Original Paper

Human Heredity

Hum Hered 2005;60:1–9
DOI: 10.1159/000087135

Received: December 23, 2004
Accepted after revision: May 12, 2005
Published online: July 27, 2005

Complex Segregation Analysis of Obsessive-Compulsive Disorder in Families with Pediatric Probands

Gregory L. Hanna[a] Tasha E. Fingerlin[b] Joseph A. Himle[a] Michael Boehnke[c]

[a]Department of Psychiatry, University of Michigan Medical School, Ann Arbor, Mich., [b]Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver, Colo. and [c]Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Mich., USA

Key Words

Obsessive-compulsive disorder · Complex segregation analysis · Regressive logistic models · Age at onset · Single major locus transmission

Abstract

Objective: The purpose of this study was to assess the mode of inheritance for obsessive-compulsive disorder (OCD) in families ascertained through pediatric probands. ***Methods:*** We ascertained 52 families (35 case and 17 control families) through probands between the ages of 10 and 17 years. Direct interviews were completed with 215 individuals. Family informant data were collected on another 450 individuals without direct interviews, forming two data sets with one contained within the other. Complex segregation analyses were performed using regressive models as programmed in REGTL in the S.A.G.E. package. All models used in the analyses included sex-specific age and type parameters. ***Results:*** All models that excluded a residual effect of an affected parent were rejected. With that parameter included, the environmental and sporadic models were rejected in comparisons with the most general model in both data sets (all $p < 0.005$). With the direct interview data, the general codominant Mendelian model was not rejected when compared with the most general model ($p = 0.140$). We could not distinguish between any of the simple Mendelian models using either data set. However, the dominant Mendelian model provided a somewhat better fit than the other Mendelian models to the direct interview data. ***Conclusions:*** The results provide evidence for a major susceptibility locus in families with OCD when age at onset is incorporated into the model. Mendelian factors at most partially explained the familial aggregation of the phenotype, and residual familial effects were necessary to fit the data adequately. The results support the importance of linkage efforts by suggesting that a major locus is segregating within a proportion of families with OCD ascertained through pediatric probands.

Introduction

Obsessive-compulsive disorder (OCD [MIM 164230]) is a heterogeneous psychiatric disorder that is considered a complex genetic trait. Estimates of the lifetime prevalence of OCD in adolescents and adults range from 1 to

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0001–5652/05/0601–0001$22.00/0

Accessible online at:
www.karger.com/hhe

Gregory L. Hanna, MD
Department of Psychiatry, University of Michigan Health System
2101 Commonwealth Boulevard, Suite C
Ann Arbor, MI 48109-0390 (USA)
Tel. +1 734 764 0234, Fax +1 734 936 8907, E-Mail ghanna@umich.edu

3% [1–4]. The average age at onset in epidemiological studies of OCD is in early adulthood [3, 5]. Males generally have earlier onset than females, contributing to a preponderance of males in most pediatric samples [5, 6]. In contrast, there is a slight preponderance of females in most adult samples [3, 7]. Although obsessive-compulsive (OC) symptoms are virtually identical in children and adults, there are important clinical differences between early- and late-onset OCD. Early-onset OCD is associated with greater symptom severity, higher rates of compulsions without obsessions, a broader range of OC symptoms unrelated to duration of illness, and comorbid tic disorders [8–11].

Twin and family studies provide substantial evidence that genetic factors are involved in the transmission and expression of OCD. Concordance rates for monozygotic twins range from 80 to 87% for monozygotic twins and from 47 to 50% for dizygotic twins, depending on the sample and diagnostic criteria [12, 13]. Estimates of the heritability of OC symptoms range from 26 to 47% [14, 15]. Controlled family studies using adult probands found that the lifetime prevalence of OCD is significantly higher in case relatives compared with control relatives, and that an early age at onset of OC symptoms in case probands is strongly associated with a more familial form of the disorder [16, 17]. A recent controlled family study using pediatric probands confirmed that early-onset OCD is highly familial [18].

Four complex segregation analyses, conducted with families mainly ascertained through adult probands, have implicated a major locus in a proportion of families with OCD [19–22]. Two studies provided evidence for a major gene in OCD without establishing a mode of inheritance [19, 20]. Another study determined in a subset of families with higher symptom-based factor scores for symmetry and ordering that the polygenic model could be rejected, indicating the involvement of a major locus in OCD [21]. However, analysis of the entire sample allowed rejection of only the no transmission model. The most recent segregation analysis of OCD supported an autosomal dominant or codominant model and rejected a recessive model [22]. Nonetheless, Mendelian factors only partially explained the familial aggregation of the phenotype, and residual familial effects were necessary to adequately fit the data. The four studies together indicate that genes of major effect are important in the transmission of OCD. However, differences in the likelihoods of alternative models of transmission are not large, indicating that it is difficult to distinguish between transmission models of OCD in families.

Our initial genome scan of families with early-onset OCD found suggestive evidence for genetic linkage on chromosome 9 using a dominant Mendelian model [23]. The finding on 9p24 was replicated by another research group using the same genetic model [24]. However, the model used in those parametric analyses had no empirical basis. Further molecular genetic studies of early-onset OCD are likely to be done because that form of OCD is more familial with possibly less etiological heterogeneity [16–18, 25]. Because of uncertainty about the mode of inheritance in early-onset OCD, a complex segregation analysis of that form of the disorder is warranted. Hence, this study was done to assess the mode of inheritance for OCD in families ascertained through pediatric probands. The results provide evidence for a major susceptibility locus in OCD when age at onset is incorporated into the model.

Materials and Methods

Subject Ascertainment

We ascertained 35 case and 17 control families through single probands between the ages of 10 and 17 years. The ascertainment and diagnostic procedures used in the study have been described previously [18, 23]. The case probands were 25 boys and 10 girls with a current diagnosis of OCD who were recruited from clinics in the University of Michigan Health System and local chapters of the Obsessive-Compulsive Foundation. Age at onset of OC symptoms in the case probands ranged from 4 to 14 years (8.9 ± 3.0 years, mean ± SD). Furthermore, 31 (89%) of the case probands had a lifetime history of at least one other psychiatric disorder. In particular, 14 (40%) had a history of Tourette's disorder or another chronic tic disorder. The control probands were 10 boys and 7 girls recruited from clinics in the University of Michigan Health System and local advertisements.

All probands were directly interviewed to determine whether they met DSM-III-R criteria for OCD [26]. Exclusion criteria for the case probands were (1) lifetime DSM-III-R diagnosis of mental retardation, autistic disorder, schizophrenia, or bipolar disorder; (2) currently living away from both biological parents, and (3) adoption. Exclusion criteria for the control probands were (1) any lifetime DSM-III-R Axis I disorder as well as (2) and (3) as above. Written informed consent was obtained from both parents and informed assent from each proband. The study was approved by the Institutional Review Board of the University of Michigan Medical School.

After completing the proband diagnostic evaluation, permission to contact other relatives was requested from the parents. Direct structured diagnostic interviews were completed with 215 individuals (all 52 probands, 136 first-degree relatives, 15 second-degree relatives, and 12 other relatives). Diagnostic information was also collected from parents or spouses on 657 individuals (all 52 probands, 133 first-degree relatives, 459 second-degree relatives, and 13 third-degree relatives). The maternal grandmother provided diagnostic information for the 13 third-degree relatives in the larg-

est family. This process provided diagnostic information on five first-degree relatives without direct interviews and 445 second-degree relatives without direct interviews.

Diagnostic Procedures

After informed consent and assent were obtained, probands and siblings between 10 and 17 years of age were interviewed with the Schedule for Affective Disorders and Schizophrenia for School Age Children-Epidemiologic Version [27]. Individuals less than 10 years were not included in the study. The interview was completed independently with a parent of the subject as well as with the subject. Relatives 18 years and older were interviewed with the Structured Clinical Interview for DSM-III-R [28]. Both interviews were supplemented with sections on OCD and tic disorders from the Schedule for Tourette and Other Behavioral Syndromes [16, 29]. The OCD section included a series of screening questions designed to cover all criteria for a DSM-III-R diagnosis of OCD [16] and a checklist from the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [30] modified to obtain information about the lifetime occurrence and age at onset of OC symptoms.

Further information on relatives 18 years and older was obtained with the Family Informant Schedule and Criteria (FISC) [31]. The mother of each affected offspring was interviewed with the FISC regarding her spouse, adult offspring, parents, and siblings. The father of each affected offspring was interviewed with the FISC regarding his spouse, parents, and siblings. Thus, two types of data were obtained on directly interviewed adult subjects: (1) information from structured interviews, and (2) personal history information from a biological relative and/or spouse.

All interviews were audiotaped and coded on paper. All interviewers had at least a master's degree and clinical training in either child or adult psychopathology; they were trained to at least 90% diagnostic agreement with the individual instruments. The interviewers were confined to interviewing either probands and their relatives between 10 and 17 years of age or adult relatives. The interviewer for a given proband was not involved with the interviews of other family members. Because control probands and their relatives were included in a family study of pediatric OCD, the interviewers were blind to proband status.

After completion of all interviews for an individual, all available materials (personal interview data, family history data, and clinical records) were collated. All information identifying or describing the proband was removed so that diagnostic ratings could be completed by raters blind to proband diagnosis. The blinded diagnosticians were never given a complete family to evaluate at one time, and all proband diagnostic evaluations were done separately from those of their relatives.

Best-estimate lifetime diagnoses were made independently for directly interviewed subjects by two investigators using DSM-III-R criteria. Definite OCD was diagnosed only if a directly interviewed subject met all diagnostic criteria. Subthreshold OCD was diagnosed if a directly interviewed subject met criteria for obsessions and/or compulsions, but lacked compelling evidence for any of the following criteria: (1) marked distress; (2) duration of obsessive-compulsive symptoms for more than one hour a day, or (3) significant interference in the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships with others. To avoid forcing closure on inadequate diagnostic information, subjects were reinterviewed if necessary to clarify incomplete or contradictory information. When disagreements occurred between two diagnosticians, consensus diagnoses were reached with the assistance of a third diagnostician following established procedures developed for the diagnosis of other psychiatric disorders [32].

Directly interviewed individuals with a lifetime diagnosis of definite OCD were considered affected. Directly interviewed relatives with either a lifetime diagnosis of subthreshold OCD or a history of probable obsessions or compulsions were considered unknown. Subjects assessed by the FISC but not by direct interviews were considered affected if they met FISC criteria for definite or probable OCD. This broader definition of OCD was used because individuals with OCD are often secretive about their symptoms and a relatively low rate of definite OCD was reported by family informants.

After single ascertainment, nuclear families found to have at least two affected individuals were extended by sequential sampling using a nuclear family sequential sampling rule [33, 34]. (1) All first-degree relatives and spouses of the proband were sampled with the assessment and diagnostic procedures outlined above. (2) If any sampled individual was affected, all first-degree relatives and spouses of that individual who had not already been sampled were sampled with the same assessment and diagnostic procedures. (3) We returned to step 2 until no further such relatives and spouses remained. The advantage of a sequential approach is that it results in a more detailed consideration of families with substantial numbers of affected individuals while still permitting appropriate ascertainment correction for segregation analysis [33]. It also ascertains families for genetic linkage studies in which the disorder has occurred in at least three generations [23].

Statistical Analyses

Complex segregation analyses were performed with the REGTL program in the S.A.G.E computer package (version 3.1) [35]. The REGTL program uses a regressive logistic model developed by Bonney [36] that was modified to incorporate age at onset information [37]. The model assumes that (1) age at onset follows a logistic distribution; (2) the parameters of the age at onset distribution do not depend on an individual's type, and (3) susceptibility to OCD is a function of an individual's type. The model tests for the presence of a major susceptibility locus, residual correlations in risk among related individuals, and the effect of measured risk factors.

In this logistic regressive model, the likelihood of the data is modeled as a function of the following parameters:

1 Each person can be one of three types, AA, BB, or BB, with population frequencies ψ_{AA}, ψ_{AB}, ψ_{BB}.
2 Each type is associated with a probability that expresses susceptibility to become ill: γ_{AA}, γ_{AB}, γ_{BB}. Under a genetic model these are termed the penetrance of each genotype.
3 Since the trait has a variable age at onset, the probability of becoming ill is also a function of two age distribution parameters, β (the baseline effect) and α (the age adjustment coefficient), which determine the mean and variance of the logistic distribution of the age at onset.
4 Residual familial effects: δ_{parent}.
5 Each type is associated with a probability that an individual of the type will transmit the 'A' factor to a child. These are the transmission probabilities: τ_{AA}, τ_{AB}, τ_{BB}.

Define y = 1 if affected, 0 if unaffected, a = age of onset of OCD, and a′ = age at examination. The likelihood is formulated as [36]:

L(y,a|age at exam, type, sex, affection status of parents)

$$L(y=1,a)=\frac{\gamma_{sex,type}\alpha_{sex}\left\{\exp\left(\beta_{sex}+\alpha_{sex}a+\delta\left(I_{(parent\ affected)}\right)\right)\right\}}{\left\{1+\exp\left(\beta_{sex}+\alpha_{sex}a+\delta\left(I_{(parent\ affected)}\right)\right)\right\}^2}$$

if affected

$$L(y=0)=1-\frac{\gamma_{sex,type}\alpha_{sex}\left\{\exp\left(\beta_{sex}+\alpha_{sex}a'+\delta\left(I_{(parent\ affected)}\right)\right)\right\}}{\left\{1+\exp\left(\beta_{sex}+\alpha_{sex}a'+\delta\left(I_{(parent\ affected)}\right)\right)\right\}^2}$$

if unaffected.

The likelihoods for each case are similar; the differences reflect both the law of total probability and the fact that unaffected individuals may become affected after the age at examination. Age of onset and age at exam were transformed to the natural log scale. A single ascertainment correction was applied by conditioning on the affection status and age of onset of the proband (age at examination if unaffected) [33].

Seven models were fit to the data: (1) a general model assuming arbitrary transmission and type-specific susceptibility parameters; (2) a general codominant Mendelian model assuming arbitrary type-specific susceptibility parameters but Mendelian inheritance; (3) a Mendelian dominant model; (4) a Mendelian recessive model; (5) a Mendelian additive model; (6) an environmental model assuming no genetic transmission, and (7) a sporadic model assuming no major gene. Nested models were compared using chi-square likelihood ratio tests. The number of degrees of freedom is approximate for some tests for two reasons. First, in two instances, one or more parameters are fixed at a boundary of the parameter space under the reduced model (reduced codominant Mendelian and sporadic models compared to full general model). Second, for some models, some parameters converged to boundary values during maximization. We note in the Results the one case in which these conditions might change the interpretation of a test.

The analyses were carried out using two nested samples. The first sample consisted of the 215 directly interviewed individuals (all 52 probands, 136 first-degree relatives, 15 second-degree relatives, and 12 other relatives). The second sample also included the five first-degree relatives and 445 second-degree relatives for whom information was obtained only by interviews of first-degree relatives (family informant-only data in addition to direct interview data). Other statistical comparisons were done using Student's t test and Pearson χ^2 as appropriate. Data are reported as mean ± standard deviation. Statistical significance was stipulated as $p \leq 0.05$.

Results

Demographic and Clinical Characteristics

There were no significant differences between the case and control families in gender distribution or age at the time of interview. As expected, the prevalence of definite OCD assessed by direct interview was significantly greater among case families than among control families (42.1% case subjects vs. 1.8% control subjects; $p<0.0001$). Similarly, the prevalence of definite OCD assessed by either direct or family history interview was significantly greater among case families than among control families (15.2% case subjects vs. 1.0% control subjects, $p < 0.0001$). As described in a previous report, the lifetime prevalence of definite OCD was significantly higher in case than in control first-degree relatives (22.5 vs. 2.6%, $p < 0.05$) [18]. Of the 35 case probands in the study, 19 (54%) had at least one first-degree relative with definite OCD. In contrast, the lifetime prevalence of definite OCD was not significantly increased in the case second-degree relatives compared to controls (1.6 vs. 0.7%, $p = 0.42$). The lifetime prevalence of definite OCD was significantly higher in case first-degree relatives with a history of tics than in case first-degree relatives without a tic history (57.1 vs. 20.9%, $p < 0.01$). However, the lifetime prevalence of chronic tic disorders (Tourette's disorder and chronic motor or vocal tic disorder) and tic disorders altogether was only slightly higher in case than in control first-degree relatives (4.1% vs. 2.6 and 7.1 vs. 5.3%, respectively).

In the 35 case families, males and females did not differ significantly with respect to their mean age at direct interview (~33 years) or the proportion diagnosed with definite OCD by direct interview (43.5% males vs. 40.5% females, $p = 0.85$). However, the mean age at onset of OC symptoms in case subjects with either definite OCD or subthreshold OCD diagnosed by direct interview was significantly lower in males than in females (9.4 vs. 12.2 years, $p < 0.03$). Directly interviewed case relatives ascertained through either a male or female proband had similar mean age at interview (~39 years), age at onset of OC symptoms (~12 years), and proportion diagnosed with definite OCD (~26%). Neither gender of the proband nor of the first-degree relative was predictive of definite OCD in case first-degree relatives [18].

Complex Segregation Analyses

All models that excluded gender effects were considered implausible and not tested. All models that excluded a residual effect of an affected parent were rejected (all $p < 0.005$).

For both samples, we rejected the environmental and sporadic models when compared to the most general model (all $p < 0.005$). With the direct interview data, the general codominant Mendelian model was not rejected when compared with the most general model ($p = 0.14$);

Table 1. Segregation analysis of OCD using only directly interviewed subjects

Parameter	General	Sporadic	Environmental	Mendelian models			
				codominant	dominant	additive	recessive
q_A	0.007	(1.0)	NR	0.031	0.029	0.055	0.289
τ_{AA}	0.766	–	q_A	(1.00)	(1.00)	(1.00)	(1.00)
τ_{AB}	0.896	–	q_A	(0.50)	(0.50)	(0.50)	(0.50)
τ_{BB}	0.007	–	q_A	(0.00)	(0.00)	(0.00)	(0.00)
δ_{parent}	–1.431	–1.105	NR	–1.328	–1.327	–1.304	–1.348
α_{Female}	4.135	4.012	NR	4.112	4.112	4.121	4.122
α_{Male}	8.504	8.859	NR	8.743	8.757	8.765	8.717
β_{Female}	–11.566	–10.964	NR	–11.364	–11.362	–11.355	–11.429
β_{Male}	–23.586	–23.790	NR	–23.919	–23.950	–23.924	–23.916
$\gamma_{AA-Female}$	1.000*	0.264	NR	1.000*	0.723	1.000*	1.000*
$\gamma_{AB-Female}$	0.721	$\gamma_{AA-Female}$	NR	0.685	$\gamma_{AA-Female}$	0.506[a]	$\gamma_{BB-Female}$
$\gamma_{BB-Female}$	0.020	$\gamma_{AA-Female}$	NR	0.015	0.016	0.011	0.008
$\gamma_{AA-Male}$	0.001*	0.170	NR	1.000*	0.527	0.859	0.768
$\gamma_{AB-Male}$	0.576	$\gamma_{AA-Male}$	NR	0.502	$\gamma_{AA-Male}$	0.430[§]	$\gamma_{BB-Male}$
$\gamma_{BB-Male}$	0.010	$\gamma_{AA-Male}$	N/A	0.007	0.008	0.001*	0.001*
–2lnL	84.198	108.391	108.391	89.668	89.897	90.538	92.044
χ^2	–	24.193	24.193	5.47	0.229	0.870	2.376
N	15	7	12	12	10	10	10
d.f.	–	8	3	3	2	2	2
p	–	0.002[b]	<0.001[b]	0.140[b]	0.892[c]	0.647[c]	0.305[c]

NR = not reported (see results); N = number of independent parameters. * Parameter converged to preset bound.

[a] $(1/2)(\gamma_{AA-Female} + \gamma_{BB-Female})$.

[b] Compared to general model.

[c] Compared to codominant Mendelian model.

however, with the combined direct interview and family informant-only data, that model was rejected in comparison with the most general model ($p < 0.001$). Because the number of degrees of freedom may be overestimated for this test (see Statistical Analyses), it is possible that the most general model is a better fit to the data than the general codominant Mendelian model even with the direct interview data. We were unable to distinguish between any of the simple Mendelian models using either data set. Nonetheless, we note that the parameter estimates for the dominant Mendelian model are closest to those of the general codominant Mendelian model.

For each model including a residual effect of an affected parent, table 1 presents the parameter estimates derived using only the direct interview data. Parameter estimates for the environmental model are not included since models with virtually identical likelihoods had quite disparate parameter estimates, indicating that the likelihood surface is quite flat. Table 1 also provides the likelihood ratio tests comparing (1) the sporadic, environmental, and general Mendelian models to the most general model, and (2) the three simple Mendelian models to the general Mendelian model.

Estimates from the dominant model using only the direct interview data indicated that 0.08% of subjects were homozygous for the high-risk genotype (AA), 5.7% were heterozygous carriers (AB), and 94.2% had the low-risk genotype (BB). With the dominant model, as depicted in figures 1a and b, the genetic penetrance approached 53% by age 31 years in heterozygous males without an affected parent and reached 72% by 60 years in heterozygous females without an affected parent. In contrast, as shown in figures 2a and b, the genetic penetrance approached 53% by age 36 years in heterozygous males with one affected parent and reached 72% by age 83 years in heterozygous females with an affected parent. The penetrance models suggest that age at onset is delayed in susceptible individuals by having an affected parent; however, the apparent difference is within statistical error.

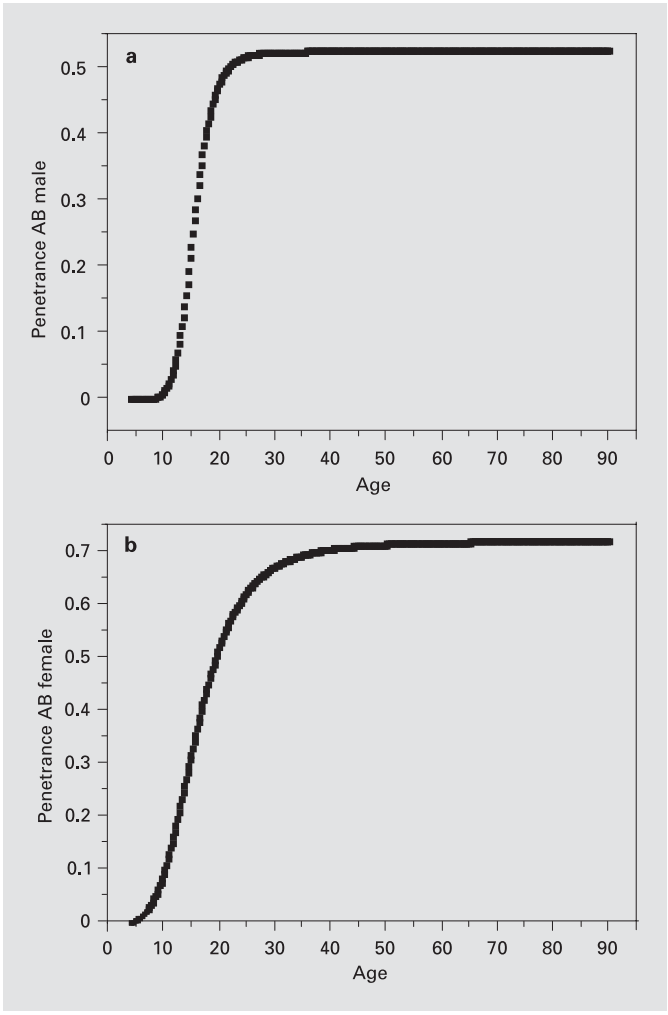

Fig. 1. a Penetrance of OCD in a heterozygous male without an affected parent. **b** Penetrance of OCD in a heterozygous female without an affected parent.

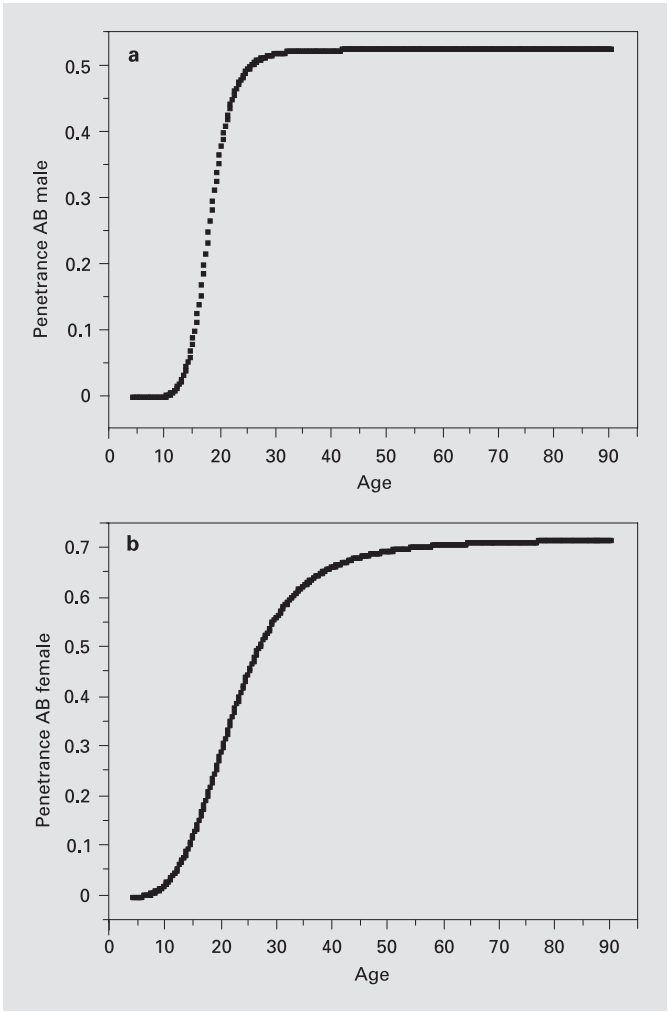

Fig. 2. a Penetrance of OCD in a heterozygous male with one affected parent. **b** Penetrance of OCD in a heterozygous female with one affected parent.

Discussion

Major Locus and Other Effects

The results from our complex segregation analysis provide further evidence for a major susceptibility locus or other transmissible effect in families with OCD when age at onset is incorporated into the model. Previous segregation analyses of OCD have not explicitly incorporated age at onset information [19–22]. All models in our analysis that excluded the residual effect of an affected parent were rejected. Hence, Mendelian factors at most partially explained the familial aggregation of the phenotype, and residual familial effects were necessary to fit the data adequately. A previous segregation analysis of OCD also rejected all models omitting residual familial effects [22].

The use of pediatric probands may have contributed to our ability to detect transmission of a major effect, because of the high recurrence risk of OCD in relatives of probands with early-onset OCD [16–18]. It is important to note, however, that the results cannot determine whether the same genetic locus is segregating across families in our data set. Furthermore, the results cannot be used to assess the number of genetic loci segregating in OCD or the extent to which genetic heterogeneity is present in the disorder [38]. Nonetheless, the results provide support for linkage efforts in that they indicate that a major locus is

segregating within a proportion of families with OCD ascertained through pediatric probands.

Mendelian Models

We rejected the general codominant Mendelian model with the combined data set but not with the direct interview data set, although it should be noted that the p values for those tests are approximate (see Statistical Analyses). Our diagnoses were almost certainly more reliable and valid for the directly interviewed subjects than for the subjects with only family informant information, so that the rejection of the codominant model in the extended data set may be due to diagnostic misclassification (see Limitations). However, the codominant model may have been rejected with a larger sample of directly interviewed subjects. Furthermore, there was a trend to reject that model in the study by Nestadt et al. [22] and that model was rejected when the affected phenotype was expanded to include chronic tics in the study by Cavallini et al. [20].

In the analyses with the direct interview data, the dominant model provided a marginally better fit to the data than did the other models. Our initial genome scan of early-onset OCD found suggestive evidence for genetic linkage on 9p24 with a dominant Mendelian model [23] that was replicated in a subsequent linkage analysis using the same genetic model [24]. The results from our segregation and linkage analyses, as well as from other segregation and linkage analyses, suggest that a dominant model be considered in future linkage studies of early-onset OCD [20, 22–24].

The mode of inheritance suggested by our study is generally consistent with a previous segregation analysis that found that neither the dominant nor the codominant model could be rejected, but that the recessive model could be rejected along with the sporadic and environmental models [22]. The dominant model was the most parsimonious explanation for the inheritance of OCD in the total sample of that study. However, there was strong evidence for etiologic heterogeneity between families ascertained through female probands and male probands, and only families ascertained through female probands allowed rejection of the recessive model. Other previous segregation analyses of OCD have not rejected a simple Mendelian model [19–21].

Several studies with adults indicate that OCD consists of four separate symptom dimensions [39–42]. Furthermore, it is likely that several genes influence components of OCD. A segregation analysis of OC symptom dimensions in families with two affected siblings with Tourette's disorder found that the transmission of two symptom-based factor scores is consistent with a dominant mode of inheritance and the transmission of the two other factor scores is consistent with a recessive mode of inheritance [43, 44]. It is uncertain whether the OC symptom patterns in our sample differed significantly from those in previous segregation analyses [19–22]. Larger studies of OCD using a dimensional characterization of OC symptoms are necessary to determine whether symptom-based factor scores differ in their transmission patterns and susceptibility loci.

Our disease allele frequency estimate of 0.029 using a dominant model is comparable to previous estimates using dominant models of 0.01 in the Cavallini et al. study [20] and of 0.045 in the Nestadt et al. study [22]. The penetrance estimates with our dominant model indicate that females have a higher penetrance than males. This is consistent with estimates from previous segregation analyses [20, 22] and with the slight preponderance of females in most epidemiological and clinical studies with adults [3, 7]. The age at onset curves suggest that individuals with OCD without an affected parent have an earlier onset than those with an affected parent. This seems counterintuitive, and the apparent difference is within statistical error. This apparent difference could be attributed to non-genetic factors or to genetic factors separate from a major susceptibility locus. Notwithstanding, given this trend, the data do not support the hypothesis of anticipation of age at onset as has been proposed in a previous report on OCD [45].

Limitations

Several limitations of our segregation analysis require consideration. The number of directly interviewed subjects in our sample was low so that the statistical power of the smaller data set was limited. The inclusion of subjects with only family informant data probably underestimated the rate of OCD in the second-degree relatives and lead to distortions in the segregation analysis with the larger sample. For example, a simple Mendelian model may have been more clearly implicated if all of our subjects had been directly interviewed. The case probands were recruited mainly through a tertiary health care center, so that the case families in our sample may not be representative of families with early-onset OCD in the general population. In particular, the recruitment of case probands with comorbid conditions may have selected for families with a high rate of assortative mating or other etiologic factors. Only a minority of individuals in this study were genotyped, so that it is possible that the bio-

logical relationships of certain individuals may have been misclassified [23].

A strength of our study is that the sample included both case and control families. Thus, the estimates of disease frequencies and penetrances are likely to be less biased than in a study based solely on case families. An additional strength is the use of intermediate-sized pedigrees spanning three generations that provide more information on transmission parameters than nuclear families.

OCD was the only phenotype considered in this study. Only strict DSM-III-R criteria were used for directly interviewed subjects, whereas broader FISC criteria were used for those not directly interviewed because of the limitations of family history data. If the susceptibility alleles involved in OCD have variable expression, other disorders could be assessed in future studies. Those disorders include subthreshold OCD [17, 18], Tourette's disorder and other tic disorders [16, 46, 47], body dysmorphic disorder [48], generalized anxiety disorder and agoraphobia [49], and eating disorders [50].

Conclusions

Our results provide evidence for a major susceptibility locus in OCD when age at onset is incorporated into the model. The results suggest that the mode of inheritance may be influenced by the residual effect of an affected parent, providing further evidence for the etiologic heterogeneity of OCD. In a comparison of simple Mendelian models, the dominant model provided a somewhat better fit to the data than the other Mendelian models, which is consistent with some segregation analyses that ascertained families through adult probands [20, 22]. The parameters derived from this segregation analysis for a dominant Mendelian model with age- and sex-dependent penetrance may be useful in future molecular genetic studies of early-onset OCD.

Acknowledgments

The authors thank Diane Q. Koram, M.S.W., Kristin R. Chadha, M.S.W., Katherine J. Gold, M.S.W., M.D., and Aileen H. Prout, M.S.W. for their thorough interviews and George C. Curtis, M.D. for assistance in diagnostic reviews. The authors are especially grateful to the families who participated in the study. This work was supported by NIH K20 MH01065 (GLH).

References

1 Zohar AH, Ratzoni G, Pauls DL, Apter A, Bleich A, Kron S, Rappaport M, Weizman A, Cohen DJ: An epidemiological study of obsessive-compulsive disorder and related disorders in Israeli adolescents. J Am Acad Child Adolesc Psychiatry 1992;31:1057–1061.

2 Valleni-Basile LA, Garrison CZ, Jackson KL, Waller JL, McKeown RE, Addy CL, Cuffe SP: Frequency of obsessive-compulsive disorder in a community sample of young adolescents. J Am Acad Child Adolesc Psychiatry 1994;33:782–791.

3 Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, Lee CK, Newman SC, Oakley-Browne MA, Rubio-Stipec M, Wickramaratne PJ, Wittchen H-U, Yeh E-K: The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. J Clin Psychiatry 1994;55(suppl):5–10.

4 Douglass HM, Moffitt TE, Dar R, McGee R, Silva P: Obsessive-compulsive disorder in a birth cohort of 18-year-olds: prevalence and predictors. J Am Acad Child Adolesc Psychiatry 1995;34:1424–1431.

5 Burke KC, Burke JD Jr, Regier DA, Rae DS: Age at onset of selected mental disorders in five community populations. Arch Gen Psychiatry 1990;47:511–518.

6 Hanna GL: Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. J Am Acad Child Adolesc Psychiatry 1995;34:19–27.

7 Nestadt G, Bienvenu OJ, Cai G, Samuels J, Eaton WW: Incidence of obsessive-compulsive disorder in adults. J Nerv Ment Dis 1998;186:401–406.

8 Rosario-Campos MC, Leckman JF, Mercadante MT, Shavitt RG, Prado HS, Sada P, Zamignani D, Miguel EC: Adults with early-onset obsessive-compulsive disorder. Am J Psychiatry 2001;158:1899–1903.

9 Geller D, Biederman J, Jones J, Park K, Schwartz S, Shapiro S, Coffey B: Is juvenile obsessive-compulsive disorder a developmental subtype of the disorder? A review of the pediatric literature. J Am Acad Child Adolesc Psychiatry 1998;37:420–427.

10 Sobin C, Blundell ML, Karayiorgou M: Phenotypic differences in early- and late-onset obsessive-compulsive disorder. Comp Psychiatry 2000;41:373–379.

11 Eichstedt JA, Arnold SL: Childhood-onset obsessive-compulsive disorder: A tic-related subtype of OCD? Clin Psychol Review 2001;21:137–158.

12 Inouye E: Similar and dissimilar manifestations of obsessive-compulsive neurosis in monozygotic twins. Am J Psychiatry 1965;21:1171–1175.

13 Carey G, Gottesman II: Twin and family studies of anxiety, phobic and obsessive disorders; in Klein DF, Rabkin J (eds): Anxiety: New Research and Changing Concepts. New York, Raven Press, 1981, pp 117–136.

14 Clifford CA, Murray RM, Fulker DW: Genetic and environmental influences on obsessional traits and symptoms. Psychol Med 1984;14:791–800.

15 Jonnal AH, Gardner GO, Prescott CA, Kendler KS: Obsessive and compulsive symptoms in a general population sample of female twins. Am J Med Genet Neuropsychiatr Genet 2000;96:791–796.

16 Pauls DL, Alsobrook JP II, Goodman W, Rasmussen S, Leckman JF: A family study of obsessive-compulsive disorder. Am J Psychiatry 1995;152:76–84.

17 Nestadt G, Samuels J, Riddle M, Bienvenu OJ III, Liang K-Y, LaBuda M, Walkup J, Grados M, Hoehn-Saric R: A family study of obsessive-compulsive disorder. Arch Gen Psychiatry 2000;57:358–363.
18 Hanna GL, Himle JA, Curtis GC, Gillespie BW: A family study of obsessive-compulsive disorder with pediatric probands. Am J Med Genet Neuropsychiatr Genet 2005;134B:13–19.
19 Nicolini H, Hanna GL, Baxter L, Schwartz J, Weissbecker K, Spence M: Segregation analysis of obsessive compulsive and associated disorders: Preliminary results. Ursus Medicus 1991;1:25–28.
20 Cavallini MC, Bertelli S, Chiapparino D, Riboldi S, Bellodi L: Complex segregation analysis of obsessive-compulsive disorder in 141 families of eating disorder probands, with and without obsessive-compulsive disorder. Am J Med Genet 2000;96:384–391.
21 Alsobrook JP II, Leckman JF, Goodman WK, Rasmussen SA, Pauls DL: Segregation analysis of obsessive-compulsive disorder using symptom-based factor scores. Am J Med Genet Neuropsychiatr Genet 1999;88:669–675.
22 Nestadt G, Lan T, Samuels J, Riddle M, Bienvenu OJ III, Liang K-Y, Hoehn-Saric R, Cullen B, Grados M, Beaty TH, Shugart YY: Complex segregation analysis provides compelling evidence for a major gene underlying obsessive-compulsive disorder and for heterogeneity by sex. Am J Hum Genet 2000;67:1611–1616.
23 Hanna GL, Veenstra-VanderWeele J, Cox NJ, Boehnke M, Himle JA, Curtis GC, Leventhal BL, Cook EH: Genome-wide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. Am J Med Genet Neuropsychiatr Genet 2002;114:541–552.
24 Willour VL, Shugart YY, Samuels J, Grados M, Cullen B, Bienvenu OJ III, Wang Y, Liang KY, Valle D, Hoehn-Saric R, Riddle M, Nestadt G: Replication study supports evidence for linkage to 9p24 in obsessive-compulsive disorder. Am J Hum Genet 2004;75:508–513.
25 Lander E, Schork N: Genetic dissection of complex traits. Science 1994;265:2037–2048.
26 American Psychiatric Association on Nomenclature and Statistics: Diagnostic and Statistical Manual of Mental Disorders, ed 3, revised. Washington, DC, American Psychiatric Association, 1987.
27 Orvaschel H: Schedule for Affective Disorders and Schizophrenia for School Aged Children-Epidemiologic Version (K-SADS-E), Fourth Edition. Philadelphia, PA, Medical College of Pennsylvania, 1987.
28 Spitzer RL, Williams JB, Gibbon M, First MB: Structured Clinical Interview for DSM-III-R (SCID). Washington, DC, American Psychiatric Press, 1990.
29 Pauls DL, Hurst CR: Schedule for Tourette and Other Behavioral Syndromes. New Haven, CT, Child Study Center, Yale University, 1991.
30 Goodman W, Price L, Rasmussen S, Mazure C, Fleischmann R, Hill C, Heninger G, Charney D: The Yale-Brown Obsessive Compulsive Scale: I. development, use, and reliability. Arch Gen Psychiatry 1989;46:1006–1011.
31 Mannuza S, Fyer AJ, Endicott J, Klein DF: Family Informant Schedule and Criteria (FISC). New York, NY, Anxiety Disorders Clinic, New York Psychiatric Institute, 1985.
32 Roy MA, Lanctot G, Merette C, Cliche D, Fournier JP, Boutin P, Rodrigue C, Charron L, Turgeon M, Hamel M, Montgrain N, Nicole L, Pires A, Wallot H, Ponton AM, Garneau Y, Dion C, Lavallee JC, Potvin A, Szatmari P, Maziade M: Clinical and methodological factors related to reliability of the best-estimate diagnostic procedure. Am J Psychiatry 1997;154:1726–1733.
33 Cannings C, Thompson EA: Ascertainment in the sequential sampling of the pedigrees. Clin Genet 1977;12:208–212.
34 Boehnke M, Young MR, Moll PP: Comparison of sequential and fixed-structure sampling of pedigrees in complex segregation analysis of a quantitative trait. Am J Hum Genet 1988;43:336–343.
35 S.A.G.E. (Statistical Analysis for Genetic Epidemiology), version 3.1. Computer program package, available from the Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, 1997.
36 Bonney GE: Regressive logistic models for family disease and other binary traits. Biometrics 1986;42:611–625.
37 Elston R, George V: Age of onset, age at examination, and other covariates in the analysis of family data. Genet Epidemiol 1989;6:217–220.
38 Khoury MJ, Beaty TH, Cohen BH: Fundamentals of Genetic Epidemiology. New York, Oxford University Press, 1993.
39 Baer L: Factor analysis of symptom subtypes of obsessive compulsive disorder and their relation to personality and tic disorders. J Clin Psychiatry 1994;55:18–23.
40 Leckman JF, Grice DE, Boardman, J, Zhang H, Vitale A, Bondi C, Alsobrook, J, Peterson BS, Cohen DJ, Rasmussen SA, Goodman WK, McDougle CJ, Pauls DL: Symptoms of obsessive compulsive disorder. Am J Psychiatry 1997;154:911–917.
41 Summerfeldt LJ, Richter MA, Antony MM, Swinson RP: Symptom structure in obsessive-compulsive disorder: A confirmatory factor-analytic study. Behav Res Ther 1999;37:297–311.
42 Mataix-Cols D, Rosario-Campos MC, Leckman JF: A multidimensional model of obsessive-compulsive disorder. Am J Psychiatry 2005;162:228–238.
43 Zhang H, Leckman JF, Pauls DL, Tsai C-L, Kidd KK, Campos MR, the Tourette Syndrome Association International Consortium for Genetics: Genomewide scan of hoarding in sib pairs in which both sibs have Gilles de la Tourette Syndrome. Am J Hum Genet 2002;70:896–904.
44 Leckman JF, Pauls DL, Zhang H, Rosario-Campos MC, Katsovich L, Kidd KK, Pakstis AJ, Alsobrook JP, Robertson MM, McMahon WM, Walkup JT, van de Wetering BJM, King RA, Cohen DJ, the Tourette Syndrome Association International Consortium for Genetics: Obsessive-compulsive symptom dimensions in affected sibling pairs diagnosed with Gilles de la Tourette Syndrome. Am J Med Genet Neuropsychiatr Genet 2003;116B:60–68.
45 Cavallini MC, Albertazzi M, Bianchi L, Bellodi L: Anticipation of age at onset of obsessive-compulsive spectrum disorders in patients with obsessive-compulsive disorder. Psychiatry Res 2002;111:1–9.
46 Walkup JT, LaBuda MC, Singer HS, Brown J, Riddle MA, Hurko O: Family study and segregation analysis of Tourette syndrome: Evidence for a mixed model of inheritance. Am J Hum Genet 1996;59:684–693.
47 Grados MA, Riddle MA, Samuels JF, Liang K-Y, Hoehn-Saric R, Bienvenu OJ, Walkup JT, Song D, Nestadt G: The familial phenotype of obsessive-compulsive disorder in relation to tic disorders: the Hopkins OCD Family Study. Biol Psychiatry 2001;50:559–565.
48 Bienvenu OJ, Samuels JF, Riddle MA, Hoehn-Saric R, Liang K-Y, Cullen BAM, Grados MA, Nestadt G: The relationship of obsessive-compulsive disorder to possible spectrum disorders: results from a family study. Biol Psychiatry 2000;48:287–293.
49 Nestadt G, Samuels J, Riddle MA, Liang K-Y, Bienvenu OJ, Hoehn-Saric R, Grados M, Cullen B: The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. Psychol Med 2001;31:481–487.
50 Cavallini MC, Bertelli S, Chiapparino D, Riboldi S, Bellodi L: Complex segregation analysis of obsessive-compulsive disorder in 141 families of eating disorder probands, with and without obsessive-compulsive disorder. Am J Med Genet 2000;96:384–391.