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Adolescent Cannabis Use, Psychosis and Catechol-O-Methyltransferase Genotype in African Americans and Caucasians

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Abstract

Cannabis has been reported as a likely risk factor for the development of psychosis, and a gene $\times$ environment interaction with the catechol-O-methyltransferase (*COMT*) gene has been proposed. Moreover, *COMT* has been separately linked to affective symptoms in psychosis. Despite a high rate of cannabis abuse and affective symptoms in African Americans, no studies exploring a relationship between *COMT* and psychosis in this group have been reported. An existing database of psychotic patients with and without adolescent cannabis use/affective symptoms was examined, and chi-square analyses for independence were applied separately for both Caucasians and African-Americans to examine genotype associations with adolescent cannabis use and affective symptoms (past or present). The two subject groups did not differ with respect to the prevalence of adolescent cannabis abuse or presence of affective symptoms. Further study is needed, with non-psychotic controls and larger samples.

Keywords

Schizophrenia; Cannabis; Gene-environment interaction; *COMT*; Affective symptoms

Introduction

Although the risk may be modifiable by atypical antipsychotics [1], cannabis consumption is often associated with a worse course of schizophrenia in African Americans [2]. Moreover, cannabis has been reported as a likely risk factor for the development of psychosis [3], and a proposed etiology for this is a potential gene $\times$ environment interaction with the catechol-*O*-methyltransferase (*COMT*) gene [4]. This gene encodes an enzyme that metabolizes dopamine in neural synapses. A common variant at codon 158 generates a valine (Val) to methionine (Met) substitution, which results in a substantial, 3 to 4-fold difference in enzyme activity [5]. In a sample of Caucasian New Zealanders, adolescent cannabis use was associated with an increased risk of schizophrenia in adulthood among Val/Val individuals with an odds ratio of 10.9 [4]. This link was further supported by an experimental study in which schizophrenia patients with the Val allele were significantly more likely to experience worsening psychotic symptoms in response to Δ -9-tetrahydrocannabinol inhalation [6], but was not replicated in a large cohort of patients with schizophrenia [7].

In addition to a link with cannabis, a positive correlation between the Val allele and the affective symptoms, particularly depression, in psychosis was reported [8] for a sample of ethnically homogenous Irish families, consistent with studies suggesting *COMT* as a common risk factor for schizophrenia and bipolar disorder [9]. Overall, however, the evidence for such a link is mixed, as many studies have found either no association between *COMT* and bipolar disorder or major depression [10], or associations with the Met allele rather than the Val allele [11-13].

Previous studies on this topic have included only Caucasians or Asians. The race of subjects is relevant, as the allele frequencies at this locus are variable across different populations. Africans have a higher Val allele frequency (approximately 0.67) in comparison to Caucasians (approximately 0.48) [14,15]. Less attention has been given in the literature to possible gene $\times$ environment interactions of cannabis use and psychosis in African-Americans, despite a possible higher rate of cannabis abuse in this population [16,17]. An examination of affective symptoms in African Americans with schizophrenia is complicated by possible overdiagnosis of psychotic illnesses in this group [18].

There are only a few studies specifically focusing on the risk of psychosis with cannabis use for patients of African descent, and no studies exploring a relationship between the *COMT* gene and psychosis/affective psychosis in this group were found in a literature search. Based on the studies done in Caucasian populations, increased rates of adolescent cannabis abuse and affective symptoms among *COMT* Val+ in African American and Caucasian schizophrenia patients are expected. Because prior studies were done in Caucasian subjects and because we know that the *COMT* genotype distributions differ in African Americans and Caucasians, the effects of each trait (adolescent cannabis use or affective symptoms) were examined separately to see if there are racial differences.

Materials and Methods

An existing database of genotyped, SCID interviewed, psychotic patients with and without adolescent cannabis use was examined. All patients were diagnosed with an Axis I psychotic disorder, and SCID interview included detailed history of substance use and affective symptoms.

Ninety-two patients (33 Caucasian and 46 African-American men and 5 Caucasian and 8 African-American women) with Structured Clinical Interview for DSM IV Axis I Disorders (SCID) [19] diagnoses of schizophrenia ($N = 65$), schizoaffective disorder ($N = 20$) or psychosis NOS ($N = 6$) were recruited from Rockland Psychiatric Center ($N = 82$) and Yale

Psychiatric Hospital ($N = 10$). The Yale group was recruited prospectively, and subsequently, the Rockland patients were added from a cohort initially recruited for another study [20] to increase the sample size. Prior to initial genotyping, written informed consent was obtained from all subjects. All had at least one inpatient psychiatric hospitalization. Adolescent use of cannabis (defined as any use more than once prior to age 18) and history of affective symptoms (defined as past or present mood episode) was determined by SCID. For the Rockland sample, the *COMT* codon 158 polymorphism was determined by restriction fragment length polymorphism analysis through use of polymerase chain reaction amplified gene fragments and *Nla* III restriction digestion, as previously described in detail [20]. Genotyping was performed by individuals who were blind to substance history. For the Yale sample, 20 ng of each DNA sample was amplified by PCR with the primers CCGTGATTTCAGGAGCACCAGCCCT and GAACGTGGTGTGAACACCTGGTGGG in 25 μ l PCR reactions. 15 μ l of each PCR product was then digested with 0.5 μ l of *Nla*III (New England Biolabs) for 2 h and run on 3.5% agarose gels and stained with ethidium bromide alongside 10 μ l of undigested PCR product. Samples were then scored visually for predicted DNA fragments [18, 42, 54, 71, 96 bp for the A (Met) allele; 42, 54, 71, 114 bp for the G (Val) allele].

Chi-square analyses for independence were applied separately for both Caucasians and African-Americans to examine genotype associations with adolescent cannabis use and affective symptoms.

Results

The two subject groups did not differ with respect to the prevalence of adolescent cannabis abuse or presence of affective symptoms. Sixty-five percent of African-American patients and 63% of the Caucasian patients had used cannabis prior to age 18. Fifty-two percent of the African-American patients and 55% of the Caucasian patients had affective symptoms. There was no significant association between cannabis use and affective symptoms in either group. *COMT* genotypes and allele frequencies are shown in Table 1 for adolescent cannabis use and in Table 2 for affective symptoms. Observed genotype frequencies were consistent with Hardy-Weinberg equilibrium in both groups. Separate analyses for both genotype and the individual alleles are shown. There was no association between *COMT* genotype and either cannabis use or affective symptoms in either group.

To further examine potential associations, Val homozygotes were contrasted with subjects having one or more Met alleles. Once again, there were no significant associations with either adolescent cannabis abuse or presence of affective symptoms in either subject group.

Discussion

To our knowledge, this is the first study of its kind in African-Americans. In the cannabis analysis, similar to recent findings [7], no significant associations were found between the Val/Val genotype of the *COMT* gene and adolescent cannabis use in either African-American or Caucasian patients. Since the magnitude of the effect reported by Caspi et al. was large (OR 10.9 for risk of schizophrenia in Val homozygote adolescent cannabis users), it is possible that the absence of an effect in this sample is due to insufficient power.

An association between the *COMT* gene and affective symptoms was also examined, and again did not find any significant associations. However, while the ratio of the genotypes was in the expected direction for the African-Americans, there was a trend for more Val/Val in the Caucasians without affective symptoms.

An important difference between this analysis and previous studies [4,8], is that the relationship between cannabis and *COMT* appears to have been a post hoc evaluation, while we attempt to replicate the finding of a strong gene $\times$ environment interaction between the Val/Val genotype and adolescent cannabis use or affective symptoms. Additionally, a group of psychotic patients with/without adolescent cannabis use or affective symptoms was used as the experimental and control groups, instead of a prospectively followed group of patients who have either developed psychosis or not.

There are several important caveats to consider in the interpretation of these results. First, there is likely a higher baseline proportion of the Val allele in African-Americans, and it is possible that the *COMT* allele plays a lesser role in the development of schizophrenia in these patients. A larger sample may be required to demonstrate a relationship. Second, the retrospective collection of affective symptoms and cannabis use may be less accurate than prospective methods used in other studies. In particular, reliance on SCID interviews for these data may have reduced sensitivity, although the use of a structured interview may have increased accuracy for the Axis I diagnosis. Third, the prevalence of adolescent cannabis use was considerably higher in this sample than is typically reported in population-based studies (e.g., Caspi). Finally, and perhaps most importantly, it is possible that the inclusion of a cohort of predominantly state hospitalized, non-cannabis using, patients with psychosis as a control was not as sensitive as a non-ill cohort, as used in the original finding [4], particularly since the *COMT* gene may play an independent role in schizophrenia. If the val allele plays an independent role for schizophrenia, a larger sample would also be needed to separate out the potential additive effects of cannabis. This supposition is supported by a recent negative finding in a homogenous Caucasian population [7]. The lack of a significant association between affective symptoms and *COMT* is not inconsistent with previous mixed findings [8-13].

Despite evidence for high use [16,17] and high morbidity [2] in this population, the relationship of cannabis and psychosis development in African Americans is understudied. A definitive link between schizophrenia and cannabis would illuminate a modifiable risk factor for a debilitating illness. Clearly, further study is needed, particularly in a longitudinal, larger sample with a non-ill control group.

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Adolescent cannabis use and COMT genotype and allele frequencies in African American and Caucasian patients with psychotic disorders

Table 1

Race	Use of cannabis prior to age 18					Chi-square, df, <i>P</i>
		Yes	No	Total		
African American	Genotype	Met/Met	4	0	4	2.9, 2, <i>P</i> = 0.23
		Met/Val	18	9	27	
		Val/Val	13	10	23	
	Alleles	Met	26	9	35	2.04, 1, <i>P</i> = 0.15
		Val	44	29	73	
Caucasian	Genotype	Met/Met	7	2	9	1.45, 2, <i>P</i> = 0.49
		Met/Val	11	9	20	
		Val/Val	6	3	9	
	Alleles	Met	25	13	38	0.23, 1, <i>P</i> = 0.63
		Val	23	15	38	

Table 2
Affective symptoms and COMT genotype and allele frequencies in African American and Caucasian patients with psychotic disorders

Race	Affective symptoms					Chi-square, df, <i>P</i>
		Yes	No	Total		
African American	Genotype	Met/Met	3	1	4	1.01, 2, <i>P</i> = 0.6
		Met/Val	14	13	27	
		Val/Val	11	12	23	
	Alleles	Met	20	15	24	0.58, 1, <i>P</i> = 0.45
		Val	36	37	32	
Caucasian	Genotype	Met/Met	4	5	9	3.9, 2, <i>P</i> = 0.14
		Met/Val	14	6	20	
		Val/Val	3	6	9	
	Alleles	Met	22	16	38	0.21, 2, <i>P</i> = 0.65
		Val	20	18	38	