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Influence of kynurenine 3-monooxygenase (*KMO*) gene polymorphism on cognitive function in schizophrenia☆,,☆☆

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Abstract

Background—Cognitive deficits compromise quality of life and productivity for individuals with schizophrenia and have no effective treatments. Preclinical data point to the kynurenine pathway of tryptophan metabolism as a potential target for pro-cognitive drug development. We have previously demonstrated association of a kynurenine 3-monooxygenase (*KMO*) gene variant with reduced *KMO* gene expression in postmortem schizophrenia cortex, and neurocognitive endophenotypic deficits in a clinical sample. *KMO* encodes kynurenine 3-monooxygenase (KMO), the rate-limiting microglial enzyme of cortical kynurenine metabolism. Aberration of the *KMO* gene might be the proximal cause of impaired cortical kynurenine metabolism observed in schizophrenia. However, the relationship between *KMO* variation and cognitive function in schizophrenia is unknown. This study examined the effects of the *KMO* rs2275163C>T C (risk) allele on cognitive function in schizophrenia.

Methods—We examined the association of *KMO* polymorphisms with general neuropsychological performance and P50 gating in a sample of 150 schizophrenia and 95 healthy controls.

Results—Consistent with our original report, the *KMO* rs2275163C>T C (risk) allele was associated with deficits in general neuropsychological performance, and this effect was more marked in schizophrenia compared with controls. Additionally, the C (Arg^{452}) allele of the

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Contributors

Dr. Wonodi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Wonodi, Gold. *Acquisition of data*: Wonodi, Gold, Krishna, Glassman, Hong, Liu. *Analysis and interpretation of data*: McMahon, Gold, Wonodi, Hong, Mitchell. *Drafting of manuscript*: Wonodi, Gold, McMahon. Critical revision of the manuscript for important intellectual content: Gold, McMahon, Mitchell, Hong, Wonodi. *Statistical analysis*: McMahon, Mitchell, Gold, Wonodi. *Obtained funding*: Wonodi. *Administrative, technical, and material support*: Wonodi, Gold, McMahon, Mitchell, Liu, Krishna, Glassman, Hong. *Study supervision*: Wonodi.

Conflict of interest

All authors declare that they have no conflict of interest.

missense rs1053230C>T variant (*KMO Arg*^{452}*Cys*) showed a trend effect on cognitive function. Neither variant affected P50 gating.

Conclusions—These data suggest that *KMO* variation influences a range of cognitive domains known to predict functional outcome. Extensive molecular characterization of this gene would elucidate its role in cognitive function with implications for vertical integration with basic discovery.

Keywords

Kynurenine; KMO; Genetic association; Cognition; P50; Schizophrenia

1. Introduction

Cognitive deficits profoundly reduce the quality of life of individuals with schizophrenia, and have no effective treatments (Green, 1996; Gold et al., 2000; Green et al., 2000; Harvey et al., 2003; Jaaskelainen et al., 2013). Cognitive impairments predict functional outcomes (Green et al., 2000; Prouteau et al., 2005; Martinez-Aran et al., 2007), including unemployment status (Gold et al., 2002; Caspi et al., 2003; Goldberg and Gomar, 2009; Harvey et al., 2012; Sheffield et al., 2013), which partly underlie the high healthcare costs associated with schizophrenia (Insel, 2008; Kessler et al., 2008; Soni 2009). Elucidating the neurobiological substrates of cognition could identify targets for developing rational pro-cognitive pharmacology for schizophrenia (Hyman and Fenton, 2003; Gold, 2004; Tamminga, 2006; Millan et al., 2012).

Preclinical evidence indicates that the kynurenine pathway (KP) of tryptophan metabolism is a valuable target for pro-cognitive drug development (Shepard et al., 2003; Erhardt et al., 2004; Chess et al., 2007, 2009; Potter et al., 2010; Wonodi and Schwarcz, 2010; Pocivavsek et al., 2012; Stone and Darlington, 2013). In the brain as in the periphery (Wolf, 1974; Stone, 1993; Guillemin et al., 1999), the KP generates two neuroactive metabolites - kynurenic acid (KYNA) and quinolinic acid (QUIN) - shown to modulate critical glutamatergic and cholinergic systems that regulate cognitive processes (Morris et al., 1986; Davis et al., 1992; Buffalo et al., 1994; Krystal et al., 1994; Newcomer and Krystal, 2001; Stone and Darlington, 2013) (Fig. 1). The excitotoxin QUIN is an agonist at glutamatergic N-methyl-D-aspartate receptors (NMDAR) (Stone and Perkins, 1981; Schwarcz et al., 1983), while KYNA is a competitive, broad-spectrum antagonist at ionotropic glutamate receptors, with its greatest affinity at the allosteric site on NMDAR (Perkins and Stone, 1982; Birch et al., 1988; Moroni et al., 1988; Foster et al., 1992; Stone, 1993; Parsons et al., 1997; Scharfman et al., 2000; Carpenedo et al., 2001; Erhardt et al., 2001b; Rassoulpour et al., 2005; Stone et al., 2013).

Another action attributed to KYNA is antagonism of α7 nicotinic acetylcholine receptors (α7nAChR) (Hilmas et al., 2001; Alkondon et al., 2004; Lopes et al., 2007; Alkondon et al., 2011a, 2011b), although some studies failed to demonstrate this (Mok et al., 2009; Dobelis et al., 2012). Notwithstanding, the emerging hypothesis of KYNA's role in cognition is based on the established roles of NMDAR (Krystal et al., 1994; Malhotra et al., 1996; Newcomer et al., 1999; Lahti et al., 2001) and α7nAChR (Kim and Levin, 1996; Newhouse

et al., 1997; Levin and Simon, 1998; Rusted et al., 2000) in fundamental cognitive processes.

Elevated KYNA levels have been demonstrated in several psychiatric diseases marked by cognitive dysfunction, including schizophrenia (Schwarcz et al., 2001; Erhardt et al., 2001a; Nilsson et al., 2005; Linderholm et al., 2010; Sathyasaikumar et al., 2011), psychotic bipolar disorder (Olsson et al., 2010, 2012; Lavebratt et al., 2014), HIV-associated neurocognitive disorders (Baran et al., 2000, 2012), and Alzheimer's disease (Baran et al., 1999). Relevant to schizophrenia, KYNA's role as an endogenous primary NMDAR antagonist converges with the established *hypoglutamatergic hypothesis of schizophrenia* (see reviews, Coyle, 1996; Coyle et al., 2003; Javitt, 2007). Evidence from our group suggests that downregulation of the *KMO* gene (OMIM 603538), which encodes kynurenine 3-monooxygenase (KMO) (EC 1.14.13.9), the rate-limiting microglial enzyme of the KP, might be the proximal cause of elevated KYNA levels observed in schizophrenia (Sathyasaikumar et al., 2010; Wonodi et al., 2011), a relationship recently investigated in *KMO* knockout mice (Giorgini et al., 2013). We previously showed an association between the CC genotype of *KMO* single nucleotide polymorphism (SNP) rs2275163C>T and significantly reduced *KMO* gene expression in postmortem schizophrenia prefrontal cortex from a region related to cognitive function; and in a clinical sample, the *KMO* risk allele (C) was associated with poor performance on oculomotor measures of predictive pursuit and visuospatial working memory (Wonodi et al., 2011). However, the relationship between *KMO* variation and cognitive function in humans is unknown. In the present study, we hypothesized that the rs2275163C>T risk allele, which was associated with reduced *KMO* messenger RNA (mRNA) expression (which would shunt KP metabolism towards enhanced KYNA formation) in our original report, would be associated with poor cognitive performance. Because a second non-synonymous variant in *KMO*, the C (Arg^{452}) allele of rs1053230>NT ($Arg^{452}Cys$) has also recently been associated with reduced *KMO* mRNA expression in brain and lymphoblastoid tissues, and with increased KYNA levels in cerebrospinal fluid (Holtze et al., 2012; Lavebratt et al., 2014), we additionally tested as a secondary aim, the association of this SNP with cognitive function in our sample. Lastly, we explored the effect of the *KMO* risk allele on P50 gating. Since P50 gating has been shown to not be correlated with general cognitive abilities, we anticipated association between the risk allele and cognitive function, but not necessarily with P50 suppression.

2. Methods

2.1. Participants

We enrolled a total of 245 unrelated individuals with minimal overlap with participants in our original study. Schizophrenia participants (n = 150) were recruited from outpatient clinics at the Maryland Psychiatric Research Center. Healthy controls (n = 95) were recruited through media advertisements. Since neurophysiological measures may be affected by age, particularly in individuals above 60 years (Ross et al., 1999), our endophenotypic studies are restricted to subjects between 18 and 58 years. Participants were evaluated with the Structured Clinical Interview for DSM-IV (SCID-IV) (First et al., 1997). Diagnosis of schizophrenia was based on SCID-IV (patient version). Healthy controls did not meet the

criteria for Axis I or II disorders (SCID-IV, nonpatient version). Respondents were excluded if they had substance dependence within 6 months prior to study enrollment, current substance abuse, or mental retardation. All participants provided written informed consent.

2.2. Cognitive assessment

All participants (n = 245) were administered a broad battery of tests assessing general intellectual ability (the Wechsler Abbreviated Scale of Intelligence (WASI)) (Wechsler, 1999), reading (Wechsler Test of Adult Reading), episodic memory (Logical Memory subtest from the WMS III and the Warrington Recognition Memory Test administered with a 60 minute delay) (Warrington, 1984), processing speed (Digit Symbol Substitution, Trail Making Tests A and B, Semantic Fluency), problem solving (the Wisconsin Card Sorting Test and the Making Groups Test), and working memory using the Spatial Span and Letter-Number Sequencing Tests from the WMS III (Battery, 1944; Reitan and Wolfson, 1971; Wechsler, 1997).

2.3. Laboratory procedures

2.3.1. P50 suppression—The P50 gating measures were recorded and processed as previously described (Hong et al., 2008) in a subsample of 184 participants (118 schizophrenia) (Table 1). Smokers refrained from smoking 1 h prior to testing. Participants sat in a semi-reclining chair in a sound-attenuated booth and 150 paired-click auditory stimuli were presented through headphones. Single trial records were baseline-corrected, bandpass filtered, and averaged to obtain the P50 waves. P50 response to the first stimulus (S1) was defined as the largest positive-going wave occurring 35-75 ms after the stimulus, measured from the trough of the preceding wave to the P50 peak. The S2 P50 was set to ±10 ms of the latency to S1 P50. Scoring was blinded to diagnostic grouping. The P50 gating endpoint outcome measure was the S2/S1 ratio.

2.3.2. SNP genotyping—We genotyped rs2275163C>T and rs1053230C>T (Table 2), using TaqMan technology as previously described (Wonodi et al., 2009).

2.4. Statistical analysis

2.4.1. Cognitive and P50 analyses—To combine results from the individual tests in the neuropsychological battery into a single global cognitive composite score, we used the following procedure. The primary analysis was done using the composite score calculated using weights for individual test scores estimated from analysis of the first principal component of the cognitive tests. This composite score (“global cognitive composite score”) explained 52% of the variance from the cognitive measures, and was examined using ANOVA with diagnosis, genotype (presence of minor allele genotype), and diagnosis by genotype interaction. The diagnosis by genotype interaction tested whether the magnitude of genotype effects was similar between schizophrenia and control participants. Similar models were used to examine scores on individual cognitive tests, and P50 gating analysis (S1/S2 ratio).

2.4.2. Phenotype and SNP association analyses—Prior to SNP analysis, the distributions of rs2275163C>T and rs1053230C>T genotypes were evaluated, separately, in

European-American and African-American participants for their fit with expectations under the Hardy Weinberg equilibrium (Hardy, 1908). Furthermore, we determined the minor allele frequencies (MAF) of both SNPs in both ethnic groups and compared them with the Global MAF (GMAF) for rs2275163C>T (0.30) and rs1053230C>T (0.12) from dbSNP based on 1000 Genomes (Consortium and Abecasis GR, 2010). We further compared allele frequencies of rs2275163C>T between our control groups and 1000 Genomes and found similar MAF in both European Americans (34.00 in our control samples vs. 35.00 in 1000 Genomes European Ancestry) and African Americans (17.00 in our control samples vs. 16.00 in 1000 Genomes African Ancestry). Based on our previous findings (Wonodi et al., 2011), we compared phenotypes across 2 genotype groups (homozygous CC vs. combined CT/TT genotypes). We restricted secondary analysis of the effects of rs1053230C>T on cognitive measures to European-American participants only because the current sample of African-Americans was too small to reliably test whether the effects of this genotype were different in that population.

3. Results

3.1. Cognitive performance and P50 suppression

Schizophrenia and controls were not significantly different on the demographic variables of age, sex, or ethnicity (Table 1). Schizophrenia participants had significantly reduced global cognitive composite scores (mean [SD], −0.31 [0.96]; n = 150) compared with controls (0.46 [0.83]; n = 95) ($P < .001$), and worse P50 gating (mean [SD], 0.76 [0.27]; n = 118) compared with controls (0.62 [0.21]; n = 66) ($P < .001$).

3.2. Phenotype and SNP association

3.2.1. KMO rs2275163C>T and Cognition (Table 3)—Individuals homozygous for the rs2275163C>T (risk) C allele genotype (CC) had a significantly reduced global cognitive composite score (mean [SD], −0.23 [1.02]; n = 144) compared with CT/TT genotype individuals (0.31 [0.84]; n = 101) ($P < .001$; effect size = .57). The effect of CC vs. CT/TT was smaller in control compared with schizophrenia [Cohen's $d = -0.22$ versus $d = -0.76$, respectively; test for interaction; ($P = .03$)]. In controls, estimated effect sizes for CC vs. CT/TT genotype effect were small for all measures (all effect sizes < ±0.3; all $P > 0.15$). In schizophrenia participants, only 3 tests (Logical Memory Test, immediate recall; Warrington Recognition Memory Test for Words; Trail Making Test: Part A) for CC vs. CT/TT genotype differences were not statistically significant ($P < 0.05$); for the remainder of the tests in schizophrenia individuals, effect sizes for CC vs. CT/TT genotype ranged from Cohen's $d = -0.37$ to $d = -0.76$, with all but one > $d = -0.50$ (Table 3).

3.2.2. KMO rs2275163C>T and P50—There was no main effect of genotype on P50 gating ($P = .16$; effect size = −.25), and no statistically significant genotype by diagnosis interaction ($P = .70$). P50 gating in controls with CC genotype was not different from CT/TT genotype controls ($P = .45$; effect size = .19). P50 gating was not different between CC and CT/TT genotype schizophrenia participants ($P = .17$; effect size = −.24) (Fig. 2).

3.2.3. KMO rs1053230C>T (Arg^{452}Cys) and cognition—Exploratory analyses of rs1053230C>T effects on global cognitive composite score in pooled European-American control and schizophrenia participants showed a significant main effect of genotype with C (*Arg*^{452}) homozygotes showing poorer global cognitive composite scores (mean [SD], 0.01 [1.08]; n = 107) compared with CT/TT genotype individuals (0.37 [0.96]; n = 51) (*P* = .04; effect size = .35). However, there was no main effect of diagnosis (*P* = .33) or genotype × diagnosis interaction (*P* = .80). Global cognition composite score in C (*Arg*^{452}) homozygous controls (0.73 [0.77]; n = 32) was not different from CT/TT genotype controls (0.85 [0.65]; n = 25) (*P* = .56; effect size = −0.16). Global cognition composite score in C (*Arg*^{452}) homozygous schizophrenia participants (−0.30 [1.06]; n = 75) was not different from CT/TT genotype patients (−0.10 [1.00]; n = 26) (*P* = .37; effect size = −0.21).

3.2.4. KMO rs1053230C>T (Arg^{452}Cys) and P50—Exploratory analyses of rs1053230C>T effects on P50 gating in pooled European-American control and schizophrenia participants showed no main effect of genotype in P50 gating between C (*Arg*^{452}) homozygotes (mean [SD], 0.69 [0.24]; n = 76) and CT/TT genotype individuals (0.69 [0.32]; n = 40) (*P* = .80). While the CC vs. CT/TT genotype difference was not significantly different from zero in either control or schizophrenia participants, the effects of genotype were in opposite directions in the two groups and were significantly different (test for genotype × diagnosis interaction, *P* = .02). P50 gating in C (*Arg*^{452}) homozygote controls (0.64 [0.19]; n = 21) was not significantly different from CT/TT genotype controls (0.53 [0.21]; n = 19) (*P* = .10; effect size = 0.54). P50 gating in C (*Arg*^{452}) homozygous schizophrenia participants (0.72 [0.28]; n = 55) was not significantly different from CT/TT genotype patients (0.85 [0.33]; n = 21) (*P* = .07; effect size = −0.44).

4. Discussion

To our knowledge, this is the first report suggesting that *KMO* could be a valid candidate gene for general cognitive abilities in humans. While there was some variability in the extent of impairment across cognitive measures, the rs2275163C>T CC group performed more poorly (arithmetically) on each and every measure. These findings are consistent with our original report and preclinical data that demonstrate impairments in spatial working memory (Chess et al., 2007) and cognitive flexibility (Pocivavsek et al., 2012, Alexander et al., 2013) in rodents following experimental manipulation of KMO function. Of note however, two of three measures that did not differ significantly as a function of genotype in our sample (effect sizes of −.14 and −.25) were both measures of verbal memory, raising the possibility that this particular cognitive function may be less sensitive to *KMO* variation. It is conceivable that the growing evidence linking *KMO* variation and elevated KYNA levels to schizophrenia and psychotic bipolar disorder may be explained by indirect relationships with cognitive deficits intrinsic to both disorders. Notably, the original report of association of rs2275163C>T and schizophrenia in a Japanese sample was not replicated in an independent Japanese sample (Aoyama et al., 2006). We initially used a well-phenotyped *discovery sample* for an endophenotype-based genome wide association screen to prioritize biologically plausible candidate genes based on top SNP-hits. Two *KMO* SNPs, including rs2275163C>T, were among the top SNP-hits, which met our criteria to prioritize *KMO* as a

plausible candidate for schizophrenia-related impairments. This motivated further studies leading up to our original report in which we found no association with schizophrenia but demonstrated an effect on neurocognitive endophenotypes and *KMO* gene expression (Wonodi et al., 2011).

A recent report by Lavebratt et al. (2014) supports and extends our original findings by showing downregulated *KMO* in schizophrenia and psychotic bipolar disorder cortical tissues compared with normal control and non-psychotic bipolar disorder specimens. The study further showed that *KMO* polymorphism influenced both KYNA levels in cerebrospinal fluid of psychotic bipolar disorder individuals, and *KMO* mRNA expression in lymphoblastoid cell lines. Importantly, similar to schizophrenia, individuals with psychotic bipolar disorder exhibit more impaired cognitive performance compared with non-psychotic bipolar disorder patients (Martinez-Aran et al., 2008; Hill et al., 2009, 2013; Reilly et al., 2013). In participants with minimal overlap with our original sample, we show that rs2275163C>T CC genotype individuals display marked deficits on a number of measures of cognitive performance compared with CT/TT genotype individuals. These genotype differences were significantly enhanced in schizophrenia relative to controls, and the effect is broad, impacting cognitive functioning in general, rather than being limited to specific cognitive abilities. Based on our original findings, we hypothesized that this intronic *KMO* SNP might be in linkage disequilibrium (LD) with a causal variant(s) (Reich et al., 2001; Consortium, 2003) that reduces *KMO* gene function. Further, this risk variant might also be in LD with multiple biologically active variants, which interact with each other, epigenetic factors, and the environment to increase the risk of cognitive impairments, perhaps, by effects on NMDAR function (Maher and LoTurco, 2012; Wang and Zhu, 2014; Wei et al., 2014) via interaction with *AKT3*, a recently identified schizophrenia risk gene that maps to the same chromosomal region (1q42-44) as *KMO* (Ripke et al., 2013). Indeed, rs2275163C>T is a haplotype tagging SNP, which indicates that it maps to a genomic region with high LD and “tags” variation in a particular combination of alleles (Johnson et al., 2001; Gabriel et al., 2002). Alternatively, rs2275163C>T might influence *KMO* mRNA expression by post-transcriptional and post-translational modifications, including effects on microRNAs (miRNAs), which are regulated by genes in intronic regions of protein-coding genes via interactions with the 3′ UTRs (Conne et al., 2000; Hobert, 2008; Dahan et al., 2011; Schizophrenia Psychiatric Genome-Wide Association Study, 2011; Ripke et al., 2013).

Our finding of a more marked influence of this *KMO* risk variant on cognitive abilities in schizophrenia compared with controls is consistent with “multiple hit” theories of schizophrenia (Bayer et al., 1999). In this model, the interplay of multiple susceptibility genes (“first hit”) disrupts the intra-and intercellular signaling pathways involved in neurodevelopment and primes them for a sustained pathological response to environmental insults (“second hit”) that contribute, additively, to increased vulnerability and pathogenesis in schizophrenia (Maynard et al., 2001; Cannon et al., 2003). Thus, as previously shown with *COMT* gene (Egan et al., 2001; Thaker et al., 2004) a putative risk variant may be associated with more severe cognitive impairments in schizophrenia than in controls. Further, evidence suggests that several schizophrenia candidate genes converge on NMDAR

function (Stahl, 2007). Exploratory analyses in European-Americans in the current sample showed an effect of the functional *KMO* Arg^{452}Cys variant on global cognitive composite score in pooled patients and controls, although there was no genotype by diagnosis interaction. Nevertheless, this trend level effect accords with reports showing effects of this variant on *KMO* expression and KYNA levels in European samples (Holtze et al., 2012; Lavebratt et al., 2014).

We found no statistically significant association of either *KMO* variant with P50 suppression. This implies that *KMO* variation may influence complex cognition through interactions with brain circuitry that are distinct from the inhibitory neuronal mechanisms involved in sensory gating (Adler et al., 1982; Freedman et al., 1983). Although the P50 gating deficit is a highly validated schizophrenia endophenotype (Adler et al., 1992; Leonard et al., 1996; Freedman et al., 1997; Adler et al., 1998; Hong et al., 2008), the strongest evidence for a relationship of P50 with cognition has been with measures of sustained attention and vigilance (Cullum et al., 1993; Erwin et al., 1998; Potter et al., 2006; Smith et al., 2010). Accordingly, our results tentatively provide genetic evidence indicating that the P50 gating deficit is unrelated to complex cognitive abilities in schizophrenia (Thoma et al., 2003; Sanchez-Morla et al., 2013). However, for the Arg^{452}Cys, we did find that the estimated effects of genotype in control and schizophrenia participants, while not significantly different from zero in either group, were significantly different from each other, suggesting further investigation of the effects of this genotype on P50 is warranted. Important limitations of this study include the absence of measures of *KMO* gene expression, KYNA, and QUIN. Additionally, we acknowledge that cryptic population substratification may have confounded our results in this sample of self-reported ethnicity (Pritchard and Rosenberg, 1999). Though we conducted analyses separately in both ethnic groups prior to combined genotype-phenotype analyses, and limited the exploratory analyses of the functional Arg^{452}Cys variant to European-American participants, we did not use a full ancestry informative marker (AIMS) panel for ancestry inference and thus could not adjust for potential population admixture (Pritchard et al., 2000). Lastly, the lack of comprehensive information on participants' educational levels is a further limitation in this study.

In summary, our results support the need for further studies to extensively characterize the diversity of *KMO* variation in combination with expression quantitative trait loci (eQTLs) (Nica et al., 2010; Montgomery and Dermitzakis, 2011) to ascertain their relationship with cognitive abilities in humans. This would generate new knowledge for vertical integration with basic discovery and could uncover novel targets for developing procognitive pharmacology for people with schizophrenia.

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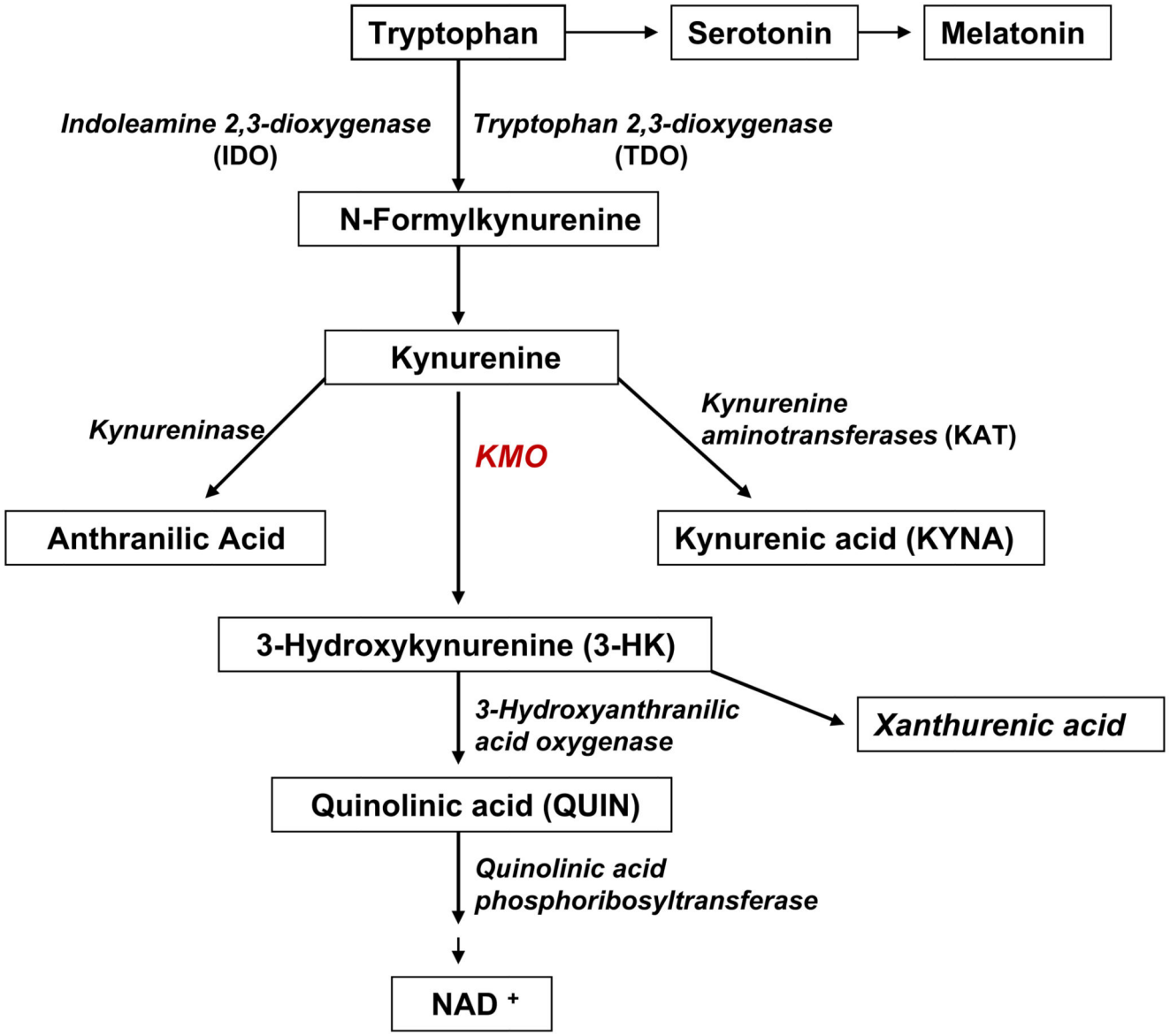

Fig. 1.

The kynurenine pathway of tryptophan metabolism. Tryptophan metabolism is initiated by oxidative cleavage by tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO). In the brain, the pivotal metabolite and substrate kynurenine is enzymatically converted to the neuroactive metabolites, quinolinic acid (QUIN) and kynurenic acid (KYNA) in microglia and astrocytes, respectively. No neuroactivity has been determined for anthranilic acid and 3-HK to date (Stone, 1993). A persistent downregulation of microglial *KMO* mRNA would shunt KP metabolism towards enhanced KYNA formation, which would result in increased inhibition of NMDA receptors (NMDA-R) and neuronal α7 nicotinic receptors (α7nACh-R), with effects on fundamental cognitive processes.

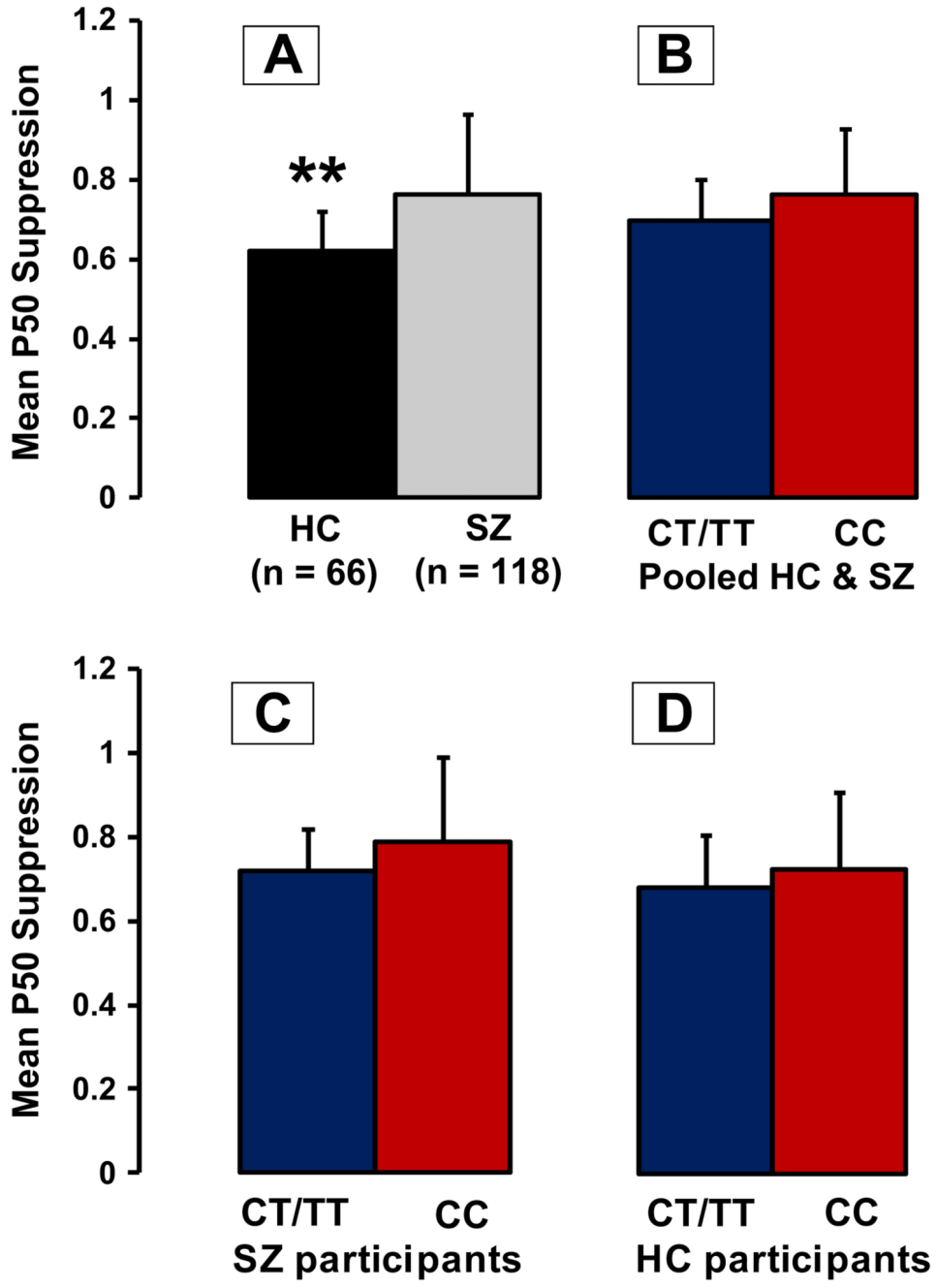

Fig. 2.

No effect of *KMO* rs2275163C>T risk variant on P50 suppression. A: Schizophrenia participants showed significantly reduced mean P50 suppression compared with healthy controls: ***P* = .001 (analysis of variance). Error bars indicate SD. HC, healthy control: n = 66; SZ, schizophrenia: n = 118. B: No effect of *KMO* risk variant on mean P50 suppression in pooled schizophrenia and healthy control participants. The collapsed carriers of the minor allele (TT and CT) (blue bar) are compared with carriers that are homozygous for the major allele (CC) (red bar): *P* = .16 [NS] (analysis of variance). TT and CT: n = 68; CC: n = 116.

HC, healthy control: n = 66; SZ, schizophrenia: n = 118. Error bars indicate SD. C: No effect of *KMO* risk variant on mean P50 suppression in schizophrenia participants. The collapsed carriers of the minor allele (TT and CT) (blue bar) are compared with carriers that are homozygous for the major allele (CC) (red bar): $P = .17$ [NS] (analysis of variance post hoc test). TT and CT: n = 42; CC: n = 76. Effect size, Cohen's $d = -.24$. SZ, schizophrenia: n = 118. Error bars indicate SD. D: No effect of *KMO* risk variant on mean P50 suppression in healthy control participants. The collapsed carriers of the minor allele (TT and CT) (blue bar) are compared with carriers that are homozygous for the major allele (CC) (red bar): $P = .45$ [NS] (analysis of variance post hoc test). TT and CT: n = 26; CC: n = 40. Effect size, Cohen's $d = .19$. HC, healthy control: n = 66. Error bars indicate SD.

Table 1

Demographic and phenotypic measures of study participants.

	Mean (SD)[a]		
	Healthy control participants[b]	**Schizophrenia patients[c]**	***P* value**
Age, years	39.24 ± 12.6	40.97 ± 11.0	.26
Female sex, %	43.2	48.7	.43
Ethnicity (EA/AA), %	62.1/37.9	72.0/28.0	.12
Global cognitive composite score[d]	0.46 ± 0.83	−0.31 ± 0.96	<.001
P50 Gating[e]	0.62 ± 0.21 (n = 66)	0.76 ± 0.27 (n = 118)	<.001

Abbreviations: AA, African-American; EA, European-American.

[a] Data are presented as mean (SD) unless otherwise indicated.

[b] n = 95 unless otherwise indicated.

[c] n = 150 unless otherwise indicated.

[d] On the basis of the first principle component of the Neuropsychological Test Battery.

[e] Based on P50 suppression of auditory event-related potential.

Table 2

SNP genotyping.

Gene symbol	Chromosome	TaqMan assay identification no.	SNP	Function	RefSNP alleles	MA	Context sequence
KMO	1q42-q44	(C_8856260_10)	rs1053230	Nonsyn	T/C	T	CTACATGTCACCACGATCTTTCCTC[C/T]GCTTGAGAAGACCATGGAACTGGAT
KMO	1q42-q44	(C_16183814_10)	rs2275163[a]	Intron	C/T	T	CAGAAACCTACATTAGAGCAAAAGT[C/T]TAAGTGGATATTGTGCTGTGAGCAG

Abbreviations: RefSNP alleles, National Center for Biotechnology Information reference SNP alleles; MA, minor allele; Nonsyn, nonsynonymous; TaqMan assay ID, ABI Life Technologies TaqMan Genotyping Assay.

[a]Haplotype-tagged SNP (htSNP).

Table 3

Influence of *KMO* rs2275163C>T risk allele on cognitive performance in control and schizophrenia participants.

	Healthy controls[c]						Schizophrenia[d]						Combined schizophrenia and healthy controls	
	CC (n = 51)		CT/TT (n = 44)				CC (n = 94)		CT/TT (n = 56)				Main effect of genotype	Interaction
Cognitive performance	**Mean**	**SD**	**Mean**	**SD**	***P*-value**	**Effect size (*d*)**	**Mean**	**SD**	**Mean**	**SD**	***P*-value**	**Effect size (*d*)**	***P*-value**	***P*-value**
WCST PE[a]	−.13	.99	−.28	.61	.38	.18	−.36	1.16	.24	.73	<.001	−.62	.003	.08
WCST Cat[a]	.11	.92	.19	1.01	.67	−.08	−.37	.92	.26	.94	<.001	−.68	.004	.03
Digit Symbol[a]	.34	1.11	.36	.77	.92	−.02	−.42	.93	−.07	.91	.02	−.38	.14	.18
Logical MemM1SS[a]	.42	.78	.29	.94	.45	.15	−.30	.94	−.16	1.02	.37	−.14	.97	.30
IQ[a]	.23	.86	.47	.84	.15	−.28	−.52	.97	.09	1.02	<.001	−.61	.001	.14
LNSEQ[a]	.15	1.01	.45	.99	.14	−.29	−.47	.88	.12	.91	<.001	−66	<.001	.24
MGT[a]	.27	.94	.54	.89	.17	−.29	−.52	.88	.06	.92	<.001	−.64	.001	.20
Spatial Span[a]	.27	1.04	.40	.88	.52	−.13	−.48	.97	.08	.87	<.001	−.61	.006	.08
Semantic Fluency[a]	.57	.97	.29	.88	.15	.30	−.49	.94	−.01	.94	.002	−.51	.40	.002
Trails A[a]	.38	.89	.27	.94	.57	.12	−.31	.96	−.05	.93	.09	−.27	.53	.14
Trails B[a]	.30	.96	.48	.84	.34	−.19	−.46	.99	.01	.82	.002	−.52	.008	.22
WRMT Faces[a]	.18	.89	.40	.78	.21	−.26	−.41	.99	.07	.86	.002	−.52	.004	.28
WRMT Words[a]	.21	.75	.23	.64	.92	−.03	−.19	1.04	.05	.89	.13	−.25	.27	.33
WTARSS[a]	.16	1.10	.44	.85	.17	−.28	−.40	.95	.17	.88	<.001	−.62	.001	.24
Global cognitive composite score[b]	.37	.89	.55	.73	.311	−.22	−.56	.92	.12	.88	<.001	−.76	<.001	.03

Abbreviations: WCST PE, Wisconsin Card Sorting Test (perseverative errors); WCST Cat, Wisconsin Card Sorting Test (total number of categories achieved); Digit Symbol, Digit Symbol Substitution Test; Logical MemM1SS, Logical Memory Test, Immediate Recall; IQ, Intelligence Quotient; LNSEQ, Letter-Number Sequencing; MGT, Making Groups Test; Spatial Span, Spatial Span Test; Semantic Fluency; Trails A, Trail Making Test: Part A; Trails B, Trail Making Test: Part B; WRMT Faces, Warrington Recognition Memory Test for Faces; WRMT Words, Warrington Recognition Memory Test for Words; WTARSS, Wechsler Test of Adult Reading;

[a]Based on standardized z-scores of Neuropsychological test scores.

[b] On the basis of the first principle component of the Neuropsychological Test Battery in Table 3.

[c] n = 95 unless otherwise indicated.

[d] n = 150 unless otherwise indicated.