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Absence of Linkage of Apparently Single Gene Mediated ADHD With the Human Syntenic Region of the Mouse Mutant *Coloboma*

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Attention deficit disorder (ADHD) is a complex biobehavioral phenotype which affects up to 8% of the general population and often impairs social, academic, and job performance. Its origins are heterogeneous, but a significant genetic component is suggested by family and twin studies. The murine strain, *coloboma*, displays a spontaneously hyperactive phenotype that is responsive to dextroamphetamine and has been proposed as a genetic model for ADHD. *Coloboma* is a semi-dominant mutation that is caused by a hemizygous deletion of the SNAP-25 and other genes on mouse chromosome 2q. To test the possibility that the human homolog of the mouse coloboma gene(s) could be responsible for ADHD, we have carried out linkage studies with polymorphic markers in the region syntenic to coloboma (20p11–p12). Five families in which the pattern of inheritance of ADHD appears to be autosomal dominant were studied. Segregation analysis of the traits studied suggested that the best fitting model was a sex-influenced, single gene, Mendelian pattern. Several genetic models were evaluated based on estimates of penetrance, phenocopy rate, and allele frequency derived from our patient population and those of other investigators. No significant linkage was detected between the disease locus and markers spanning this chromosome 20 interval.

KEY WORDS: hyperactivity, genetic studies, SNAP-25 gene, coloboma mouse, chromosome 20p

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a neurobehavioral phenotype estimated to affect 5 to 8% of school age children [Lambert, et al., 1977; Anderson, et al., 1987]. Characteristic personality traits include short attention span for age, impulsivity, distractibility, and motoric overactivity. The etiology of ADHD and neuroanatomic pathways subserving the characteristic behavioral dysfunctions remain unknown. A genetic influence on the pattern of occurrence of ADHD was recognized in the late 1960s when fathers of children with minimal cerebral dysfunction (ADHD) were noted to have higher than expected rates of hyperactivity, alcoholism, and antisocial behaviors [Morrison and Stewart, 1971; Cantwell, 1972; Stewart et al., 1979]. Subsequent population and family studies using DSM-III and DSM-III-R diagnostic criteria showed significantly greater numbers of first degree male and female relatives of male ADHD probands had ADHD (odds ratio 6.9–7.6), or oppositional disorder (odds ratio 6.9) than in matched comparison families [Biedermann et al., 1986, 1990, 1992]. The associations were independent of socioeconomic class, family intactness, gender, and age of relatives. Relatives of females with ADHD had similar risks for occurrence of ADHD, oppositional disorder, or major depression as reported by Faraone et al. [1991]. These results suggest a similar biogenetic mechanism for this disorder in boys and girls, despite differences in prevalence and phenotype.

Assessment of heritability in twins has also confirmed a genetic contribution to ADHD. Co-occurrence of ADHD in monozygotic twins ranges from 0.45 to 0.71; in dizygotic twins, it is 0.25 to 0.35 [Willerman, 1973; Goodman and Stevenson, 1989].

Animal models for ADHD have been sought to assist in the search for candidate genetic loci and to provide insight into the neurochemical pathways involved in motoric overactivity. Selected synthetic neurotoxins elicit the ADHD phenotype, an approach which may help elucidate critical brain pathways, but does not implicate specific chromosomal regions [Shaywitz et al., 1976; Silbergeld and Goldberg, 1974]. In general, the inbred strains of mice and rats which show sponta-

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neous motoric hyperactivity lack defined chromosomal abnormalities [Knardahl and Sagroden, 1979; Wultz et al., 1990; Schmidt et al., 1982]. One notable exception is the mouse mutant *coloboma* [Searle, 1966; Hess et al., 1992]. The *coloboma* mouse shows four to ten times more locomotor activity in a normal diurnal pattern than control littermates. Amphetamine dramatically reduces the locomotor activity in *coloboma* mice, whereas control littermates respond with increased motoric activity [Hess et al., 1994]. Thus, the *coloboma* mouse response to amphetamine is remarkably similar to that of children with ADHD treated with stimulants.

The *Cm* mutation is semidominant; the heterozygous state (*Cm*/+) results in the hyperactive phenotype [Theiler and Varnum, 1981]. The abnormalities of this mouse mutant result from a chromosomal deletion that includes the SNAP-25 gene [Hess et al., 1992, 1994] which is located on mouse chromosome 2q between Bmp-2a and Nec2, a region which is syntenic with human chromosome 20p11–p12 [Nelson et al., 1994; Loffler et al., 1994].

The phenotypic similarities between *coloboma* mice and humans with ADHD suggest that genetically mediated human ADHD may be associated with a dominant mutation in the human homolog of SNAP-25 or other gene within the deletion interval. This possible association was tested using two-point and multipoint linkage analysis with markers spanning the presumptive human SNAP-25 locus and surrounding region of chromosome 20p11–12.

MATERIALS AND METHODS

Participating families were recruited from greater than 1,100 families whose children were diagnosed to have ADHD through the Developmental Disabilities Clinic at The Pennsylvania State University Children's Hospital during the last 14 years.

Selection criteria for families recruited for this study: 1) Three or more first and/or second degree relatives with ADD or ADHD (as defined below), and 2) Apparent autosomal dominant transmission determined by inspection of the pedigree with at least two generations available for study. 3) Absence of mental retardation (IQ $\leq$75) or other known neurologic disorder (seizure disorder and cerebral palsy) in the proband. 4) Absence of diagnosed manic depressive disorder or major depression in the proband and first degree relatives.

A multidisciplinary team including a developmental pediatrician/geneticist, clinical psychologist, and an education specialist participated in the diagnosis of ADHD in each proband. A diagnosis of ADHD was made only when the three evaluators were in agreement and criteria for diagnosis outlined below were met.

The following criteria were used to confirm ADHD in children under 17 years, including the proband: 1) T score of $\geq$70 on the Hyperactivity Index of the Conners' Behavioral Rating Scale (Short Form) with parent(s) as respondent [Conners, 1990], 2) Meets DSM-III-R criteria for a diagnosis of attention deficit/hyperactivity disorder as assessed by interview of parent(s) and 3) Absence of other neurologic disorders (cerebral palsy, seizure disorder, and mental retardation) as determined by review of records results of available psychoeducational testing and neurologic examination.

The following criteria were used to confirm ADHD in family members over 17 years: 1) Score of $\geq$12 using the Conners' Abbreviated Teacher's Rating Scale completed by the individual's mother (or father if mother unavailable). The parent was instructed to complete the questionnaire based on their recollection of the behavior of their adult child as he or she had been between 6 and 10 years. 2) Persistence of symptoms into adulthood documented using a structured interview with the individual and their spouse. The questions were derived from the Utah Criteria for the diagnosis of ADD, Residual Type; scoring was based on recommendations by the authors of the Utah Criteria [Wender et al., 1985; Wender, 1990]. ADHD was considered to be present if either "spouse" or "self" questionnaire were positive. [Details of interview and scoring system available upon request.] If parents were unavailable, ADHD was diagnosed if the score on the Utah scale (subject or spouse) was positive and there was evidence of childhood school difficulties [retention, poor grades, or quit before graduation] documented in the school records.

This combination of measures was chosen with recognition of the difficulty in identification of adults with ADHD noted by many researchers. The diagnostic criteria used concur with Wender's recommendations [1990] which require documented symptoms of ADHD in childhood, and modified symptoms evident in adulthood. Adults with conduct or antisocial personality disorder may have a positive score using the Utah scale; however, the strong correlation of these behavioral profiles and ADHD in families reported by Biederman et al. [1986, 1990, 1992] makes it likely that they represent an alternative expression of ADHD in adulthood.

Genomic DNA was extracted from lymphocytes by standard methods. Unique oligonucleotide primers were used to amplify polymorphic microsatellite loci within the region of interest on human chromosome 20p [Weber and May, 1990]. Seven previously characterized microsatellites D20S27, D20S98, D20S104, D20S112, D20S114, D20S118, and D20S48 with polymorphism information content (PIC) >0.6 were employed in this study. These markers map to an ~11.4 cm region encompassing most of 20p11.2–p.12 [NIH/CEPH Collaborative Mapping Group, 1992; Weissenbach et al., 1992]. After amplification by PCR, the resulting products were resolved by denaturing polyacrylamide gel electrophoresis and family members were genotyped by scoring transmitted alleles.

Two point lod scores for each marker were computed with MLINK and maximum likelihood analysis of the markers was carried out with the program LINKMAP [Lathrop et al., 1985] using population allele frequencies for each locus retrieved from the Genome Database.

Segregation of diagnostic test results was analyzed with REGC as a single continuous variate (S.A.G.E., 1994). Conners' Behavioral Rating T scores were linearly transformed to the Utah Criteria scale by assuming that the threshold values for diagnosis of ADHD in each test were equivalent. Ascertainment was corrected by conditioning on the observed phenotypes.

Variances were assumed to be proportional to the sex- and type-specific means. All models assumed equal parent-offspring correlations.

Models were compared with either χ^2 or Akaike's information criterion [Akaike 1974; AIC]. Smaller values represent better fits to the observed data. The χ^2 test is based on the difference between the respective -2 ln (likelihood) estimates for each model (where the number of degrees of freedom is the difference between the numbers of independent parameters estimated in each model). AIC is defined as -2 ln (likelihood) + twice the number of parameters estimated.

A major challenge in this analysis was lack of well validated phenocopy rate, age, and sex dependent penetrance rates and allele frequencies for genetically transmitted ADHD. We approached this problem by using a range of values for each parameter, as suggested by Ott [1990] and Sherrington et al. [1988]. The endpoints of each range were derived from our own data (as described below) and from information available in the medical literature.

Penetrance figures were calculated in two ways: 1) using data from Biederman's study of first degree relatives of ADHD probands [1992], and 2) from actual pedigrees from our clinical files. The ratio of affected adult female to male relatives from Biederman's data was utilized as the base figure for this calculation. Incorporation of the standard error of measurement along with a penetrance value of 95% for males yielded a range of 25% to 51% for penetrance in females. We then calculated penetrance from a random sample of 25 pedigrees (who did not participate in the current study) obtained from our clinic records. Detailed family history information is obtained routinely for all new patients. The apparent penetrance rate for young females (under 11 years) was 80% and 50–60% for females over 11 years. Males of all ages had a higher penetrance rate, assessed to be 95%. The gender-specific discrepancy in penetrance may reflect under-diagnosis in adult women who typically have a lower intensity of symptoms and less childhood hyperactivity. Finally, evaluation of the pedigrees actually used in this study showed only two possibly non-penetrant females (based on equivocal questionnaire results), yielding a penetrance rate of 90–95%. For the linkage analysis, we employed values of 50% and 95% which bracket the calculated range for adult females and 80% for females under age 11 years.

Phenocopy rate was also calculated from a random subset of 100 ADHD clinic files. Tabulation of the affected to unaffected ratio in families with (n = 45) and without (n = 55) a history of ADHD in first degree relatives yielded a phenocopy rate of 23%. This figure may be falsely elevated for the following reasons: 1) some apparently sporadic probands are actually of genetic origin due to new mutation and/or to inheritance of ADHD from individuals with subthreshold symptoms, and 2) the number of affected individuals in each family is probably under-reported because information was obtained by chart review. Assessment of the families actually selected for linkage analysis suggests that these factors resulted in an approximate doubling of the phenocopy rate. Nevertheless, we conservatively tested for linkage using phenocopy rates of up to 10%, even though there was no evidence for phenocopies in the families studied.

RESULTS

Five extended families segregating ADHD were recruited (Fig. 1). The individuals with equivocal questionnaire results were coded as "unknown" for the linkage analysis. Males and females were affected in equal proportions with full penetrance, although the intensity and type of symptoms differed with gender.

As shown in Table I, the best fitting model supports primarily sex-influenced, single gene, Mendelian transmission of ADHD. Models 2 and 7, which assume that transmission of ADHD is random are, respectively, rejected against models 1 ($\chi^2 = 24$ with 6 degrees of freedom, $P < 0.001$) and 4 ($\chi^2 = 12$ with 1 degree of freedom, $P < 0.001$), each of which stipulate Mendelian transmission of the trait. Model 7 assumes random transmission due to genetic heterogeneity within these pedigrees. Although both class A and D models assume that sibling phenotypes are dependent due to common parentage, the class D structure allows for non-genetic contributions as well. The class D model for an arbitrary major gene effect (model 4) exhibits a significantly better fit than the corresponding class A dependence structure (model 2, $\chi^2 = 13.6$ with 1 degree of freedom, $P < 0.001$). The ADHD phenotype is more likely to be sex-influenced in these subjects (compare models 5 and 6; $P < 0.001$), as is frequently noted in clinical practice. Despite the apparent dominant mode of inheritance of the trait in these families, a dominant model is rejected ($P < 0.01$) when compared with one in which the mode of inheritance is not specified (models 5 vs. 6, and models 2 vs. 3). This may be due, in part, to incomplete penetrance, which is characteristic of families segregating ADHD [Biederman et al., 1992].

Data from these five families was analyzed using four different statistical models (Fig. 2) in which penetrance, allele frequency, and phenocopy rate were permitted to vary. The values of these parameters were set at the bounds of the calculated ranges for these parameters [Ott, 1990]. The analysis was completed under an autosomal dominant model as the other single gene, Mendelian patterns clearly do not fit the observed pedigrees. All two point (data not shown) and multipoint lod scores were negative in the interval spanned by the selected markers (D20S48-D20S27). Linkage between ADHD and the D20S98-S114 could be excluded for those models with high penetrance rates (models 2 and 3). Multipoint linkage analysis of individual pedigrees yielded no positive lod scores, thus excluding significant linkage between ADHD and the mouse homolog on 20p11–12 in a subset of families.

Comparison of the results of different models shows that reduced age-related penetrance values for females produced increased lod scores (model 1 vs. model 3). The lod score also increased when the phenocopy rate was decreased (model 1 vs. 4). Elevated phenocopy rates increase the uncertainty of linkage to ADHD by misassignment of the true phenotype. This most likely

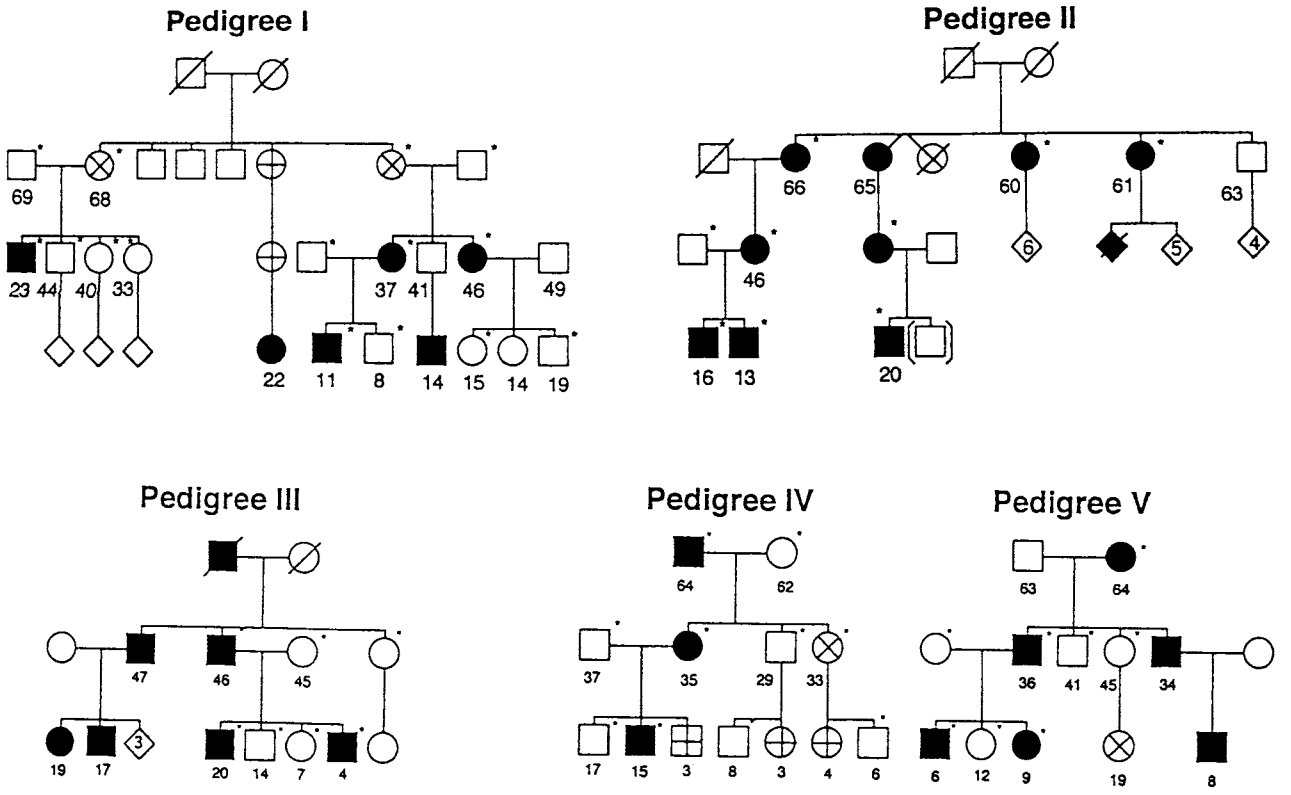

Fig. 1. Pedigrees of the five families studied. Inheritance pattern appears consistent with autosomal dominant transmission. ●, Affected individuals; ⊕, No data about affection status available; ⊗, Equivocal scores from questionnaires; [○], Adopted individual. *, Individuals for whom questionnaires were completed and blood obtained.

enhanced the probability of detecting a false association between the marker genotype and the disease state, thus, increasing the lod score. Varying the mutation rate from 3% to 8% (model 2 vs. 3) had little impact upon the results.

Computer simulations with SLINK and MSIM demonstrated that the pedigrees studied [including only those individuals from whom samples were obtained] would have been of sufficient size and structure to detect significant genetic linkage to these markers

TABLE I. Segregation Analysis of ADHD Pedigrees

	Segregation model	Number of parameters	−2 ln L	AIC[a]
1.	Class A, no parent-offspring transmission: homogenous transmission, no major gene or sex effect	3	361.7	367.7
2.	Class A, Mendelian inheritance, major gene effect, sex-dependent	9	337.7	355.7
3.	Class A, Mendelian inheritance, dominant, sex-dependent	7	356.9	360.9
4.	Class D, Mendelian inheritance, major gene effect, sex-dependent[b]	10	324.1	344.1
5.	Class D, Mendelian inheritance, dominant, sex-dependent	8	343.1	359.1
6.	Class D, Mendelian inheritance, major gene effect, not sex-dependent	7	338.8	352.8
7.	Class D, no parent-offspring transmission: possible heterogeneity between founders and non-founders, major gene effect, sex-dependent	11	336.1	358.1

[a] −2 Ln (likelihood) + 2 (number of essential parameters); Akaike [1974].
[b] Best fitting model.

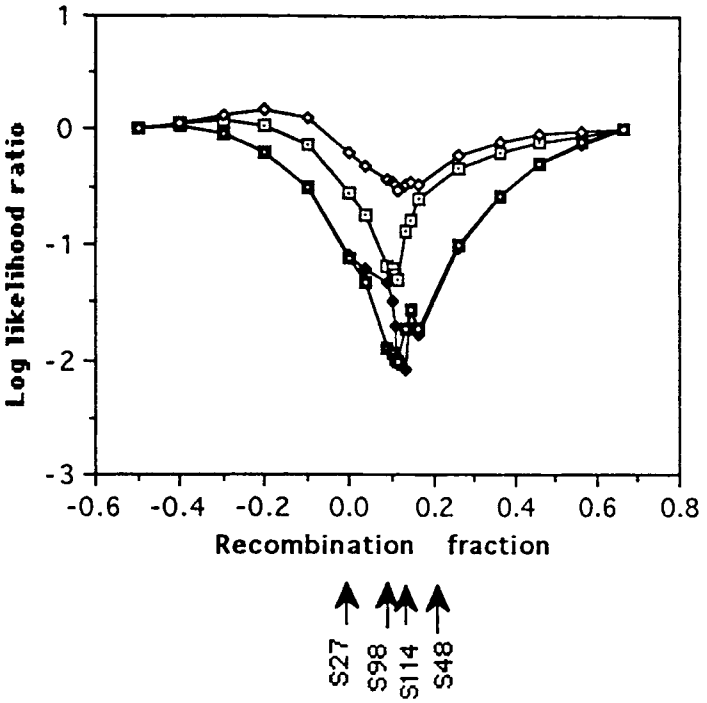

Fig. 2. The curves represent the data for the five families studied using the models noted below.

	Penetrance			Allele	Phenocopy Rate		
	M	F ≤ 11 yrs	F > 11 yrs	Frequency	M	F ≤ 11 yrs	F > 11 yrs
Model 1 (-▣-)	.95	.8	.5	.03	.088	.0960	.0960
Model 2 (-◆-)	.95	.95	.95	.08	.088	.0960	.0960
Model 3 (-■-)	.95	.95	.95	.03	.088	.0960	.0960
Model 4 (-◇-)	.95	.8	.5	.03	.001	.001	.001

were it present [Ott, 1989; Weeks et al., 1990]. Linkage for a single fixed marker close to the hypothetical ADHD locus ($\theta = 0.02$) gave average maximum lod scores of 3.03 for model 1, 3.21 for model 2, 3.12 for model 3, and 3.14 for model 4, using recombinant fractions < 0.05.

DISCUSSION

There are several possible explanations for the absence of significant linkage observed in this study. First, we recognize that our apparently single gene, Mendelian sample of families may not represent the majority of kindreds with genetically-influenced ADHD in whom no discrete Mendelian pattern is evident. However, review of our clinic files showed that 60% of families with multiple affected members appeared to follow an autosomal dominant pattern with gender-specific differential expression.

Second, it is possible that a small segment of the region, including the locus responsible for hyperactivity in the *coloboma* mouse, is located within a region of the mouse deletion which is not syntenic with human chromosome 20p. This is unlikely based on available data about those regions in the mouse and human which suggest complete synteny [Nelson et al., 1994; Loffler et al., 1994].

Third, human and murine locomotor hyperactivity may both be mediated by similar aberrations of monoamine neurotransmitter balance, but with involvement of a different component of the "critical pathway" in each species. A common neurochemical mechanism is suggested by the ameliatory effect of dextroamphetamine on motoric hyperactivity in both species. This medication appears to modulate dopamine and/or norepinephrine levels in selected neuronal pathways [Shekim et al., 1979; Zametkin and Rapoport, 1987; Shenker, 1992]. Further work with the mouse model, including quantitation of regional dopamine levels pre- and post-stimulant administration, may assist in suggesting specific components of the pathway for scrutiny. Additional work is also needed to define the role of SNAP-25 in modulating regional neurotransmission.

Lastly, although the parallels in the behavior pattern and response to stimulant medication in *coloboma* mouse and humans are striking, different genetic causations may exist. Considering the apparent clinical heterogeneity of ADHD in man, genetic heterogeneity of similar behavioral disorders in different species would not be surprising.

The clinical and statistical problems encountered in the search for the gene(s) responsible for genetically

mediated ADHD are common to linkage studies of complex biobehavioral phenotypes [Pauls, 1993]. Although the pedigrees employed in this study suggest autosomal dominant transmission with variation in expression, multifactorial inheritance or the presence of a second gene which modifies phenotype cannot be excluded with certainty. We have statistically modeled a range of penetrance values, allele frequencies, and phenocopy rates in the linkage assessment as has been done in other investigations. Despite varying these values within clinically justified ranges, the lod scores obtained were uniformly negative. Thus, dominant mutations in the human SNAP-25 homolog or at neighboring genetic loci will probably not be associated with this form of ADHD.

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