele carrier status favored the development of a hierarchical society, where resources were not shared but were concentrated in the hands of a few and formal rules governed human relationships. This first gave rise to city-states, ancient empires, and eventually the modern Western economy and society, based on monetary profit and scientific progress. Conversely, ethnic groups characterized by very low frequencies of the Met allele, but high Val frequencies, were predisposed to form deeper bonds based on reciprocity and altruism. Their higher behavioral and cognitive flexibility made it harder for them to accept the rule of formal rules or an impersonal bureaucracy.

An additional mechanism of gene–environment interaction can be included, which involves the addition of a feedback loop, with culture acting back on genes via selective pressure, which eventually increased the initial genetic differences between different, isolated populations.

Another important selective factor is climate. Indeed, even within hunter-gatherer societies there is variation which can be accounted for by different climatic conditions. Foragers living at higher latitudes usually employ more complex technologies and their hunting patterns require long-term planning, which would be enhanced in Met allele carriers. For example, complex foragers of the north-west coast of North America feed on seasonally abundant anadromous fish, a lifestyle that “promote[s] storage and investment in time-consuming technologies, such as weirs and smoke houses, with delayed returns” (Marlowe, 2005). Conversely, the Val allele, by conferring higher behavioral flexibility, might be subject to positive selection in more unpredictable, warmer environments.

Torrence (2001) argued that technology’s (weapons, traps, etc.) failure costs, and therefore the level of risk, “increase toward the poles because availability of food decreases with longer winters and there are fewer alternative resources because species diversity has an inverse relationship with latitude.” The author used latitude as a proxy for severity of risk with higher latitudes having higher risks, and showed that the diversity of tools is positively correlated with latitude because “special purpose tools are most effective at reducing the probability of risk” (Torrence, 2001). Also the complexity of tools increases at higher latitudes because “adding extra parts can decrease time spent hunting and add to the reliability of the tool.” For example, the Australian Aranda, who live in an aseasonal environment with many alternative plant and animal resources, use very few tools. In contrast, the Angmagsalik Inuit, who have very few alternative sources of food, depend on a very diverse and complex assemblage of tools in which there are many diverse harpoon forms: for example, one type of harpoon comprises 26 parts (Torrence, 2001). Storage also varies depending on climatic condition and thus the probability of loss (i.e. risk). High-risk/high-latitude groups, such as the north-west coast Indians, developed complex ways to store and smoke salmon on which their subsistence is heavily dependent for the entire winter. On the other hand, groups with low risk, such as the !Kung Bushman or Australian Aborigines, store very little food and have little special technology to do so.

Besides COMT, other genes have been linked to intelligence. FBNP1L is the most significantly associated gene for intelligence (Davies et al., 2011; Benyamin et al., 2013). This gene is strongly expressed in neurons, including hippocampal neurons, in developing brains and regulates neuronal morphology (Davies et al., 2011). A recent genome-wide association study on childhood intelligence from 17989 individuals (Benyamin et al., 2013) showed that FBNP1L is associated with childhood intelligence ($P = 0.003$).

This study replicated the findings of a previous one on adult intelligence (Davies et al., 2011) which was carried out on 3511 unrelated individuals with data on over 500000 SNPs and found a significant association between fluid intelligence and FBNP1L. More precisely, the ancestral allele, T, of the SNP rs236330 is correlated with lower intelligence (see Supplementary Table 2 in Benyamin et al., 2013).

These aim of this study are the following:

1. To test the prediction following from the hypothesis that populations with higher Met frequencies are characterized by an agricultural lifestyle (high technology, bureaucratic), whereas populations with a low Met frequency are characterized by a hunter-gatherer lifestyle (low technology, egalitarian). However, hunter-gatherers living at higher latitudes (e.g. Inuit) are expected to show higher frequencies of the Met allele.
2. Another prediction is that Met allele frequencies will be positively correlated to WM/fluid intelligence across populations.
3. To find out if climate had a selective effect on COMT Val 158 Met allele frequencies.
4. To test the hypothesis that intelligence genes (COMT and FBNP1L) have a similar geographical distribution and show similar correlations with intelligence across and within populations

In this study, IQ was used as a proxy for WM. IQ is very similar to, but not identical with, WM and fluid intelligence. Besides fluid intelligence, it comprises a component of crystallized intelligence, which varies depending on the type of test used. However, the most-used IQ test (Raven’s SPM) is considered a good measure of fluid intelligence, tapping marginally on crystallized intelligence. Two meta-analyses estimate the correlation between fluid intelligence and WM to be $r = 0.72$ (Kane et al., 2005) and the other estimated it to be $r = 0.85$ (Oberauer et al., 2005). Wacker et al. (2012) showed that Met allele carriers perform significantly better on tests of fluid intelligence (Cattel’s Culture Fair Test). Although studies of COMT’s relationship with higher cognition usually employ WM or executive function paradigms, a meta-analysis reports that IQ is the only cognitive measure to exhibit a robust and statistically significant positive association with COMT (Barnett et al., 2008). Conversely, this meta-analysis did not find statistically significant associations with other measures such as the WCST, N-back task or verbal fluency (however, a more recent meta-analysis confirmed the association between COMT and other measures of executive function, see Mier et al., 2010). The inclusion of IQ in this study is thus justified on empirical grounds and also on its neural prefrontal basis as suggested by neuroimaging evidence (Duncan et al., 2000).

Since IQ data for different populations are much more consistent and easier to find than for WM, IQ will be used as a proxy for WM. Intelligence tests administered to developing countries are usually ‘culture fair’ and thus tap primarily fluid abilities. Unfortunately, norms based on standardized scores for tasks requiring flexible cognition, such as divergent thinking or switching paradigm, are not easily found and make it impossible to compare different populations across the globe.

Methods

COMT Val158Met allele frequencies were taken from the Allele Frequency Database (Alfred, http://alfred.med.yale.edu/alfred/SiteTable1A_working.asp?siteid=SI000155L). The Alfred database reports frequencies for 142 samples from 87 populations. When a population had more than one sample, their average frequency is reported in the table. Samples from ‘European Mixed’ and African American were left out as they were mixed samples of unclear geographic origin. Frequencies for the Inuit of Greenland were obtained from a recent study (Ghisari et al., 2013). This has not yet been added to the Alfred database because of slight delays (Kenneth K. Kidd, personal communication), but it will be added soon. Data for the British population was also available in Palmatier’s landmark study (Palmatier et al., 1999) but is not reported in Alfred. Thus, this population was added to the present sample.

This resulted in a total of 87 populations. These are reported in Table 2, along with latitude values. Latitude (absolute value) taken from Alfred’s database for each population (representing two opposite corners of a rectangle encompassing the area where the population lives) was used as a proxy for climate. Frequencies of rs236330 were obtained from the HapMap database (<http://hapmap.ncbi.nlm.nih.gov/>). Unfortunately, the Alfred database did not have data for this SNP, so the analysis had to be restricted to the 11 populations sampled in the International HapMap project. There are not enough indigenous populations to compute a correlation with latitude, as some of them live in continents different from their origin (e.g. Chinese in Denver or African-Americans).

IQs were taken from Lynn (2006), Lynn and Vanhanen (2012). The reported IQ refers to the average country or population’s IQ. Countries are grouped into racial groups or clusters as found in Cavalli-Sforza et al. (1994). These are: Native American, Sub-Saharan African, European, East Asian, South-West Asian, Pacific Islanders).

Results

Hunter-gatherer and farming societies significantly differ in their COMT allele frequencies, confirming the prediction following from the hypothesis

The average Met frequency for the whole sample ($n = 87$) was 0.354.

Table 1 reports G and A frequencies for hunter-gatherers in South America and Africa plus the Inuit. Table 2 reports allele frequencies for agriculturalists in South America and Africa. These were averaged if more than one sample was

Table 1. Hunter-gatherers

Population	Met allele %	Val allele %
San (Africa)	0.080	0.920
Biaka (Africa)	0.059	0.941
Mbuti (Africa)	0.206	0.794
Sandawe (Africa)	0.321	0.680
Karitiana (South America)	0.013	0.987
Ticuna (South America)	0.219	0.781
Inuit	0.57	0.43

Table 2. Farmers

Population	Met allele %	Val allele %
Bantu (Africa)	0.365	0.635
Ewe (Africa)	0.300	0.700
Fanti (Africa)	0.230	0.770
Ga (Africa)	0.200	0.800
Ghanaian (Africa)	0.260	0.740
Hausa (Africa)	0.263	0.737
Ibo (Africa)	0.365	0.635
Yoruba (Africa)	0.367	0.632
Chagga (Africa)	0.278	0.722
Ethiopian Jews (Africa)	0.328	0.672
Masai (Africa)	0.325	0.675
Mandenka (Africa)	0.330	0.670
Mozabite (Africa)	0.420	0.580
Quechua (South America)	0.409	0.591
Surui (South America)	0.321	0.679

available for a group.

Because the Inuit live in extreme climatic conditions and at very high latitude (which is correlated to Met frequency), they were regarded as a geographical outlier, thus samples from South America and Africa (two continents located similarly relative to the equator) were compared. The average Met allele frequency among hunter/gatherers was 0.149, whereas among farmers it was 0.3174. The difference between the two samples’ means was highly statistically significant (independent samples, unequal variances Student’s t : $P = 0.015$).

Sample means were compared also within the same continent, in order to eliminate possible confounds due to continental variation in the variables or overrepresentation of one continent over the other. Since there were only four cases for South America, the analysis was re-run only for Africa. This comparison again resulted in a significant statistical difference between farming and hunter-gatherer groups (means: 0.12 and 0.31; $P = 0.0319$).

The Inuit sample was included in the analysis comparing hunter-gatherers ($n = 7$) with non-hunter-gatherer populations (farming, industrialized) from the entire sample ($n = 80$). Again, non-hunter-gatherer populations had a higher frequency of the Met allele (0.366) than hunter-gatherers (0.211) and this difference was highly significant (independent samples, unequal variances Student’s t : $P < 0.001$).

National IQs are positively correlated to Met allele frequency

Table 3 reports IQ and Met allele frequencies, taken from

Table 3. Allele frequencies of groups and tribes living within the same country and belonging to the same racial group were averaged out and the relative IQ is that of the country they live in

IQ	% Met	Countries	Tribes
(Africa)			
74	0.345	Kenya	Bantu + Masai
54	0.008	San	
53	0.059	Biaka	
70	0.2475	Ghana	Ewe, Fanti, Ga, Ghanian
71	0.332	Nigeria	Hausa, Ibo, Yoruba
53	0.206	Mbuti	
72.5	0.299	Tanzania	Chagga, Sandawe
69	0.328	Ethiopian Jews	
70.5	0.33	Senegal	
(South-west Asia)			
82.5	0.416	Syria, Lebanon	Druze
91	0.384	Yemeni Jews	
86	0.57	Palestinian	
84	0.465	Pakistan	Burusho, Kalash, Pashtun, Khanty, Brahui, Hazara, Sindhi
88.5	0.45	Turks	
83.5	0.5	Iran	
82	0.232	India	Kachari, Keralite
(Europe)			
100	0.58	Basque	
96.5	0.478	Russia	Russians, Khanty, Komi-Zhirian, Chuvash
98	0.609	Danes	
99	0.572	Estonian	
97	0.529	Finns	
98	0.47	French	
96.5	0.533	Hungarian	
93	0.512	Irish	
97	0.46	Italians	
110	0.486	Ashkenazi Jews	
N/A	0.56	Orcadian	
90	0.36	Sardinian	
97	0.43	Spaniards	
100	0.53	British	
(East Asia)			
100	0.25	Mongolia	
105.5	0.243	China	Dai, Daur, Han, Miao, Naxi, Orogen, She, Tu, Tujia, Uyghur, Yi, Hakka
105	0.304	Japan	
106	0.248	Korea	
96	0.3	Vietnam	Lahu
N/A	0.297	Cambodians	
88	0.221	Thailand	
N/A	0.295	Yakut (Siberia)	
(Pacific Islanders)			
82.5	0.44	Papua New Guinea	
82.5	0.262	Melanesia	
N/A	0.135	Micronesians	
(Native Americans)			
N/A	0.293	Cheyenne	
N/A	0.168	Pima (Arizona)	
N/A	0.352	Pima (Mexico)	
N/A	0.367	South-west Amerindians	
N/A	0.55	Maya, Yucatan	
N/A	1	Amerindians	
N/A	0.013	Karitiana	
N/A	0.409	Quechua	
N/A	0.321	Surui	
N/A	0.219	Ticuna	
86	0.369	All Native Americans	
91	0.579	Inuit (Greenland)	

Table 4. Allele frequencies for populations and latitude

Population	Met allele %	Latitude	Population	Met allele %	Latitude
Bantu (Kenya)	0.365	1	Turks	0.45	39
San (Kalahari desert)	0.080	20.5	Balochi (Iran)	0.50	28
Biaka	0.059	3.5	Brahui (Pakistan)	0.42	27.5
Ewe (Ghana)	0.300	6.525	Hazara (Pakistan)	0.52	31
Fanti (Ghana)	0.23	6.25	Keralite (India)	0.214	10.5
Ga (Ghana)	0.2	6.25	Sindhi (Pakistan)	0.42	25.5
Ghanaian	0.260	7.875	Ami (Taiwan, Austronesian)	0.1645	23.25
Hausa (Nigeria)	0.263	12.5	Atayal (Taiwan, Austronesian)	0.183	23.625
Ibo (Nigeria)	0.365	6	Dai (China)	0.2	24.5
Mbuti	0.026	1.5	Daur (China)	0.280	45.5
Yoruba (Nigeria)	0.367	8	Han (China)	0.259	31
Chagga (Tanzania)	0.278	3	Hezhe (China*, Tartar)	0.330	48.25
Ethiopian Jews	0.328	13.5	Japanese	0.304	38
Masai (Kenya)	0.325	2.5	Kachari (India)	0.250	27.25
Sandawe (Tanzania)	0.321	3.5	Korea	0.248	38.75
Mandenka (Senegal)	0.330	13.5	Lahu (Vietnam)	0.300	25
Mozabite (Algeria)	0.420	32.5	Miao (China)	0.150	27.5
Bedouin	0.410	30.25	Naxi (China)	0.110	26.5
Druze (Syria, Lebanon)	0.416	33.25	Orogen (China)	0.250	46.5
Yemenite Jews	0.384	15	She (China)	0.300	25.5
Palestinian	0.570	31.5	Tu (China)	0.300	35.75
Samaritans	0.45	32	Tujia (China)	0.200	29.5
Adygei (Northern Caucasus)	0.361	44.5	Uyghur (China)	0.450	42.5
Basque	0.58	43.125	Xibe (Mongolia)	0.170	45
Chuvash (Russia)	0.548	55.5	Yi (China)	0.250	28.25
Danes	0.609	56.3	Cambodians, Khmer	0.297	12.5
Estonian	0.572	58.5	Hakka (China)	0.167	28.5
Finns	0.529	67.5	Lao Loum (Thailand)	0.221	18.5
French	0.470	46.75	Papuan New Guinean	0.440	6
Hungarian	0.533	47	Melanesian, Nasioi	0.262	6
Irish	0.512	53.5	Micronesians	0.135	7.5
Italians	0.46	42.5	Yakut (Siberia)	0.295	64.5
Jews, Ashkenazi	0.486	N/A	Cheyenne (Oklahoma)	0.293	35.5
Orcadian	0.56	59.125	Pima, Arizona	0.168	33.5
Russians	0.562	65	Pima, Mexico	0.352	29.25
Sardinian	0.36	40	Southwest Amerindians	0.367	31.75
Spaniards	0.43	40	Maya, Yucatan	0.55	19
Burusho (Pakistan)	0.48	35	Amerindian	1	65
Kalash (Pakistan)	0.54	35	Karitiana	0.013	9.25
Pashtun (Pakistan)	0.41	31.5	Quechua	0.409	13.5
Khanty (Russia)	0.42	63	Surui	0.321	10.25
Komi-Zyrian (Russia)	0.383	64	Ticuna	0.219	3.5
Mongolian	0.25	45.5	Inuit	0.579	75

the Allele Frequency Database. IQs were taken from Lynn (2006), Lynn and Vanhanen (2012). Populations from the same country are grouped together and their average allele frequency is reported. The reported IQ refers to the average IQ for the country. Countries are grouped into racial groups or clusters as found in Cavalli-Sforza et al. (1994).

The correlation between IQ and Met frequencies for the global sample was computed. Due to unavailability of IQs for single Native American populations, their overall estimated IQ (86) was used (Lynn, 2006) and the allele frequencies of the different populations were averaged. Thus, the global correlation between IQ and Met allele frequency is $r = 0.579$ and highly statistically significant ($n = 38$; $P < 0.001$). This supports the prediction that populations with higher Met allele frequency have higher IQ, similarly to the correlation observed at the individual level.

In Africa, this correlation is $r = 0.879$ ($n = 9$; $P < 0.0001$); in Europe, $r = 0.688$ ($n = 12$; $P < 0.01$); in East Asia, $r = 0.306$ ($n = 6$; $P = 0.43$); in South-West Asia, $r = 0.198$ ($n = 7$; $P = 0.34$). These correlations are all positive and in the expected direction, albeit only the correlations within Africa and Europe are statistically significant.

Correlation for Native Americans and Pacific Islanders could not be computed due to the unavailability of IQs for the individual populations.

Met allele frequency is positively correlated to latitude

Table 4 reports allele frequencies and latitude for all the populations from the Alfred database.

The correlation between latitude and Met allele frequency was $r = 0.553$ and highly statistically significant ($n = 87$; $P < 0.001$).

Table 5. Frequencies of ancestral alleles from the HapMap databases for rs4680 and rs236330

Populations	rs4680 (G)	rs236330 (T)
ASW	0.728	0.58
CEU	0.522	0.181
CHB	0.712	0.099
CHD	0.736	0.128
GIH	0.569	0.094
JPT	0.71	0.226
LWK	0.706	0.691
MEX	0.638	0.184
MKK	0.729	0.577
TSI	0.549	0.216
YRI	0.687	0.701

ASW, African ancestry in south-west USA; CEU, Utah residents with northern and western European ancestry from the CEPH collection; CHB, Han Chinese in Beijing; China; CHD, Chinese in Metropolitan Denver; Colorado; GIH, Gujarati Indians in Houston; Texas; JPT, Japanese in Tokyo; Japan; LWK, Luhya in Webuye; Kenya; MEX, Mexican ancestry in Los Angeles; California; MKK, Maasai in Kinyawa; Kenya; TSI, Tuscan in Italy; YRI, Yoruban in Ibadan; Nigeria.

Table 6.

Populations	IQ	rs236330 (T)
ASW	85	0.58
CEU	100	0.181
CHB	105.5	0.099
CHD	103	0.128
GIH	86	0.094
JPT	105	0.226
Kenya (LWK + MKK)	74	0.634
Mex	88	0.184
TSI	100	0.216
YRI	71	0.701

See Table 5 for abbreviations.

COMT and FBNP1L have fairly similar geographical distributions

Table 5 reports the values of the frequencies of the two ancestral alleles of the two genes (COMT and FBNP1L) for all the 11 populations of the HapMap database. The correlation between them is $r = 0.437$ and approaches significance (one-tailed $P = 0.089$; two-tailed $P = 0.179$).

The T allele of rs236330 is negatively related to intelligence across ethnic groups

Table 6 reports IQs and FBNP1L frequencies for the populations of Table 5. There are 10 rather than 11 populations as Table 4 had two samples from the same country (Kenya). The correlation between IQ and the ancestral allele (T) of rs236330 is $r = -0.8055$ (non-directional $P < 0.01$).

Discussion

A survey of the population genetics database provides evidence that COMT gene (SNP Id: rs4680) frequencies vary across populations. Moreover, there is a statistically significant association between lifestyle and frequency of two alleles responsible for higher cognition and executive function

in humans. Ethnic groups whose economy is based on farming have higher frequencies of the Met allele (symbol: A), whereas societies based on a hunter-gather economy have very low frequencies of the Met allele and a disproportionate predominance of the Val allele. Moreover, hunter-gatherers living at high latitudes (Inuit) show high frequencies of the Met allele, possibly due to the higher pressure on technological skills and planning abilities posed by the adverse climatic conditions near the North Pole. This suggests that the genotype of a population influences its cultural development in fairly specific and predictable ways, by constraining its development along a predefined path. However, it is likely that natural factors (e.g. climate) can place strong demands on survival abilities and may have a selective effect on genes related to cognition. Thus, the relationship between genes and a hunter-gather lifestyle must be seen in light of natural constraints.

This study found that national IQs are positively correlated to Met allele frequency, suggesting that Met allele frequencies are positively correlated to WM and fluid intelligence across populations, replicating at the aggregate level the findings from studies on individuals. The correlations are positive both for the whole sample and also within different racial groups, reaching an extremely high value among African people ($r = 0.88$). This result in turn supports the first hypothesis, which is based on the assumption that higher population Met frequencies are reflected in different ethnic cognitive profiles.

The A mutation is likely to have been subject to positive selective pressure, due to the obvious advantages associated with higher intelligence. The correlation observed between IQ and Met allele frequency ($r = 0.57$ at the global level) is a bit higher than expected, because much lower correlations are found at the individual level. The correlation could be inflated by the presence of other genes coding for intelligence which have a similar geographical distribution to COMT. Indeed, this study also found a strong association between another important intelligence gene (FBNP1L) and population IQ ($r = 0.81$). European and East Asian people have the highest IQ in the sample but also the lowest frequency of the ancestral allele (T) rs236330 which is correlated with lower intelligence within populations. Moreover, COMT and FBNP1L seem to present a similar geographical distribution, as suggested by the positive correlation ($r = 0.47$) between them across the 11 populations sampled in the HapMap project.

This phenomenon could explain why the association of COMT and FBNP1L with intelligence between populations seems to be stronger than that within populations. Indeed, if intelligence genes have similar geographical distributions, all the individual genes' small effects on intelligence are added together, thus accounting for a substantial share of the ethnic differences in IQ. This scenario is likely if selective pressure for higher fluid intelligence or better prefrontal function has been stronger in some populations than in others. The same argument could also be made from within a larger evolutionary framework. As noted in the introduction, there has been a steady decrease in COMT activity during evolutionary history, so that it progressively diminished from the high-activity Leu allele in mice, to the Val allele in

primates to the Met allele in humans (Chen et al., 2004). Thus, a decrease in COMT activity has been accompanied by a huge increase in intelligence during mammalian evolution. However, it is unlikely that the improvement in cognitive function from mice to primates to humans has been caused by COMT mutations alone. In fact, it is likely that COMT was only one of the many genes responsible for the increase in cognitive function observed during the evolution of the mammalian brain. The same argument could be applied to differences between human populations, so that COMT's association with population IQ is not only causal but also due to the presence of other genes coding for more advanced cognitive abilities.

The present paper provided a possible factor (namely, climate) acting as selective pressure on intelligence genes, with the finding of a correlation between latitude and COMT ($r = 0.56$). The method of correlating gene frequencies with climatic variables has been employed by Cavalli Sforza and colleagues in a variety of studies (Piazza et al., 1980; Piazza and Menozzi, 1984) and interpreted as indicating selective pressure from the environment. In their study of the correlation between frequencies of 122 genetic markers and 3 climatic factors, they found only 5 correlations above 0.5 and the number of correlations above 0.30 was 19, over a total of 366 correlations examined (Cavalli-Sforza et al., 1994). Thus, the correlation found in the present study cannot simply be dismissed as a statistical fluke.

From an evolutionary perspective, it may be speculated that the personality and cognitive profile associated with the Met allele (higher stability, better planning skills) conferred higher fitness in colder climates, which are characterized by more predictable climatic conditions.

A recent study (Ghisari et al., 2013) shows that the Inuit of Greenland, an ethnic group descended from north-east Asians, has very high frequencies of the Met allele (57%). This seriously undermines the explanation of genetic variation in terms of historical migrations of people, as the two most closely genetically related racial groups (Native American and East Asians) have much lower frequencies of Met (around 0.3). Instead, this finding favours the explanation in terms of climate's selective pressure, as people who are genetically very close yet live in places with very different weather conditions also have different frequencies of the COMT gene.

At the opposite end of the genetic and geographical/climatic spectrum, pygmies are an ethnic group with the lowest frequency of the Met allele, characterized by an absolute prevalence of the Val allele. It has been reported that Aka fathers have their infant within arm's reach 47% of the time and have been described as the 'best Dads in the world' (Sullivan, 2005). It has been observed that they pick up, cuddle, and play with their babies at least five times as often as fathers in other societies. It is believed that this is due to the strong bond between Aka husband and wife. Throughout the day, couples share hunting, food preparation, and social and leisure activities. The more time Aka parents spend together, the greater the father's loving interaction with his baby (Hewlett, 1991).

In addition, the Mbuti pygmy have no ruling group or lineage, and no overlying political organization. The Mbuti are

an egalitarian society where men and women basically have equal power. Issues in the community are solved and decisions are made by consensus, and men and women engage in the conversations equally. Little political or social structure exists among the Mbuti.

The higher emotional processing abilities and higher cognitive flexibility of Val carriers are reflected in pygmy society, which is characterized by a prevalence of this allele.

However, COMT is only one of the many genes responsible for variation in cognition, although it is the best studied so far. Thus, it is probable that many other genes act along with COMT to explain cognitive and cultural differences. Particularly interesting is the relatively low frequency of COMT in East Asian populations (range 0.22–0.30), which contrasts with their reported higher IQ (105). In fact, a recent study (Wang et al., 2013) shows that the COMT polymorphism operates in the opposite fashion among Chinese subjects. In this population, the Val allele was associated with better WM performance and greater hippocampal volume. The authors interpreted this surprising finding in terms of population-specific effects of gene–gene interaction.

Whilst this study provides no conclusive evidence that genes or even a single polymorphism can account for substantial variation across human cultures, it provides an hypothesis that could be tested in future studies. These will have to use more direct measures (divergent thinking, WM, tasks of executive function, etc.) to determine whether the correlation between cognition, behavior and COMT gene that is observed at the individual level also holds in a cross-ethnic context. As more genes for intelligence are detected, it will also be possible to test the hypothesis (preliminarily advanced here) that they exhibit a similar geographical distribution.

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