

Association between the low molecular weight cytosolic acid phosphatase gene *ACP1**A and comorbid features of Tourette syndrome

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Abstract

Protein tyrosine phosphatases have been implicated in the regulation of serotonergic and dopaminergic activity in the central nervous system. In a recent study we found that nonA/nonA homozygosity at the locus coding for the low molecular weight protein tyrosine phosphatase (*ACP1*) was associated with increased rates of major depression in males ($P < 0.00003$), suggesting that the *ACP1**A single nucleotide polymorphism (SNP) may be an important marker for psychopathology. In the present study we examined the *ACP1**A SNP in 539 screened controls and 184 male Tourette syndrome (TS) cases, all Caucasians of European descent. The frequency of the nonA allele was markedly increased in TS cases relative to controls ($P < 0.0005$), but this difference was restricted to cases with comorbid attention-deficit hyperactivity disorder ($P < 0.0001$) and conduct disorder ($P < 0.0002$), while having little relevance to TS itself. © 2002 Published by Elsevier Science Ireland Ltd.

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Several recent reports show that both serotonergic and dopaminergic pathways in the CNS could be modulated by tyrosine phosphorylation phenomena. Tyrosine phosphorylation has been found to modify signaling pathways participating in the regulation of human serotonin transporter gene expression [10], and to modulate signal transduction through serotonin receptors [6]. The expression of dopamine receptors and their signal transduction machinery [8] also appear to be regulated by tyrosine kinases and phosphatases. The acid phosphatase locus 1 (*ACP1*) codifies for a low molecular weight protein tyrosine phosphatase (LMPTP) involved in the modulation of several intracellular signal transduction pathways [5]. Studies in rodent [11] and human [7] tissues showed that the phosphatase produced by the *ACP1* gene is ubiquitous, but is present in concentrations several folds higher in the brain than in other tissues. In the brain LMPTP is enriched at the synaptic terminals [15].

In a recent study we examined a T → A polymorphism of *ACP1**A in 870 depressed and non-depressed subjects, and reported an excess of nonA/nonA homozygosity among male depressives both in adolescent ($P < 0.0025$) and adult ($P < 0.0075$) samples [4]. These data suggest that the increased enzymatic activity characteristic of nonA/nonA homozygotes may, by virtue of the putative ability of this enzyme to modify serotonergic activity, play a role in the biological mechanisms generative of depression in males.

In the present study we sought to examine the relevance of the *ACP1**A gene to Tourette syndrome (TS) and its comorbid disorders. TS is a complex neuropsychiatric disorder characterized by chronic motor and vocal tics and a wide range of associated behaviors, including attention-deficit hyperactivity disorder (ADHD), conduct disorder (CD), depression and impulsive-compulsive behaviors [3]. TS occurs primarily in males, and in many cases follows a remitting course after puberty [2]. TS is highly comorbid with ADHD, and CD has been shown to be much more

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common in TS children with ADHD (TS + ADHD) than in TS children without ADHD (TS – ADHD), a trend that increases in older TS cases [2].

We examined the association between the *ACPI**A single nucleotide polymorphism (SNP) in 184 TS cases and 539 controls, all Caucasians of European descent. The TS cases were all male patients undergoing treatment at the TS clinic of the City of Hope National Medical Center. Diagnoses were based on DSM-III-R criteria. The age range of TS cases was 3 to 50 years, with a mean age of 13.3 years. TS cases were comprised of 134 TS + ADHD and 50 TS – ADHD diagnoses. In order to examine possible age-related differences, the TS cases were divided into two groups: age ≤ 13 ($n = 124$) and age ≥ 14 ($n = 59$). Two control samples were obtained from the Minnesota Twin Family Study (MTFS). The firstborn male twin from MTFS families was screened for ADHD, CD, and depression using the revised version of the Diagnostic Interview for Children and Adolescents (DICA-R) and the Structured Clinical Interview for DSM-III-R (SCID-R). All twins were age 11 at the time of initial testing. This generated a sample of 145 screened adolescents providing an approximate age-matched sample for comparison with the TS sample. Parents from the MTFS were screened for depression and alcoholism using the SCID-R, generating a sample of 394 screened adult controls (160 males, 234 females) with an age range of 30–63 years and a mean age of 42.4 years. Sixty-one percent of the twin families were of monozygotic twins, and 39% were of dizygotic twins. Written informed consent was obtained from all subjects, and the study was approved by the institutional review boards of participating institutions.

DNA was isolated from blood using standard techniques. Genotyping of the *ACPI**A *Taq I* A/G 216 Gln105Arg CAA \rightarrow CAG polymorphism was performed utilizing the primers and PCR conditions described by Sensabaug and Lazaruk [12]. The frequency distributions of genotypes was evaluated by Chi square analysis using SPSS version 10.

The majority of the MTFS children (102 of 145) were unrelated to the parents studied. As shown in Table 1, there were no differences in *ACPI* genotype frequencies between

the MTFS children and the adults. Therefore, in all genotype comparisons with the TS cases, the entire sample of 539 screened controls were compared with the cases. The probability values both for Pearson (P) and Mantel–Haenszel Test (P_L) for linear association for the comparisons are shown in Table 1. The genotype distributions of cases and controls were both in Hardy–Weinberg equilibrium.

A comparison of *ACPI* genotypes of controls and all 184 TS cases revealed an increase in the frequency of the 11 (nonA/nonA) genotypes in TS cases ($\chi^2 = 15.71$, $P = 0.00007$), and in the frequency of the 1-allele ($P = 0.0004$) that paralleled our earlier findings with depression. This difference was restricted to the TS + ADHD group (by genotype: $P = 0.00002$). The increase in 1-allele frequency in the TS + ADHD group, relative to controls, was significant both in the younger and the older TS samples. Consistent with reports in the literature [14], the rate of CD increased from 26% in the younger TS cases to 51% in the older TS cases ($P = 0.0008$). Moreover, the strength of the association between *ACPI* and CD increased from $P = 0.02$ in the younger cases to $P = 0.0004$ in the older cases. Collectively, these findings suggest that the 1-allele of *ACPI**A is associated with an overall increase in the frequency of comorbid features in TS (e.g. ADHD and CD), while having little apparent relevance to TS itself.

As far as we know, the physiological substrate of the LMPTP in the brain has not yet been isolated, but the strong associations between genetic variability at this locus and neurodevelopmental as well as adult psychopathology suggests that LMPTP could play a fundamental role during development or in the modulation of specific synaptic activities in the CNS. Indeed, LMPTP has been reported as a possible modulator of Eph receptor signal transduction that is implicated in axon guidance during neural development [13]. Anomalous functioning at the striatal level and in the striatal connections with the cortex, thalamus and other nuclei seems to be a key pathophysiologic feature of TS [1]. The distribution of LMPTP in various brain regions, with special attention for the striatum and other basal ganglia, may warrant further investigation. A striatal enriched tyro-

Table 1
Association between *ACPI**A genotypes and TS and comorbid disorders

| Sample | N | NonA/ | NonA/A | A/A | P | P_L |
|----------------------------|-----|----------|----------|---------|--------|---------|
| Screened adolescents | 145 | 62 (43) | 68 (47) | 15 (10) | | |
| Screened parents | 394 | 159 (40) | 180 (46) | 55 (14) | | |
| All controls | 539 | 221 (41) | 248 (46) | 70 (13) | | |
| All TS, age ≤ 13 | 125 | 63 (50) | 54 (43) | 8 (6) | 0.016 | |
| All TS, age ≥ 14 | 59 | 38 (64) | 21 (36) | 0 (0) | 0.0004 | 0.00008 |
| All TS | 184 | 101 (55) | 75 (41) | 8 (4) | 0.0003 | 0.00007 |
| TS + ADHD, age ≤ 13 | 92 | 52 (56) | 34 (37) | 6 (7) | 0.013 | 0.004 |
| TS + ADHD, age ≥ 14 | 42 | 29 (69) | 13 (31) | 0 (0) | 0.0007 | 0.0002 |
| All TS – ADHD | 50 | 20 (40) | 28 (56) | 2 (4) | n.s. | n.s. |
| All TS + CD, age ≤ 13 | 32 | 19 (59) | 12 (38) | 1 (3) | 0.07 | 0.02 |
| All TS + CD, age ≥ 14 | 30 | 22 (73) | 8 (27) | 0 (0) | 0.001 | 0.0004 |
| All TS + CD | 62 | 41 (66) | 20 (32) | 1 (2) | 0.0003 | 0.00005 |

sine phosphatase has also been isolated that is able to modulate dopamine signal transduction [9], suggesting that other members of the PTPase family would be pertinent targets for further study in TS.

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