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Irritable bowel syndrome aggregates strongly in families: a family-based case–control study

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Abstract

Irritable bowel syndrome (IBS) runs in families. Prior family studies surveyed patients inquiring about family history without surveying family members. The stigma associated with IBS may lead relatives to not share information with others, resulting in underestimates of familial aggregation of IBS. The aim of the study was to evaluate the accuracy of patient-report of family history of IBS in cases and controls, and to estimate familial aggregation of IBS using both a case–control and a family-study design. Fifty cases and 53 controls completed symptom questionnaires and provided contact information for first-degree relatives. Questionnaires were mailed to relatives. Relatives were considered to have IBS if they met Rome criteria and did not have an alternate GI diagnosis. Cases and controls identified 573 relatives in their families. A total of 202 (51%) of 396 living relatives participated. The kappa statistics between proband- and relative-reported IBS for case- and control-relatives were 0.27 and 0.04. Cases reported 21% of relatives had IBS; relative-reports showed 37% ($P = 0.003$). Controls reported 4% of relatives had IBS; relative-reports showed 16% ($P = 0.013$). Regardless of whether the proband or the relative themselves were the information source, case-relatives were threefold as likely to have IBS than control-relatives ($P < 0.05$). However, overall rates were higher when data collected from relatives were used. Regardless of approach, strong familial aggregation of IBS was observed. Cases and controls underestimated the frequency of IBS in their relatives and agreement between proband- and relative-report of IBS status was extremely poor, thus emphasizing the need for direct data collection from relatives in IBS family studies.

Keywords

functional gastrointestinal disorder; genetics; irritable bowel syndrome

INTRODUCTION

Irritable bowel syndrome (IBS) is a common disorder that has been reported to aggregate in families. In primary care patients presenting with abdominal pain, reporting a family history of IBS was predictive of receiving an IBS diagnosis.¹ In outpatients with IBS, 33% of patients had a positive family history compared to only 2% of controls,² providing quantitative estimates of familial aggregation of IBS. However, these two studies utilized data provided by the patients themselves, not from relatives or their relatives' care providers. Because IBS may not be directly visible to relatives, may not be socially acceptable to routinely discuss with family and friends, and the diagnosis is dependent on healthcare seeking, these studies may have underestimated the degree to which IBS symptoms aggregate in families. To date, the only study that has directly surveyed relatives for bowel symptoms was performed in Olmsted County, Minnesota. Kalantar *et al.*³ demonstrated that 17% of first-degree relatives (FDR) of individuals with IBS-type symptoms were affected with IBS, compared with only 7% of control-relatives with IBS. However, this study used spouses as controls; therefore, children, who were related to both cases and controls, could not be included in the analysis which again may have resulted in an underestimate of affected family members.

Twin studies suggest that there may be an underlying environmental and genetic basis for this disorder,⁴⁻⁵ but the exact determinants of this familial clustering have yet to be identified. Family-based studies may provide valuable insight into the genetic and environmental factors leading to IBS. Such studies can provide the foundation for gene discovery and environment risk factors (such as infection, abuse, or learned illness behaviour) relevant to IBS. In this context, it will be critically important to study families where misclassification of affected and unaffected status is low. However, to date, there has been no detailed description of well-characterized families with IBS, nor construction of pedigrees of IBS patients.

We thus performed a survey-based study of case- and control-families by mailing surveys to relatives directly, assigned affected or unaffected status among relatives in the family structure, and constructed pedigrees. The primary study aim was methodologic – to compare affected and unaffected status of relatives by proband-report with the status obtained from relative self-report and assessing the accuracy of patient reporting of a family history of IBS in cases and controls. This step was undertaken to put prior estimates using proxy data into perspective, but also to determine whether or not direct survey of relatives is required for future studies of families. Direct survey of relatives is considerably more labour-intensive than collecting data from probands alone, and it is conceivable that proband-provided information may be sufficient for family studies. Our *a priori* hypothesis was that accuracy in patient reporting of IBS status in relatives would be only moderate at best. The second aim of the study was to quantitate familial aggregation, to determine how strongly IBS may aggregate in families.

STUDY METHODS

Study design

The study employed a family-based case-control study design conducted at a major medical centre in the Upper Midwest of the USA. This project was approved by the Mayo Clinic Institutional Review Board. A candidate-gene association study of DNA collected from the cases and controls has been reported previously,⁶ but this previous study did not utilize any data collected from family members.

Subjects

The subjects of this study were recruited between February 2004 and July 2005. All outpatients ages 18–69 who (i) were going through an IBS patient education class, or (ii) had an indication

of IBS being seen in our Motility or General GI Clinic were approached for participation. Controls were randomly selected from outpatients from the Division of General Internal Medicine, who were frequency-matched to cases on age-decile, gender and race. Potential case and control probands were excluded if they were adopted or if they could not provide any information on blood-related FDRs (e.g. parents, siblings and children). Potential controls were also excluded if they carried a diagnosis of IBS in their medical record or if they met Rome I diagnostic criteria⁷ for IBS on a screening questionnaire. All probands were asked to complete a self-reported bowel symptom questionnaire, provide contact information for at least one FDR, and donate 20-mL blood. Only the first 50 cases and 50 control subjects who met inclusion criteria and completed all aspects of the study were included in the final sample. Only relatives for whom the proband provided permission to contact were mailed recruitment letters. All FDRs younger than age 18 years were excluded from contact, nor was contact made with next-of-kin for deceased relatives. Spouses of probands were contacted if there were children from the relationship, but spouse data were not included in the analysis as they were not blood-related.

Recruitment

Recruitment of case and control probands was performed prospectively and in person at the time of their clinic appointment. After their names and addresses were provided by the probands, case-relatives were contacted by a mailed recruitment letter and a packet that included a consent form. The letter included options to participate, to not participate or to call for more information. If the letter was returned indicating willingness to participate and the consent form was returned, then a bowel symptom questionnaire along with a postage-paid return envelope was mailed. Any relative indicating that they did not wish to participate was not further contacted. If there was no response to the initial recruitment letter by a relative, a second letter requesting participation was mailed. After no response to two mailings, relatives were not contacted further.

Data collection

All cases, controls and FDRs were asked to complete a modified version of a previously validated bowel disease questionnaire⁸ that collected information about bowel symptoms. In addition, the questionnaire included a family information form that asked about family structure, the vital status of FDRs, FDR contact information (from probands only), IBS-affected status, and typical bowel habits (constipation, diarrhoea, alternating and abdominal pain) in their FDRs. Information regarding demographics, somatic symptom checklist⁹ and past medical history were also collected in the questionnaire. In addition, medical chart review was performed for all cases and controls to confirm an IBS diagnosis in the cases, to rule out an IBS diagnosis in controls, and to extract medical information such as gastrointestinal (GI) diagnoses, GI test results and social history.

Assignment of affected and unaffected status in family members

For the primary analysis, FDRs were considered to be 'affected' with IBS by self-report if they met Rome I or II criteria for IBS^{7,10} and did not report an alternate GI diagnosis that could explain their symptoms (e.g. Crohn's disease). For the sensitivity analyses, other definitions of 'affected' were utilized including: (i) report of a medical diagnosis of IBS alone, (ii) reporting constipation and/or diarrhoea without an alternate GI diagnosis, (iii) meeting Rome criteria for IBS or reporting a medical diagnosis of IBS or reporting constipation and/or diarrhoea. In the analyses where proband-provided data were utilized about relatives, 'affected' was defined as the proband responding 'yes' or 'probably yes' to the query, 'do/did they have IBS?', or indicating 'abdominal pain', 'constipation', or 'diarrhoea' to the query, 'do/did they have bowel symptoms?' When a proband did not report IBS status for a family member, that

family member's proband reported status was assumed to be no IBS. For analyses stratifying on presence of psychological or psychiatric disorders, members in each pedigree were considered to have a disorder if the proband or relative self-reported from a checklist a drinking problem, abuse, depression, anxiety, eating disorder, panic disorder, schizophrenia or somatoform disorder.

Statistical analysis

Comparison between two subject groups, cases to controls or case-FDR to control-FDR, for continuous measures was made using a two-sample *t*-test, assuming unequal variances. Proportions between subject groups were compared using a chi-square test. Paired comparisons of a family member's self-reported IBS status with proband-reported IBS status for the family member were assessed using McNemar's test. Agreement between proband-reported IBS status and self-reported status was estimated using a kappa statistic. Sensitivity, specificity, positive and negative predictive value and percent agreement were estimated for proband-reported IBS status of family members, considering the family member's self-report of IBS as the truth. A generalized estimating equation (GEE) model, using a binomial link was used to assess the association between family member type (case-type relative to control-type) and IBS-affected status (the dependent variable in the model). The GEE model has the advantage to account for the familial correlation. The odds ratio and 95% CI were also reported. All analyses were performed using SAS version 8.0 (SAS Institute, Cary, NC, USA).

RESULTS

Participation and subject characteristics

Recruitment of probands and relatives are summarized in Fig. 1. A total of 103 patients with IBS were approached for participation in the study, of which 56 (54%) agreed to participate and provided consent. Recruitment of cases continued until 50 participants completed the study. A total of 100 control patients were approached for participation in the Division of General Internal Medicine, of which 53 (53%) completed the study. When age and gender characteristics were evaluated and compared between those who participated and those who chose not to participate, participants were younger (median age 44.3 vs 53.7 years old, $P < 0.05$), but no gender bias was observed. No age or gender biases were observed between full participants and those who did not complete all aspects of the study.

Cases and controls were similar in characteristics with respect to age (median 43.5 vs 47.0), gender (82% vs 81.1% female), marital status (68% vs 77.4% married), education level and racial and ethnic background (96% vs 98.1% caucasian). Cases were less likely to be employed (66% vs 83%, $P < 0.05$). Also, somatic scores were higher among cases than controls (median somatic symptom checklist score was 1.08 vs 0.46, $P < 0.05$). There was also a higher reported psychiatric history among cases, with 44% having a documented history of depression compared with 23% of controls. However, there was no difference in reported abuse history in the medical records between cases and controls (34% vs 25%), $P = 0.29$.

Overall, 82% of cases did meet Rome II criteria for IBS, of which nearly half had diarrhoea-predominant IBS, 42% had mixed-type IBS and 12% had constipation-predominant IBS. Of the 18% who did not meet Rome II criteria for IBS, nearly 40% met criteria for functional bloating, 40% met criteria for unspecified bowel disorder, and two met criteria for functional constipation.⁷ None of the controls met Rome II criteria for IBS, although two individuals did meet diagnostic criteria for functional bloating.

Cases identified 277 FDRs in their family histories (5.5 FDRs per case). Eighty-one (29%) could not be contacted for the following reasons: 29 were deceased, 24 were underage and

contact was not permitted by the case for 28. A total of 196 (71% of 277) FDRs (3.9 FDRs per case) were mailed recruitment letters, of which 110 (56%) agreed to participate (2.2 FDRs per case). Controls identified 296 FDRs in their family histories (5.6 FDRs per control). Ninety-seven (33%) could not be contacted for the following reasons: 46 were deceased, 22 were underage, and contact was not permitted by the control for 29. 200 (68% of 296) FDRs (3.8 FDRs per control) were mailed recruitment letters. A total of 108 refused to participate or did not respond to three mailings, leaving 92 (46% of 199) full control-relative participants (1.7 FDRs per control). Comparing characteristics (provided by probands) of FDRs not permitted contact or refused or did not respond with relatives who participated, no difference in age or bowel symptoms and IBS status (by proband report) were observed. However, in general, there was a male predominance in those not allowed contact or among non-responders. The relationship of the proband to participation status is summarized in Table 1.

Participating case-FDRs and control-FDRs were comparable in age (median age of 47.3 vs 52.7), gender (68% vs 59% female), marital status, employment status, education level, race (97% vs 100% caucasian) and psychiatric history (21% vs 23%). Case-FDRs did report a higher median somatic symptom checklist score of 0.7 compared to control-relatives, who had a median score of 0.5 ($P < 0.05$). In addition, case-FDRs more often reported a history of abuse than control-FDRs (34% vs 23%, $P = 0.08$) in their questionnaires.

Accuracy of patient reporting of family history of IBS

When comparing the IBS-affected status between what the proband reported with FDR responses, case-probands reported that 21% of relatives were affected with IBS whereas the case-FDRs themselves reported a higher figure – 37% – by Rome criteria. Control-probands reported that 4% of relatives had IBS-type symptoms whereas 16% of the relatives who participated self-reported IBS-type symptoms by Rome criteria, a difference that was statistically significant (McNemar's test, $P = 0.003$ vs $P = 0.013$).

Among case-FDRs, the sensitivity of a proband report of IBS was only 37% (95% CI: 22–53) with specificity being 88% (95% CI: 78–95). The positive predictive value of a case reporting an FDR with IBS was 65% (95% CI: 43–84), and the negative predictive value was 70% (95% CI: 59–79). The kappa value assessing agreement between case-proband and case-FDRs reporting of IBS was only 0.27 (95% CI: 0.10–0.45). Among control-FDRs, control reporting only had a sensitivity of 7% (95% CI: 0–32) with a specificity of 96% (95% CI: 89–99). The positive predictive value was only 25% (95% CI: 1–81) with a higher negative predictive value of 84% (95% CI: 75–91). Overall, the kappa value was only 0.04 (95% CI: –0.15, 0.23) between control-proband reporting of IBS status in the relative vs relative self-report.

Familial aggregation of IBS

Familial aggregation estimates by source of data and case-control status are shown in Table 2. When the unit of study was the family, and a positive family history was considered as having one or more affected family members (that did not include the case proband), based on proband reporting, 54% of case-families had another family member affected with IBS, compared with 19% of control-families ($P < 0.001$). When only the data from relatives who participated were included, 60% of case-families vs 29% of control-families were found to have a positive family history of IBS ($P = 0.003$) where 'affected' was defined by meeting Rome criteria. When the data on relatives who self-reported were combined with proband-reported data for individuals with missing information, we showed that 68% of case-families had a positive family history of IBS compared with 36% of control-families ($P = 0.001$).

When the unit of study was each relative and using the data provided by probands only, 15% of case-relatives vs 4% of control-relatives were affected ($P < 0.001$). When only the relatives

who participated were included, 37% vs 16% of case-relatives and control-relatives were affected ($P < 0.001$) by Rome criteria, with an odds ratio of 3.1 (95% CI: 1.6–6.0). When the data on the families utilized relatives self-report and proband information, 22% of case relatives and 8% of control relatives were affected with IBS-type symptoms ($P < 0.001$), with an odds ratio of 3.1 (95% CI: 1.8–5.3), whereby case-relatives were nearly three times approximately as likely to experience IBS-type symptoms as control-relatives.

To assess whether or not the strength of familial aggregation varied based on relationship to the proband, the data were stratified based on relationship. This information is demonstrated in Fig. 2. Aggregation was reasonably strong in fathers, mothers, brothers and sisters, but was only statistically significant in mothers and sisters. The odds ratios were slightly lower for sons and daughters.

Sensitivity analyses based on alternate definition of affected status

The above analyses were repeated using alternate definitions of ‘affected’. When ‘affected’ was defined as a family member reporting a physician diagnosis of IBS, conclusions regarding sensitivity, specificity and agreement with the proband report changed only slightly, although the odds ratio decreased slightly to 2.1 and the 95% CI included 1.0 (95% CI: 0.7–5.8). When ‘affected’ was defined simply by reporting constipation or diarrhoea type symptoms, the odds ratio was 2.8 (95% CI: 1.7–4.6). When the most liberal definition of IBS was used where ‘affected’ was defined as meeting Rome criteria or having a physician diagnosis of IBS or reporting constipation or diarrhoea type symptoms, aggregation was again observed with an odds ratio of 2.6 (95% CI: 1.4–4.9).

Familial aggregation and psychological risk factors

Because of the concern that familial aggregation of IBS may be due to the fact that psychiatric and psychological disease may be aggregating in family members, the aggregation estimates were recalculated, stratifying on the number of family members with psychological or psychiatric disorders. We observed persistent aggregation regardless of whether we assessed the 28 families with no family members having a psychological or psychiatric disorder, the 41 families with one member, or the 19 families with two members having a psychological or psychiatric history, with odds ratios of 4.3 (95% CI: 0.7,25.9), 2.0 (95% CI: 0.6,7.2) and 4.5 (95% CI: 0.6,35.5), respectively. Furthermore, when estimates were stratified on number of parents with a psychological or psychiatric disorder, familial aggregation was observed even in those with unaffected parents (OR = 4.1, 95% CI: 1.5, 11.2).

High-penetrance families

We observed that 12 of the 50 (24%) case families had three or more affected family members. An example of a high-penetrance family is shown in Fig. 3. This figure shows an example where the mother of the proband, and two sisters, appears to be affected, along with one of two children. All eligible family members in this pedigree participated in the study.

DISCUSSION

Our study shows that accuracy of proband reporting of IBS status in family members overall is relatively low. The kappa statistic in case-families was only 0.27 for agreement between proband reports and the relatives’ self-report. In control-families, the kappa value was even lower with a value of 0.04 for agreement. In general, both case and control probands underestimated the number of affected family members. The sensitivity of proband reporting was only 37% for case-relatives and 7% for control-relatives. In part, the low sensitivity could be explained by the proband simply not knowing the relatives’ bowel symptoms (reporting ‘I don’t know’ on the questionnaire). If the case-proband indicated a family member had IBS,

the positive predictive value was 65%, but the positive predictive value was lower (25%) in control-probands. Although we confirmed familial aggregation using various sources of data (proband, FDR and combination), the analysis of agreement between the sources of information suggests that future studies of IBS families cannot rely on proband reporting alone, and suggests that many family members do not share or talk about their bowel habits with other family members. This observation has great methodological implications for future family-based studies of IBS.

Regardless of source of information (proband, relative or combination of relative-provided symptom data combined with proband-provided data), our analysis confirmed that IBS significantly aggregates in families, whereby family members of an individual with IBS will be three times as likely to have IBS than family members of an individual without IBS. We also found that the proportion of case- and control-families with at least one affected family member was quite high. Among case-families, 54% of case-probands reported at least one other affected family member, and among control-families, 19% of control-probands report at least one other affected family member. These high figures may simply reflect the fact that irregular bowel habits are quite common and that statistically, it would not be surprising to have at least one family member with altered bowel habits. Another potential explanation is that probands (cases and controls) with another family member with IBS may have been more likely to participate than probands without a family history. In this study, the primary concern regarding participation bias is that case-probands with affected relatives may be more likely to participate and, therefore, increase estimates of familial aggregation. Similarly, control-probands with affected relatives or friends with IBS may be more likely to participate, but if this occurs, it would result in a decreased estimate of familial aggregation. The impact of these factors on our study cannot be exactly quantitated as no data could be collected from proband non-participants. It did not appear that relatives were more likely to participate based on their own personal IBS status using proband-provided data about non-participating relatives. This observation suggests our estimates are reasonably accurate despite limitations imposed by incomplete relative participation, which was 51% of all contacted relatives and 35% among all living and deceased relatives in the proband's family structure.

Our study yielded three additional interesting observations: (i) familial aggregation was strong in parents and siblings but lower in offspring, and (ii) the familial aggregation did appear to be slightly stronger in female relatives (mothers and sisters) compared with the other relatives and (iii) aggregation still persisted regardless of the presence of psychological disorders in the family members. It is unclear if this first point reflects true parental transmission of symptoms to offspring that may disappear with future generations, or may simply reflect the fact that offspring was too young to have yet developed IBS-type symptoms. The second observation will require reproducibility in future, larger studies, as the sample sizes became quite small when evaluating specific relationships to the proband, and thus, firm conclusions regarding the gender of affected family members and its effects on other family members cannot be made. Although somatic scores were slightly higher in case-probands and the proportion of case-probands with a current or past history of psychiatric disorders was higher than control-probands, the fact that aggregation persisted despite stratifying on family history of psychiatric disorders provides evidence that IBS is not a pure psychiatric disorder.

Our method of quantitating familial aggregation bears further discussion, as the source of the data (proband, FDR and combination) and definition of affected and unaffected is not as objective or confirmable as some other diagnoses (e.g. cancer diagnosis by histology). Ideally, construction of pedigrees would consist of direct survey of relatives and review of relevant medical records. However, in family-based studies, <100% participation of family members in studies is a reality – because of death, co-morbid conditions (e.g. dementia), family dysfunction (e.g. proband will not permit contact with estranged relatives or estranged relatives

will not participate when asked), or lack of willingness to participate for various reasons including privacy concerns or personal time constraints – limiting researchers' ability to construct family pedigrees. Strategies to collect disease status on missing relatives include querying next-of-kin, asking next-of-kin to provide permission to release medical records to researchers, or searching public records such as death certificates for cause of death. The last option cited is not possible for IBS, and our study suggests that relatives may not be able to accurately provide IBS status on their relatives, although it remains to be determined whether specific relatives or spouses are able to provide proxy information. Review of medical records may be difficult in a chronic disorder that may have been present for decades and without objective diagnostic testing and with inconsistent testing practices among physicians. Thus, using a combination of direct survey of symptoms and medical history and proxy reporting by probands for our aggregation, estimates were justified, but nonetheless, our experience highlights the unique difficulties of performing family-based studies in IBS.

The definition of 'affected' and 'unaffected' also bears further discussion. Pedigrees require dichotomous outcomes, even for a complex, heterogeneous disorder such as IBS. We utilized the commonly accepted Rome criteria, but it should be noted that the sensitivity of the Rome criteria may only be 50–60%^{11–16} in outpatients and variable healthcare seeking behaviour of individuals with IBS. Using more restrictive and liberal definitions of IBS (e.g. report of physician diagnosis of IBS, report of altered bowel habits such as constipation or diarrhoea), our analyses confirmed the aggregation of IBS in families and reinforces the idea that altered bowel habits aggregate in families, despite the use of different clinical definitions for IBS.

Our study was relatively small with recruitment of only 50 case-families and 50 control-families. Although we did frequency-match our controls to our cases by age-decile, gender and race, we did not collect data on healthcare utilization, and thus it is conceivable that controls differed from cases in types of illness, level of care and healthcare seeking behaviour. Nonetheless, although our study was relatively small in scale, contact and data collection were attempted from nearly 400 live relatives and is the first such study of its kind. This study was illustrative in that it showed that cases and controls typically underestimated the frequency of IBS-type symptoms in their relatives, and that this observation supports our hypothesis that family members do not discuss their bowel habits with other family members because of an underlying stigma. This does suggest that any future family studies of IBS, whether genetic or environmentally oriented, will require direct data collection from family members. In our study, IBS and bowel dysfunction appear to aggregate more strongly in case-families than control-families, but will require reproduction in a larger study. The confirmation of familial clustering of bowel dysfunction is an interesting observation, and the genetic and environmental determinants for this phenomenon certainly deserve further intensive study.

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Proband and relative recruitment flow chart

Figure 1.
Proband and relative recruitment flow chart.

Figure 2.
Recurrence risks to relatives by relationship status to proband.

Figure 3.

An example of a high-penetrance family with at least three affected family members. The proband is indicated by an asterik (*). Irritable bowel syndrome (IBS) status is designated in solid in four ways, as indicated by quadrant: upper right quadrant indicates the individual met Rome criteria on the questionnaire; lower right quadrant indicates if the individual reported a physician diagnosis of IBS; lower left quadrant indicates reporting chronic constipation, diarrhoea or alternating bowel habits; upper left quadrant indicates the proband's IBS status report for this individual.

Table 1Comparison of first-degree relatives' relationship to proband and participation status, *n* (row %)

	Deceased	Under 18 years of age	Not allowed to contact	Refused or did not respond	Participated	Total
Total, <i>n</i>	75	45	57	194	202	573
Father, <i>n</i> (%)	37 (36)	0 (0)	9 (9)	31 (30)	26 (25)	103
Mother, <i>n</i> (%)	21 (20)	0 (0)	6 (6)	21 (20)	55 (53)	103
Brother, <i>n</i> (%)	11 (9)	0 (0)	19 (16)	52 (44)	35 (30)	117
Sister, <i>n</i> (%)	5 (4)	1 (1)	11 (9)	49 (40)	55 (45)	121
Son, <i>n</i> (%)	0 (0)	19 (32)	9 (15)	21 (35)	11 (18)	60
Daughter, <i>n</i> (%)	1 (1)	25 (35)	3 (4)	20 (28)	22 (31)	71

Table 2

Familial aggregation estimates by source of data and case or control status

Source of information	% with positive family history of irritable bowel syndrome (IBS) (≥ 1 affected family member) (unit = family)		% relatives with IBS (unit = relative)		P-value
	Case-family	Control-family	Case-relative	Control-relative	
Proband only	54% 27/50	19% 10/53	15% 42/277	4% 13/296	<0.001
Relative self-report	60% 26/43	29% 12/42	37% 41/110	16% 15/92	0.002
Combined	68% 34/50	36% 19/53	22% 60/277	8% 24/296	<0.001