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The DRD2 *Taq1A A1* Allele May Magnifiy the Risk of Alzheimer's in Aging African Americans

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Abstract

Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys cognitive skills and the ability to perform the simplest tasks. More than 5 million Americans are afflicted with Alzheimer's; a disorder which ranks third, just behind heart disease and cancer, as a cause of death for older people. With no real cure and in spite of enormous efforts worldwide, the disease remains a mystery in terms of treatment. Importantly, African Americans are two times as likely as Whites to develop late-onset Alzheimer's disease and less likely to receive timely diagnosis and treatment. Dopamine function is linked to normal cognition and memory and carriers of the DRD2 ***Taq1A A1*** allele have significant loss of D2 receptor density in the brain. Recent research has shown that A1 carriers have worse memory performance during long-term memory (LTM) updating, compared to non-carriers or A2-carriers. A1-carriers also show less blood oxygen level dependent (BOLD) activation in left caudate nucleus which is important for Long Term Memory (LTM) updating. This latter effect was only seen in older adults, suggesting magnification of genetic effects on brain functioning in the elderly. Moreover, the frequency of the A1 allele is 0.40 in African-Americans, with an approximate prevalence of the DRD2 A1 allele in 50% of an African American subset of individuals. This is higher than what is found in a non-screened American population (≤28%) for Reward Deficiency Syndrome (RDS) behaviors. Based on DRD2 known genetic polymorphisms, we hypothesize that the DRD2 ***Taq1A A1*** allele magnifies the risk of Alzheimer's in aging African Americans. Research linking this high risk for Alzheimer's in the African American population, with DRD2/ANKK1-TaqIA polymorphism and neurocognitive deficits related to LTM, could pave the way for novel, targeted pro-dopamine homeostatic treatment.

Keywords

Dopamine; Alzheimer's Disease; Reward Deficiency Syndrome; DRD2 gene; Long-term Memory (LTM); Early Life Stress; African Americans

Introduction

Based on the current literature, we hypothesize that the DRD2 ***Taq1A A1*** allele, heretofore referred to as A1, may magnify the risk of Alzheimer's disease (AD) in aging African Americans. This hypothesis is based on growing scientific evidence linking the minor DRD2 allele with memory problems and with structural changes in reward centers of elderly patients. This hypothesis is presented to stimulate further research of this concept, which will provide genetic information that could result in precision medicine targeted to potentially high risk African Americans.

Following the initial work of Noble, Blum and associates showing the first association of the DRD2 ***A1*** allele and severe alcoholism [1], there have been 4,374 articles published on this gene in Pubmed (7-30-17). A carrier of this A1 allele of the DRD2 gene may display many risky behaviors, neurological disorders, and cognitive impairment associated with altered circuitry, and these may be manifested in the form of impulsivity, decision-making problems, addiction, mood disorders and other reward deficiencies [2–16]. These clinical presentations include alcoholism, drug dependence (opioids, cocaine, nicotine, marijuana,

glucose sedative – hypnotics); pathological gambling, internet gaming, post-traumatic stress disorder, inability to cope with stress, aggression, antisocial behavior; Parkinson Disease; spectrum disorder (ADHD, Tourette's, Autism) magnification of aging, early onset intercourse, juvenile delinquency, anger issues, obesity, lower education status, higher hospitalization rates, higher mortality rates, suicide ideation, depression, anxiety disorder, anorexia nervosa, binge eating behavior, schizophrenia, paranoia, avoidant behavior, general cognition, temporal cognition, working memory and motivation problems.

DRD2 Gene and Polymorphisms

DA receptor D_2, also known as DRD2, is a G protein-coupled receptor protein encoded by the *DRD2* gene which encodes the D_2 subtype of the DA receptor in humans. Two transcript variants encode different isoforms and a third variant that has been described are the result of alternative splicing of the gene. The *Taq*1A is a single nucleotide polymorphism (SNP) (rs: 1800497), originally thought to be located in the 3′-untranslated region of the DRD2 but has since been shown to be located within exon 8 of an adjacent gene, the ankyrin repeat and kinase domain containing 1 (ANKK1). Importantly, while there may be distinct differences in function, the mislocation of the *Taq*1A allele may be attributable to the ANKKI and the DRD2 being on the same haplotype or the ANKKI being involved in reward processing through a signal transduction pathway [17]. However, it is also possible that the ANKKI and the DRD2 gene polymorphisms may have distinct and different actions with regard to brain function [18] Presence of the $A1^+$ genotype (A1/A1, A1/A2) compared to the $A1^-$ genotype (A2/A2) is associated with reduced receptor density [1,19–21]. This reduction causes hypodopaminergic functioning in the DA reward pathway. The *Taq*1 A allele is a predictive risk allele in families [22]. The association between ANKK1/DRD2 *Taq*1A A2/A2-genotype and higher novelty seeking and lower reward dependence was shown in men but not in women. Finally the binding potential of the DRD2 gene as reported by others suggest an altered dopamine release across the brain reward circuitry, with evidence that carriers of the DRD2 A1 allele are at high relapse risk for alcoholism compared to carriers of DRD2 A2 allele [23].

The neurological and neuropsychiatric manifestation of the DRD2 A1 allele in any given population is influenced by co-expressed enhancing or repressive genetic factors, chemical and psychosocial environment of individuals, their history, ancestry, and co-morbid medical conditions.

Alzheimer's Disease—Alzheimer's disease (AD) is an irreversible, progressive brain disorder that slowly destroys memory and cognitive skills, eventually impairing the ability to carry out the simplest tasks. In most people with Alzheimer's, symptoms first appear in their mid-60s. Estimates vary, but experts suggest that more than 5 million Americans may have Alzheimer's. AD is currently ranked as the sixth leading cause of death in the United States [24], but recent estimates indicate that the disorder may rank third, just behind heart disease and cancer, as a cause of death for older people. The March 2014 issue of *Alzheimer's and Dementia*, reported that approximately 600,000 people aged ≥65 years with Alzheimer's died in 2010, estimated to rise to 900,000 deaths in 2030 and to 1.6 million by 2050 [25]. Therefore, in 2050 the percentage of AD deaths of individuals ≥65 years will increase to

43% of this population compared to 32% for 2010. Moreover, a concurrent 2014 *Neurology* [25] article found that the actual number of deaths due to AD in people ≥75 years could be six times higher than the official count. The projected number of people age 65 and older (total and by age group) in the U.S. population with AD by 2050 is projected at 13.8 million [25–27]. Table 1 presents a number of facts regarding the epidemiology and societal costs of worldwide AD.

Here, in addition to a thorough discussion of the current state of the disparity in identifying AD in different ethnic groups, we also review disparate genetic allelic states and social factors that render African Americans more susceptible than Whites to AD. We also review dopamine function in memory and in aging individuals. Based on evaluation of the literature, we propose that the abnormally high prevalence of a DRD2 minor allele previously associated with addiction, may account for the increased incidence of AD in African Americans.

Observations and Discussion

Awareness and Diagnosis of Alzheimer's Disease in African Americans

It is puzzling that the rate of AD in the African-American population between the ages of 65–74 is 3.13 times more prevalent compared to Whites; is 1.82 times more prevalent between ages 75–84, and remains 1.95 (2 times) more prevalent by ages 85 and above [27,28]. Notably, although this health concern is increasing for African Americans, a study by Jett [29] suggested that many African-American communities consider AD to be a normal part of the aging process. Thus, the actual incidence may be higher and under-reported if dementia is accepted as a normal part of aging. Importantly, medical care professionals must themselves be aware of cultural attitudes, as well as the bias (cultural insensitivity) of cognitive tests, to properly diagnose AD in African Americans, to help bring focus to the incidence disparity and to advocate allocation of medical resources and attention to the care of the aging African-American patient. In 2002, the Alzheimer's Association released an assessment of the so-called "silent epidemic" of dementia within the African-American community. It was reported that African Americans were not well represented at Memory Disorder Centers or Alzheimer's Disease Centers. There is emerging recognition of the disproportionately high rate of Alzheimer's disease within the African-American community [26] and an increasing attitude that dementia within the family unit must be met with care and support for patients and their caretakers alike. Still, many African American communities receive reduced treatment options because they do not self-report due to a lack of trust toward mental health care professionals, and their use of unconventional non-medical terms to describe the condition may not be understood by physicians. To assist in bridging the trust and communication gap between provider and patient, it may be important to adopt a more sensitive approach to capture the diagnosis. For example, Jett [29] has suggested to change the terms used during interactions: "instead of cognitive dysfunctioning, we can ask about mind slippage".

Rovner et al. [30] reported that most African American subjects (56.7%) were unaware that African Americans were at higher risk for AD than Whites. They suggested that cultural diversity within older African Americans may contribute to disparities in the detection and

treatment of AD in this high-risk population. Although this hypothesis paper focuses on the disparity of diagnosis and potential risk-conferring alleles in African-Americans, Table 2 shows that other ethnicities including Hispanics have disparate risks for Alzheimer's.

Genetic Associations of Alzheimer's Disease

Reitz et al. [31] studied 5,896 African Americans; 1,968 with AD, and 3,928 control participants 60 years or older, using datasets collected between 1989 and 2011 at multiple sites. The association of Alzheimer's disease with genotyped and imputed single-nucleotide polymorphisms (SNPs) was assessed in case-control and in family-based data sets. They concluded that AD in African Americans was significantly associated with variants in rs115550680, allele = G of the ABCA7 (ATP-binding cassette transporter), with the APOE e4 allele and with certain other genes. However, many susceptibility loci associated with late onset Alzheimer's disease in European Americans did not reach significance in African Americans even after multiple corrections. The most significant SNPs in African Americans differed from the top-ranked SNPs in Europeans or European Americans [31]. This is concomitant with decidedly higher incidences of AD in African Americans nationwide [26] and when compared to Whites in the same communities [32]. Along these lines, Logue et al. [33] carried a comprehensive genetic association study of AD in African Americans by analyzing a genome-wide set of 2.5 million imputed markers. Genetic risk association was observed with SNPs in Clusterin (CLU), phosphatidylinositol binding clathrin assembly protein (PICALM), bridging integrator 1 (BIN1), ephryn type A (EPHA1), membrane-spanning 4A (MS4A), ABCA7, and myeloid-associated antigen CD33 (CD33), although the effect direction for some SNPs and the most significant SNPs differed from findings in data sets consisting of Europeans. Interestingly, Ghani et al. [34] found an association of recessive long runs (ROHs) of homozygosity with AD among African-Americans. However, the researchers suggest that sequencing is required to uncover AD variants in these individuals. In terms of neurogenetic antecedents to cognitive functioning, although one study suggests the presence of 1 or 2 ApoE epsilon(ε)4 alleles is a determinant of AD risk in African-Americans and Whites [35]; others reported evidence suggesting the ApoE ε4 allele was not associated with cognitive functioning in African Americans diagnosed with AD [36]. Adjusting for sex and education, in the presence of ApoE(ε)4, the risk was approximately equal for African-Americans and Whites, whereas in the absence of ApoE(ε)4 the risk was 4- and 2-fold for African-Americans and Hispanics, respectively, compared to Whites. This allows inference that traditional risk associations associated with European Americans are not applicable to African Americans or Hispanics [37]. Our interpretation of these results do not allow for a simplistic explanation concerning the African American prevalence disparity as genetic associations with memory loss may not hold for African-American

Early Life Adversity and Cognition Disparity in Ethnic Groups

Barnes et al. [38] provided some evidence that in models stratified by ethnic groups, and adjusted for age and sex, early-life adversity was differentially related to cognitive decline in African Americans and Whites. They found in African Americans, unlike Whites, early-life adversity, both food deprivation and being thinner than average in early life, were associated with a slower rate of cognitive decline in older African Americans. It is not yet known if or

how other life stressors such as the experience of violence, socioeconomic status, abuse, or neglect differentially impact different ethnic groups. Consistent with reports for hippocampal structures in Whites with AD [39], in 2001, Sencakova et al. [40] reported that hippocampi of African American AD patients were atrophic with respect to those of healthy African American subjects. Moreover, it was found that there were significant direct correlations between hippocampal volumes and performance on several different neuropsychological tests when patients and healthy subjects were combined. These findings are in agreement with that found for non-African American populations in Braverman et al. [41] who used 3T MRI with sophisticated NeuroQuant® software to measure both evoked potentials and memory/cognition in a mixed gender and age group of cognitively impaired patients. The study revealed hippocampal, central and temporal lobe atrophy, with delayed latency of evoked potentials marginally associated with temporal lobe atrophy. Additionally, reduced fractional anisotropy (FA) in frontal lobes correlated with aging, delayed P300 latency, and decreased visual and working memory. Moreover, the higher the P300 amplitude, the lower the bilateral atrophy, and the higher the immediate memory, the lower the central atrophy. Hippocampal atrophy negatively affected auditory memory, especially in males.

Structural magnetic resonance imaging (MRI) provides key biomarkers to predict onset and track progression of Alzheimer’s disease (AD). Most published reports of relationships between MRI variables and cognition in older adults include racially, ethnically, and socioeconomically homogenous samples. However, recent work by Zahodne et al. [42] using structural MRI as a predictor of late–life cognition compared African-Americans, Hispanics and Whites. They found white matter hyper-intensity (WMH) volumes associated with worse language and speed i.e., executive functioning among African Americans, but not among non-Hispanic Whites. In addition, they also found that larger hippocampal volume was more strongly associated with better memory among non-Hispanic Whites compared with Hispanics.

Other work by Gibbons et al. [43] involving the impact of stress (environment) on cognitive life history strategies (LHS), genetic moderation and the role of discrimination of African-American adolescents helps dissects resilience related to risky behaviors. There is evidence that early risky/impulsive behavior, regardless of race or ethnicity, during critical periods of brain development can influence brain wiring and thus adult cognition and behavior. The role of stress and racial discrimination and African-American risk-taking behavior or development of resilience can be considered in the context of carrying the risk (“sensitivity”) alleles of 2 monoamine-regulating genes, the serotonin transporter gene (5HTTLPR) and the dopamine D4 receptor gene (DRD4). These alleles have been shown to mediate the impact of early stress and perceived racial discrimination in African-American adolescents on LHS cognition. These same parameters were not investigated in Whites or Hispanics. We are proposing that the combination of risky reward gene alleles, impacted by life conditions, could induce unwanted epigenetic effects that may confer risk for AD.

It is known that many genetic polymorphisms are linked to individual differences in cognitive performance [44]. For example, striatal dopamine functions, associated with cognitive performance, are linked to the DRD2 ***Taq A1*** allele polymorphism. The role of

dopamine and memory has been extensively explored and we provide an abridged synopsis in the following section of this article. A Pubmed search (04-01-17) using the search terms “DRD2 gene and Alzheimer’s” retrieved 15 publications loosely related to the topic, and “DRD2 gene and Alzheimer’s in African Americans” retrieved no results.

Dopamine Function and Cognition

Neuroscientists have investigated dopamine and memory for many years, and this information has filled textbooks and review articles [45–48]. In fact, the Nobel Prize in Medicine was awarded to Greengard and Kandel (2000) for their seminal studies of learning and memory, relating to dopamine signaling. Therefore, this section is not exhaustive of the topic, but rather allows for a brief summary to contextualize this review. Dopamine neurons are found in the arcuate nucleus of the hypothalamus, as well as the ventral mesencephalon from which they project to multiple targets in the forebrain. Although dopamine neurons constitute a small sample of the brain’s neuronal population (<1/100,000), they are involved in neuroendocrine regulation, mood, motivation, and psychological processes, such as memory [44].

Flood, et al. [49] had previously demonstrated that the formation of long-term memories was impaired by protein synthesis inhibitors which interfered with the biosynthetic pathways that underlie long-term memory formation. While the specific mechanisms are not clear, protein synthesis inhibitors that induced amnesia, also inhibited tyrosine hydroxylase activity *and* the conversion of tyrosine to dopamine and norepinephrine [49].

Subsequent research showed that neuropeptides and neurotransmitters influence the actions of dopamine. Vasopressin, a hypothalamic neuropeptide, facilitates memory through its interaction with dopamine in the amygdala, and serotonin in the dentate gyrus of the hippocampus [50]. Excitatory N-methyl-D-aspartate neurotransmitter enhances the release of dopamine in rat hippocampal neurons, suggesting a relationship between dopamine activity, synaptic long-term potentiation (LTP) in the hippocampus and long-term memory [51]. Likewise, reductions in acetylcholinesterase (AChE) in rat hippocampus and increased brain acetylcholine and serotonin levels improved learning and memory and were associated with LTP [52]. Lastly, spatial novelty lowered the threshold for LTP in rat CA1 hippocampal synapses, and this facilitation of LTP was dependent upon dopamine activity [53], a finding supported by rodent studies demonstrating that dopamine and norepinephrine release within the hippocampus (not cortex) is necessary for novel contextual learning independently of object recognition [54].

Dopaminergic Mechanisms of Memory

Seminal studies continue to be added to the literature strengthening the importance of dopamine and receptor subtypes in memory formation [55–66]. Aversive, long-term memories were recently shown to be mediated by activation of medial prefrontal cortex localized D1 and D5 receptor activation [67]. Yamagata et al. [68] found that distinct groups of neurons, in Drosophila, support reward for short and long-term memories. The traces of long-term memory, that is, the abstract memory that provides the rules or strategies that organize behavior over time, are stored in the prefrontal cortex (PFC) [69]. Otani et al. [69]

have suggested that long-term synaptic plasticity might provide the cellular mechanism for this type of memory and that dopamine facilitates long-term, synaptic plasticity. Reichenbach, Hermann, Kahne et al. [70] reported that reduced dopamine signaling in alpha-synuclein deficient mice was associated with reduced memory consolidation. These results are consistent with other findings that blocking dopamine signaling, after learning, reduces memory consolidation in guinea pigs [71]. Work in Drosophila demonstrated the importance of a feedback circuit with reward signaling of dopamine neurons in the transformation of a short-term olfactory memory trace into a long-term memory [72]. Finally, Kim et al. [73] described a unique type of dopamine neuron in the monkey substantia nigra pars compacta that stores a stable representation of the past reward value of visual stimuli. The responses of these neurons are strengthened by learning, and are evoked by presentation of the visual stimuli, after the learning has been completed. Thus, this group of neurons supports learning and the retention of learned behavior.

Aging and Dopamine Function Decline

The role of neurogenetics in memory consolidation has been controversial [74]. Individual differences in cognitive performance have been related to genetic polymorphisms. The role of D2 in memory formation, and motivation is well documented in rodent studies which suggest that the D2 receptor surface expression is regulated by interacting proteins like the calcium sensor NCS-1 which can control motivation, exploration, synaptic plasticity, and memory formation [75–77]. The activity of striatal dopamine (DA), which influences cognitive function, is linked to the Taq1A polymorphism of the DRD2/ANKK1 gene. The A1 allele of this genetic polymorphism, in humans, relates to reduced density of striatal DA D2 receptors [1]. Recent research suggests that SNPs in dopamine receptor genes (DRD1, DRD2Taq1A A1, DRD3/Ser9Gly) may impair associative memory specifically, whereas SNPs that confer risk for AD induce general disruption of episodic memory in aging individuals [78].

The A1 allele of the Taq1A polymorphism was associated with an age-dependent reduction in memory performance, LTM updating, and reduced blood oxygen level dependent (BOLD) activation in the left caudate nucleus [79]. This result, which was only seen in older adults, suggests that effects of the Taq1A genetic polymorphism on memory functions are accentuated with age. Moreover, non-1A carriers demonstrated a positive association between BOLD activation of the caudate nucleus and memory updating, supporting the relevance of caudate activation to memory processes. These findings support an association between the DRD2/ANKK1-Taq1A genetic polymorphism and deficits in LTM, a relationship that is amplified in the aging brain.

In addition, studies by Papenberg, Backman, Nagel et al. [80] found that older adults with SNPs of the D2 and D3 receptors, as well as the dopamine transporter gene (DAT1), forgot more information than older individuals with genotypes associated with increased dopamine availability and receptors. This effect was not observed in younger individuals with the same SNPs, supporting the hypothesis that genetic effects on memory are magnified by aging. This hypothesis is consistent with Positron Emission Tomography (PET) research that demonstrated an age-related decline in the dopamine system [81], possibly linked to

structural defects in reward centers of aged individuals carrying a dopamine minor alleles. Roussotte et al. showed that the DRD2 polymorphism rs1076560 predicted an increase in volume of the lenticular nucleus, hippocampus, and other brain regions associated with reward processing, and individuals with this SNP were more susceptible to cognitive decline and dementia [82,83]. They did not however separate this cohort based on ethnicity. In a study of aging, Matuskey et al. [84] have found an age-related decrease in the availability of D2 receptors in the striatum, while D3 receptor availability in this area remained constant or increased with age. Another factor that can change dopamine metabolism in the brain is the chronic exposure to drugs of abuse and chronic stress during early life. These adverse environmental factors can influence hippocampal neuron development and connectivity [85,86] and decrease dopaminergic neurons in the midbrain [87] persistently in adulthood. Therefore, it is plausible that a reduction of dopamine terminals of the hippocampus due to these adverse life experiences could interact with abnormal regional brain architecture due to genetic risks, to enhance memory loss in AD.

Prevalence of the DRD2 Taq A1 allele as a function of Ethnicity

A very important question and even criticism of the early work on the DRDD2 Taq A1 allele frequency in many ethnic groups, centers around the suggestion of Barr and Kidd [88] that allelic differences using samples from Whites do not adequately take into account stratification based on ethnicity, and as such reflect a lack of heterogeneity and inclusiveness in research samples studied. While the studies of Finish Alcoholics [89] American Indian alcoholics [90] and German Alcoholics [91] would support the view of Barr and associates [88], deeper scrutiny reveals that the issue of appropriately categorizing subjects according to severity of alcoholism or dependence was not fully addressed. It is important to realize that just carrying the DRD2 A1 allele by itself may not translate to, for example, alcoholism. We must take into account the environment, especially epigenetic impact on gene expression. Along these lines, Goldman and associates [90] found a very high frequency of the A1 allele in Cheyenne Indians and failed to show an association with this allele of the DRD2 gene in subjects with alcoholism and drug abuse upon subjective questioning. This finding is not surprising since others, Levy & Kunitz [92] found a 60% abstention (i.e. “they took an oath not to use drugs”) rate among native Americans compared to 25% for the general population. However, Arinami et al. [93] found a significantly higher frequency of the DRD2 A1 allele in severe alcoholics than in less severe alcoholics. In fact, other work by the same group found that 100% of the alcoholics carrying the A1/A1 genotype were in the severe category [93].

In order to appreciate the varying frequencies amongst various ethnic groups Barr & Kidd [88] produced a gene map revealing that for example, the frequency of the DRD2 A1 allele in Yemenite Jews is only 0.09 (known to have very low rates of alcoholism) compared to 0.75 in Cheyenne American Indians (known in most studies to have high rates of alcoholism). Of particular importance is that the frequency of the DRD2 A1 allele in African Pygmies is 0.25 compared to almost 0.40 in US African-Americans (Blacks) (see Figure 1, [94]). This difference could be explained by admixture and interracial impact on DRD2 A1 frequency rate. With this stated we are faced with the problem of “cultural disparity” whereby US African-Americans have a disproportional higher rate of a genotype that

predisposes them to reduced dopamine function and as such a “magnification” of the aging process and possible higher rate of Alzheimer’s in this ethnic population. Future work will allow us to evaluate behaviors associated with the DRD2 TAq A1 Allele in African Americans, similar to what has been done for other populations.

Prognosis

Unfortunately, there is no real cure for Alzheimer’s Disease, and in spite of enormous efforts worldwide the disease remains a mystery in terms of treatment. African Americans are two times more likely to develop late-onset Alzheimer’s disease than Whites and less likely to have a timely diagnosis resulting in less time for treatment and planning. Connel et al. [95] examined differences between African Americans and Whites with regard to their attitudes, beliefs, and knowledge about AD. They pointed out that the 2 groups differed in terms of the following: (1) their knowledge about the disease (e.g., recognizing that AD is not a part of normal aging); (2) concern about AD (e.g., worry about developing the disease); (3) beliefs about putative causes of AD (e.g., stress); and (4) beliefs about the effectiveness of various options for reducing risk of and treating AD (e.g., physical activity). A societal effort is needed to change these attitudes. An important, well-established fact is that dopamine function is linked to normal cognition and memory. Carriers of the DRD2 ***A1*** allele have significant reduction of D2 receptor density in the brain. Most recently, it has been shown that A1 carriers have worse memory performance during Long-Term Memory (LTM) updating, compared to non-carriers or A2. It has also been shown that A1 carriers show less blood oxygen level dependent (BOLD) activation in the left caudate nucleus, an area important for LTM updating. This latter effect was only seen in older adults, suggesting magnification of genetic effects on brain functioning in the elderly. Tantamount to this finding is the fact that the prevalence of the DRD2 A1 allele is found with an allelic frequency of 0.40 or approximately 50% in the African-American community which is higher than what is found even in a non-screened American population, (≤28%) for Reward Deficiency Syndrome (RDS) behaviors.

Conclusions

Based on the importance of dopamine on learning and memory, the role of the A1 allele in downregulating dopamine receptors and reducing function in memory-related tasks, the prevalence of the A1 SNP in African Americans, and the high, increased, prevalence of Alzheimer’s disease in African Americans, we hypothesize that the DRD2 ***Taq1A A1*** allele magnifies the risk of Alzheimer’s in aging African Americans, and that this risk may be modified/amplified based on traumatic, stressful life experiences. Additional required research, further linking this disparaging high risk for Alzheimer’s in the African American population, with DRD2/ANKK1-TaqIA polymorphism and neurocognitive deficits related to LTM updating and magnification of aging, could pave the way for novel, targeted personalized medicine involving pro-dopamine homeostatic treatment, including Repetitive Transcranial Magnetic Stimulation (rTMS) [96].

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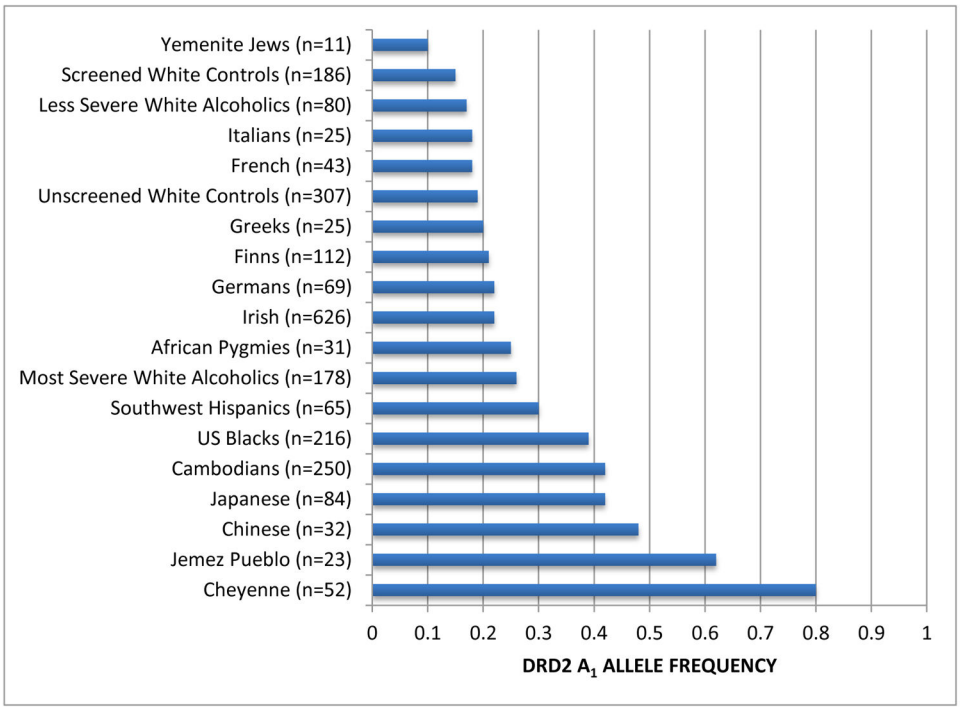

Figure 1.

DRD2 frequency as a function of ethnicity. The DRD2 *Taq 1* allele frequency as a function of ethnicity was derived from a number of independent investigations. The number in parentheses denotes the proband size. Modified from Barr & Kidd[46]

Table 1

Alzheimer's Epidemiological and Burden of Disease facts [25–27].

Worldwide Alzheimer's disease:

- Worldwide, nearly 44 million people have Alzheimer's or a related dementia. (Alzheimer's Disease International)
- Only 1-in-4 people with Alzheimer's disease have been diagnosed. (Alzheimer's Disease International)
- Alzheimer's and dementia are **most common in Western Europe** (North America is close behind).
- Alzheimer's is **least prevalent in Sub-Saharan Africa.** (Alzheimer's Disease International)
- Alzheimer's and other dementias are the **top cause for disabilities** in later life. (Alzheimer's Disease International)

The cost of AD Care:

- The cost of caring for Alzheimer's patients in the U.S. is estimated to be **$236 billion in 2016**. (Alzheimer's Association) http://act.alz.org/site/DocServer/2012_Costs_Fact_Sheet_version_2.pdf?docID=7161
- The global cost of Alzheimer's and dementia is estimated to be $605 billion, which is equivalent to 1% of the entire world's gross domestic product.
- Medicare and Medicaid are expected to pay $154 billion in 2017 for health care, long-term care and hospice for people with Alzheimer's disease and other dementias.
- Aggregate Cost of Care by Payer for Americans Age 65 and Older with Alzheimer's Disease and Other Dementias: Medicare $113 Billion, Medicaid $41 Billion, Out of pocket $44 Billion, Other $29 Billion.

Alzheimer's in the United States

- 1-in-9 Americans over 65 has Alzheimer's disease. (Alzheimer's Association)
- When the first wave of baby boomers reaches age 85 (in 2031), it is projected that more than 3 million people age 85 and older will have Alzheimer's. (Alzheimer's Association)
- One-third of Americans over age 85 are afflicted with the illness. (Alzheimer's Association)
- 5.3 million Americans are living with Alzheimer's disease. (Alzheimer's Association)
- Unless a cure is found, more than 16 million Americans will have the disease by 2050. (Alzheimer's Association)
- Alzheimer's disease is the 6th leading cause of death in America. (Centers for Disease Control)
- 1-in-3 seniors die with Alzheimer's or another kind of dementia. (Centers for Disease Control)
- Typical life expectancy after an Alzheimer's diagnosis is 4-to-8 years. (Alzheimer's Association)
- In 2016, the 85-years-and-older population includes about 2 million people with Alzheimer's disease, or 40% of all people with Alzheimer's age 65 and older. (Alzheimer's Association)
- By 2050, there could be as many as 7 million people age 85 and older with Alzheimer's disease, accounting for half (51%) of all people 65 and older with Alzheimer's. (Alzheimer's Association)
- Proportion of people with Alzheimer's Disease in the United States by age: (Alzheimer's Association) 85+ years – 38%, 75–84 years, 44%, 65–74 years, 15%, <65 years, 4%

Alzheimer's Incidence by Age and Ethnicity

Table 2

Incidence of Alzheimer's Disease by Age and Ancestry [26]

Age of Onset (yrs.)	**African American***	**European American**	**Hispanic**
65–74	**9.1%**	2.9%	7.4%
75–84	19.9%	10.9%	27.9%
85+	**58.6%**	30.2%	62.9%

* African American includes people of African and Caribbean descent living in America whether or not born in the US.