Association between Intelligence and COMT genotypes in Chinese healthy children

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Abstract—**Catechol-O-methyl transferase (COMT) influences dopamine concentration in the pre-frontal cortex (PFC). The G/A transition in the exon 4 of the COMT gene, which results in a valine (Val) to methionine (Met) amino acid substitution (Val158Met), can bring on different enzymatic activities. Much research has found that the Met/Met genotype associated with low enzymatic activity and may enhance cognitive function. We applied one-way ANOVA to detect the effect of the COMT genotypes to intelligence in 108 Chinese children with polymerase chain reaction (PCR) methods. We found COMT Val158Met polymorphism had a significant main effect on intelligence ($F_{(2, 102)} = 3.47$, $p=0.035$) and it could predict 4.7% of intelligence. Our results also suggest that Met/Met genotype has a positive effect on intelligence. However, we found no significant interaction between gender and COMT genotype to intelligence.**

Keywords- Intelligence; Catechol-O-methyl transferase (COMT); functional polymorphism

I. INTRODUCTION

Intelligence is one of the most important psychological constructs that can predict academic achievement and success in daily life [1]. As general cognitive ability (intelligence, often measured by IQ scores) is highly heritable [2], psychologists have begun to explore the molecular basis of intelligence through orientating intelligence-related genes [3].

COMT gene is a genetic marker documented to impact cognitive functioning, which is coded by catechol-O-methyltransferase (COMT) enzyme. This enzyme is a major enzymatic inactivator of the neurotransmitter dopamine and regulates the duration of dopamine effect by catabolizing more than 60% of the dopamine in the prefrontal lobe [4]. Prefrontal cortex was the central system of human cognitive activities and was directly associated with human intelligence [5]. Functional variation in the human COMT gene occurs at a single nucleotide polymorphism (SNP), which is a G→A transition coding for the synthesis of the amino acid methionine (Met) instead of valine (Val) in codon 158 of the COMT gene located at the q11 band of human chromosome 22 (GenBank accession no. AY341246), bringing on 3- to 4-fold difference in COMT enzyme activity [6]. The Val allele associates with high enzymatic activity while the Met allele associates with low. In addition, dopaminergic neurotransmission in the PFC contributes to individual cognitive differences [7], thus COMT genotype may influence cognitive performance, especially intelligence.

Many researches support the association between COMT genotypes and the performance of the prefrontal lobe in children [8, 9]. With these data, individuals with the low activity Met allele are hypothesized to perform better on cognition tests that are specific for PFC functions [10]. Consistent with the hypothesis, Egan et al (2001) observed that the met allele was related to the better performance on the Wisconsin Card Sorting Test (WCST), which was replicated by Malhotra et al. (2002) [7, 11]. Another research reported that individuals with Met allele performed better in the processing speed and attention domain [12]. Consistent with these findings, Goldberg et al. (2003) also found the MET/MET genotype carriers perform best in working memory while VAL/VAL genotype carriers perform worst in an n-back task [13]. Another research support a general effect of COMT Val158Met polymorphism on cognition with biophysical data: P300 latency was lower in young Chinese women with the Met/Met genotypes [14]. Ho et al. (2005) found prefrontal cortical inefficiency in schizophrenic Val carriers with positron emission tomography (PET), which confirmed the relationship between COMT genotype and cognition [15]. Zhang et al.（2006）found no association between COMT genotypes and mental retardation (MR) but an association between COMT genotype and general cognitive ability of Chinese healthy children in mountain areas [16]. Recent study also found that the Met/Met carriers had better scores on executive function tests than Val-carriers [17].

However, there are still some studies showing different results. With a community sample of 120 young female subjects, Tsai et al. (2003) didn't replicate the experiment done by Egan et al (2001). Another research found no association between WCST performance and COMT genotype in healthy subjects but in schizophrenic patients [18]. Stefanis et al. (2004) reported no association between the COMT genotype and cognitive function with sustained attention and WM tasks [19]. Harris et al. (2005) found COMT genotype was not associated with childhood IQ of 79 healthy olds [20]. Other researchers using older participants found no significant association between COMT genotype and any cognitive abilities, although they reported that gender interacted with COMT genotype to impact cognitive performance [21].

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Why there exist inconsistent results about the association between COMT genotype and cognition? For example, Joober et al (2002) reported an association between WCST performance and COMT genotype in patients, while other researchers found no association in patients but in healthy siblings [22]. Whether COMT gene has its effect on children's intelligence? We noticed that previous studies got different conclusions from different samples and with different measurements for cognitive ability. In this report, we will focus on the association between COMT gene and intelligence in Chinese healthy children to check whether the association exists.

II. MATERIALS AND METHODS

A. Subjects

A total of 108 healthy unrelated Chinese children volunteers who were recruited from a compulsory education school in Bei Jing with two excluded for their uncompleted CFT test. The participants consisted 49 from grade 1 and 59 from grade 7. There were 51 boys and 57 girls.

B. Methods

1) Intelligence assessment

All children participants were tested with the culture fair test (Cattell's CFT-3) [23]. We chose it for following reasons. The most important reason is that CFT can avoid culture bias, so we can compare the IQ scores with children in other nations in our future research. Furthermore, CFT examines concept formation and reasoning ability, which is the core of intelligence and basal cognitive abilities [2]. Given the age differences and no norms for CFT, we computed Z scores for the calculation of CFT raw scores. Then we T score which is calculated by 50+10*Z as the IQ index to make the data more descriptive.

2) DNA preparation

All participants and their parents agreed to participate in this research and provided written informed consent after explanation of the study. 2 ml peripheral blood leukocytes was phlebotomized to extract DNA with the standard alcohol-trichlomethane method and it was immediately transported to the genetics laboratory and store at -20℃.

3) PCR assay

The primers used to amplified the target 217 bp COMT gene fragment were the same as those in previous report (Ruth et al. 2006). The upstream sense primer was 5'-TCG TGG ACG CCG TGA TTC AGG-3' and the downstream reverse primer was 5'-AGG TCT GAC AAC GGG TCA GGC-3'. The PCR reactions were carried out in a final volume of 15μl consisting of 50 ng of genomic DNA, 0.4μl of each primers (10pM), 10* PCR Buffer, 0.2 μl of 500U Taq, 0.2 μl of 10mM dNTP, 1.0 μl of 25mM Mg_2Cl and 10% DMSO.

We found the best PCR conditions for our experiment was touchdown protocol. It began with an initial denaturation step at 95 ◦C for 3 min, followed by 20 cycles of denaturation at 94 ◦C for 1min, annealing at 68◦C for 30s in the first cycle and lowering the annealing temperature sequentially from 68◦C to 58◦C over these 20 cycles, and extension at 72 ◦C for 45s. Then, there were 20 more cycles for further amplify which annealing at 58◦C for 30s per cycle. In the end, the samples were extended at 72 ◦C for 10 min.

4) Digestion

The PCR products were digested at 37 ◦C for 3h with 5 U of the restriction enzyme NIa III (New England Biolabs). Products were electrophoresed on a 4% agrose gel. A DL500 Marker was used to measure the fragments size.

III. RESULTS

The H allele, high activity Val-108, was cleaved into 2 bands in theory, the 136 bp band and the 81 bp band. The L allele, low activity Met-108, was cleaved into 3 bands in theory, the 114 bp band, the 81 bp band and the 22bp band. But the shortest band, the 22bp one can't be shown on the gel. The COMT genotype distribution in our experiment for the 108 subjects was: Val/Val=26, Val/Met=65, Met/Met =17. Allele frequencies did not differ significantly from Hardy-Weinberg equilibrium (Chi-square=4.86; p=.088). We conducted a one-way ANOVA to compare cognitive performance across the three allele groups (Val/Val, Val/Met and Met/Met).

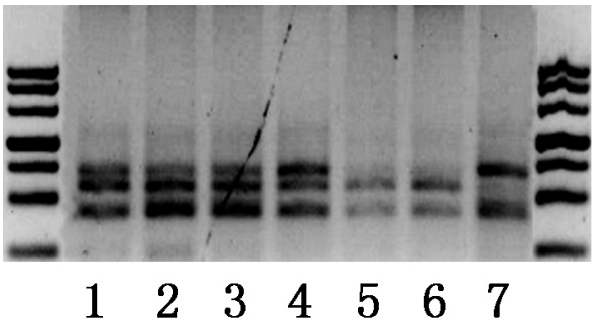

Fig. 1 Polymorphism assays for COMT genotypes in children: The first fourth lane are Val/Met genotypes; the fifth and the sixth lane are Met/Met genotypes and the last lane is Val/Val polymorphism.

Results of the genetic data showed significant main effects of the COMT genotypes on intelligence measures ($F_{(2, 102)} = 3.47$, p=0.035). COMT genotypes can predict 4.7% of intelligence scores. With Post hoc test estimates of univariate effects, we found that Met/Met carriers performed better than both Val/Val and Val/Met carriers (p=.012, p=.028 separately). There was no significant difference between Val/Val and Val/Met genotypes on their CFT scores. However, with more conservative Bonferroni calculation, we found the only significant difference is between Val/Val and Met/Met genotype (p=.036). We haven't found significant interaction of gender and COMT genotype on the CFT test ($F_{(2, 102)}$=1.621, p=.203).

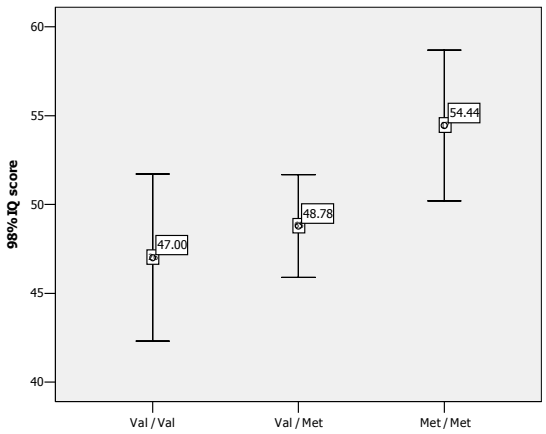

Fig. 2. Main effect of COMT genotype on intelligence as measured by the CFT test ($F_{(2, 102)} = 3.47$, p=0.035)

IV. DISCUSSION

This study adds to the evidence that the Met/Met genotype has a positive effect on intelligence. And it confirms the conclusion drawn by previous study that heterozygotes (Val/Met genotype) which have intermediate levels of COMT activity also have intermediated levels of CFT scores [6, 20, 24]. As mentioned before, there are still many inconsistencies about the effect of COMT gene to cognitive ability. There maybe several reasons. The first reason is that the inconsistencies are partly due to sampling. Studies with different subjects (healthy olds, healthy children, schizophrenics, patients with attention deficit disorder) may draw different conclusions. For example, De Frias et al. (2004) reported that Met/Met individuals got higher scores on measures of executive function, visuospatial abilities and memory but among the older participants [25]. Furthermore, as intelligence is complex and normally distributed in the population, it is coded by many genes called quantitative trait loci (QTLs) [26]. So the fact that not all studies detected statistically significant differences among the COMT genotypes on cognition may suggest that the effects are relatively small or population-specific. In our study, the COMT genotypes can only explain 4.7% of intelligence. In addition, many researches studied the COMT genotype with different cognitive tests emphasizing on different abilities, such as working memory, verbal fluency and creativity [2, 21, 27]. So it is possible that the COMT genotypes are associated with some basal cognitive abilities related to intelligence and reasoning but some higher cognitive abilities such as creativity.

However, we observed no interactions of gender and COMT genotype, which is different from previous study done by Ruth et al. (2006), who found no main effect of COMT genotypes and intelligence but a significant interaction of gender and COMT genotype by sampling older adults. However, other studies reported no or less consistent effect of the COMT genotype with young subjects [13, 20, 28]. The study of Mattay et al. may be possible to explain the different results. Their finding that Met/Met carriers performed worse after the DA- agonistic substance amphetamine intake suggests that the association between performance and DA levels has an inverted "U" shape characteristic [29]. So there maybe a shift in the dopamine signaling and PFC function curve with ageing [17].

Overall, our study shows an association between COMT Val158Met polymorphism and intelligence. We haven't observed that the Val/Val genotype had a detrimental effect on cognition, which was found by Starr et al. (2007). However, with conservative Bonferroni calculation, we can still draw the conclusion that the Met/Met genotype has a positive effect on intelligence and gender doesn't interact with COMT genotype significantly to affect intelligence.

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