Psychological Medicine, 2005, **35**, 237–243. © 2004 Cambridge University Press
DOI: 10.1017/S0033291704003253 Printed in the United Kingdom

Admixture analysis of age at onset in obsessive–compulsive disorder

RICHARD DELORME[1,2]*, JEAN-LOUIS GOLMARD[3], NADIA CHABANE[1,2], BRUNO MILLET[4], MARIE-ODILE KREBS[4], MARIE CHRISTINE MOUREN-SIMEONI[2] AND MARION LEBOYER[1,5]

[1] *INSERM U513, Faculté de Médecine, Créteil, France*; [2] *Service de Psychopathologie de l'Enfant et de l'Adolescent, Hôpital Robert Debré, Assistance Publique-Hôpitaux de Paris, Paris, France*; [3] *INSERM U436, Département de Biostatistiques et Informatique, CHU Pitié-Salpétrière, Université Paris VI, Paris, France*; [4] *INSERM E0117, Hôpital Sainte-Anne, Paris, France*; [5] *Service de Psychiatrie, Hôpital Henri Mondor et Albert Chenevier, Assistance Publique-Hôpitaux de Paris, Créteil, France*

ABSTRACT

Background. Age at onset (AAO) has been useful to explore the clinical, neurobiological and genetic heterogeneity of obsessive–compulsive disorder (OCD). However, none of the various thresholds of AAO used in previous studies have been validated, and it remains an unproven notion that AAO is a marker for different subtypes of OCD. If AAO is a clinical indicator of different biological subtypes, then subgroups based on distinct AAOs should have separate normal distributions as well as different clinical characteristics.

Method. Admixture analysis was used to determine the best-fitting model for the observed AAO of 161 OCD patients.

Results. The observed distribution of AAO in OCD is a mixture of two Gaussian distributions with mean ages of $11{\cdot}1 \pm 4{\cdot}1$ and $23{\cdot}5 \pm 11{\cdot}1$ years. The first distribution, defined by early-onset OCD, had increased frequency of Tourette's syndrome and increased family history of OCD. The second distribution, defined by late-onset OCD, showed elevated prevalence of general anxiety disorder and major depressive disorder.

Conclusions. These results, based on a statistically validated AAO cut-off and those of previous studies on AAO in OCD, suggest that AAO is a crucial phenotypic characteristic in understanding the genetic basis of this disorder.

INTRODUCTION

Improvement of the phenotype definition is recognized to be of critical importance for understanding the genetic basis of complex diseases. Subdivision according to age at onset (AAO) has been particularly useful in delineating homogenous subgroups and facilitating gene identification. Differences in AAO have helped to separate genetic from sporadic cases in Alzheimer's disease (Goate *et al*. 1991) and Parkinson's disease (Polymeropoulos *et al*. 1997). AAO may also be used to identify different vulnerability genes, as in breast cancer (Scott *et al*. 2003), or to identify different mutations in the same gene, as in Duchenne and Becker muscular dystrophy (Hoffman & Kunkel, 1989). Furthermore, about half of the variation in AAO in Huntington disease can be explain by the size of the expanded CAG repeat within the coding region of the Huntington gene (Andrew *et al*. 1993).

In obsessive–compulsive disorder (OCD), clinical, neurobiological and genetic differences have been reported according to AAO (Eichstedt & Arnold, 2001). For instance, early-onset OCD

* Address for correspondence: Dr Richard Delorme, INSERM U513, Faculté de Médecine, 8 rue du Général Sarrail, 94010 Créteil cedex, France.
(Email: delorme@im3.inserm.fr)

https://doi.org/10.1017/S0033291704003253 Published online by Cambridge University Press

is associated with male preponderance (Zohar *et al*. 1997), higher rates of co-morbid tic disorder (Swedo *et al*. 1989; Miguel *et al*. 2001), and higher frequency of tic-like compulsions, sensory phenomena or compulsions not preceded by obsessions (Geller *et al*. 1998; Rosario-Campos *et al*. 2001). Treatment and follow-up studies report that, independent of the length of illness, AAO is one of the most consistent predictors of poorer pharmacological response and prognosis in OCD (Skoog & Skoog, 1999). In addition, inconsistent findings concerning the involvement of brain structures in OCD could be due to heterogeneity between individuals in terms of AAO. Recently, differences in frontal-subcortical circuits were found between early- and late-onset OCD subjects, consisting of a focus of reduced cerebral blood flow in the right thalamus in the early-onset OCD group (Busatto *et al*. 2001). Family studies also suggest that AAO of obsessive–compulsive symptoms is strongly related to familiality. Specifically, the morbidity risk for OCD in family members of OCD subjects whose symptoms started between 5 and 9 years of age is twice as high as in relatives of late-onset OCD probands (Pauls *et al*. 1995). Recently, this finding was confirmed in a study reporting no occurrence of OCD in the relatives of probands with an AAO later than 18 years of age (Nestadt *et al*. 2000). Finally, a strong association between sequence variants of the brain-derived neurotrophic factor (BDNF) gene was found only in childhood-onset OCD (Hall *et al*. 2003), suggesting that stratification by AAO can decrease genetic heterogeneity and increase power to identify susceptibility genes.

If AAO seems to be useful in exploring the clinical, neurobiological and genetic heterogeneity of OCD, none of the various thresholds of AAO used in previous studies have been validated. And it remains an unproven notion that AAO is a marker for different subtypes of OCD. If AAO is a clinical indicator of different biological subtypes, then subgroups based on distinct AAOs should have separate normal distributions with different means, variances, and population proportions as well as different clinical characteristics. In contrast, if patients with different AAOs represent a continuum, with qualitatively similar forms of OCD but distinct in terms of severity, it would be expected that they should form a single normal distribution with similar phenotypic and genetic characteristics. To explore these questions, we performed an admixture analysis of AAO in a sample of patients with OCD.

METHOD

Participants

Patients seeking treatment at two university-based OCD clinics (Hôpital Saint Anne and Hôpital Robert Debré, Paris) and meeting the criteria of DSM-IV (APA, 1994) for OCD were systematically included between 1999 and 2003. In order to confirm the diagnosis of OCD and co-morbid disorders, to assess AAO of symptoms and to assess family history of psychiatric disorders, a direct interview was performed by a trained psychiatrist using the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger *et al*. 1994) for patients aged over 17 years, or the Kiddie Schedule for Affective Disorders and Schizophrenia – Epidemiologic version (K-SADS-E; Orvaschel *et al*. 1982) for probands aged under 17 years. Probands and their families were asked to fill in the adult or the child version of the family self-report questionnaire designed by the Tourette Syndrome Association Genetic Consortium (January 1995 version). In a second stage, an experienced clinician (R.D., N.C. or B.M.) performed a clinical interview and reviewed symptom ratings with each proband and with their parents in the case of children to ensure their accuracy. AAO was the age at which the first disturbing symptoms occurred, as assessed by the family self-report questionnaire and the clinician's interview. The clinicians who conducted the interviews were blind to the hypothesis tested.

The local Research Ethics Board reviewed and approved the study. Written informed consent was obtained from all participating subjects. If the proband was under 18 years old, his or her consent and written parental consent were obtained.

Data analysis

We used admixture analysis, a method for identifying the model that best fits the observed distribution of a continuous variable. This method was used to test whether the observed AAO distribution was a mixture of Gaussian distributions. This was based on the theoretical

https://doi.org/10.1017/S0033291704003253 Published online by Cambridge University Press

assumption that AAO, as other natural phenomena observed in a large number of subjects, is likely to be distributed normally. The number of components was determined using forward stepwise estimation and maximum likelihood ratio tests as criteria for adding a component. The criterion used for adding a component was the threshold value of a χ^2 distribution with three degrees of freedom at the 0·05 level. For each number of components, the weights, means, and variances of each component were estimated using the stochastic expectation maximization algorithm (Celeux & Diebolt, 1990).

The probability of belonging to a given AAO subgroup was calculated for each patient. This probability, *i*, is:

$$P(Gi/x) = \frac{f(x/Gi)P(Gi)}{\sum_j f(x/Gj)P(Gj)}$$

$$\text{with} \quad f(x/Gj) = \frac{1}{\sigma j\sqrt{2\pi}} e^{\frac{-1}{2\sigma_j^2}(x-\mu j)^2},$$

where x is the AAO for a given subject, and Gi and Gj are the AAO subgroups defined by μ (mean), σ (standard deviation), and $P(G)$ (proportion of the population).

The clinical characteristics of patients belonging to the different AAO distributions identified by the admixture analysis were compared using a Pearson χ^2 test or Fisher's exact test when required.

RESULTS

One hundred sixty-one patients (72 females, 89 males) were included; the mean (±S.D.) age at interview was 23·9±13·8 years. The likelihood ratio criterion between the models with 1 and 2 distributions was χ^2 (3 df)=71·35, $p<0·001$. No further improvement was obtained using the 3-component model [χ^2 (3 df)=6·75, $p=0·08$]. Thus, assuming a conservative approach, the model that best fits the observed AAO distribution was a mixture of two Gaussian distributions.

The patients were thus divided into two subgroups (first or second distribution), with each patient assigned to the distribution to which he or she had the highest probability of belonging. Patients in the overlapping part of the distribution were assigned to a group when their probability of belonging to this group was higher than the probability of belonging to the other group. As may be seen in Fig. 1*b*, this threshold is characterized by the intersection between the two curves, i.e. between 20 and 21 years. When AAO is 20 years, the probability is higher of belonging to the first group than to the second (54% *v.* 46% respectively). Conversely, when AAO is 21, the probability is higher of belonging to the second group than to the first (60% *v.* 40% respectively). The mean AAO of the first distribution was 11·1±4·1 years, corresponding to 87·5% of the population ($n=141$); the mean AAO of the second distribution was 23·5±11·1 years ($n=20$). The mean age at interview in the first and second groups was 21·8±12·7 and 38·7±12·5 years respectively. The observed and the theoretical distribution of AAO are shown in Fig. 1.

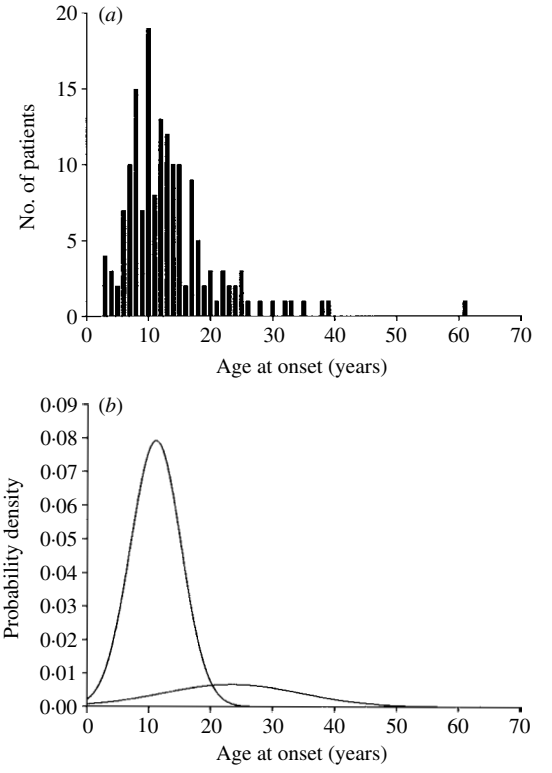


FIG. 1. (*a*) Observed and (*b*) theoretical distributions of age of onset in obsessive–compulsive disorder.

We compared the two classes for personal history of Tourette's syndrome, attention deficit-hyperactivity disorder, anxiety disorders, and

https://doi.org/10.1017/S0033291704003253 Published online by Cambridge University Press

Table 1. *Clinical characteristics of patients belonging to the two distributions identified by the admixture analysis of age at onset*

	Early-onset class ($n=141$, 87·5%)	Late-onset class ($n=20$, 12·5%)
Personal history of		
Major depressive disorder	46 (36·2%)	12 (66·6%)*
Attention-deficit hyperactivity disorder	40 (31·2%)	5 (25%)
Tourette's syndrome	35 (26·9%)	0 (0%)†
General anxiety disorder	14 (11·3%)	7 (41·2%)‡
Social phobia	23 (18·3%)	5 (27·7%)
Single phobia	33 (26·2%)	3 (16·6%)
Panic disorder with or without agoraphobia	10 (7·9%)	2 (11·1%)
Family history of		
Obsessive–compulsive disorder	35 (24·6%)	0 (0%)§
Tourette's syndrome	12 (8·6%)	0 (0%)
Sex ratio		
Male	78 (55·3%)	11 (55%)

* χ^2 (1 df) = 6·09, $p<0·01$.
† χ^2 (1 df) = 6·01, $p<0·01$.
‡ χ^2 (1 df) = 10·53, $p<10^{-3}$.
§ χ^2 (1 df) = 6·34, $p<0·01$.

major depressive disorder; family history of OCD and Tourette's syndrome; and sex ratio (Table 1). The univariate analysis showed that the two groups differed in terms of personal history of Tourette's syndrome ($p<0·01$), general anxiety disorder ($p<0·001$), major depressive disorder ($p<0·01$), and family history of OCD ($p<0·01$). The first distribution, defined by early-onset OCD (<21 years), had increased frequency of Tourette's syndrome and increased familial aggregation of OCD. The second distribution, defined by late-onset OCD (⩾21 years), showed elevated prevalence of general anxiety disorder and depression. Similar results were obtained when using age of interview as a covariate in the analysis of covariance (ANCOVA) analysis.

As may be seen in Fig. 1*a*, there is one outlier, a woman aged 72 years, who developed OCD at 61 years. Results were not significantly affected by the exclusion of this patient. We still observed that a mixture of two Gaussian distributions best fits the observed distribution of AAO. The mean AAO of the first corrected distribution was $10·7 \pm 3·9$ years and of the second $21·8 \pm 7·9$ years. The AAO threshold used to generate the two subgroups was also slightly decreased, but remained near 20. Only 2% (3/160) of the patients that previously belonged to the first distribution belonged to the second one when the outlier was excluded from the analyses. The differences between the two groups in terms of co-morbidity remained unchanged.

DISCUSSION

This study was designed to test the unproven notion that AAO is a marker for different subtypes of OCD. Using admixture analysis, we demonstrated that the observed distribution of AAO in OCD is a mixture of two Gaussian distributions. To our knowledge, this is the first demonstration that AAO does not have a normal distribution in OCD. These results validate the distinction between early- and late-onset OCD used for distinguishing more homogenous subgroups.

This approach was previously used in bipolar I affective disorder, demonstrating that the observed distribution of AAO was a mixture of three Gaussian distributions, where each subgroup was characterized by specific clinical features and familial vulnerability factors (Bellivier *et al.* 2001, 2003). Gaussian mixture analyses applied to individual studies may have limited power because of small sample sizes. However, our sample of 161 OCD patients provides sufficient power, as several authors have recommended the use of samples of more than 100 subjects for such analyses (Fleiss, 1972; Gibbons *et al.* 1984).

Although previous epidemiological studies in adult OCD samples did not report bimodality of AAO (Canino *et al.* 1987; Kolada *et al.* 1999; Karno *et al.* 1988), they all reported significant variance of mean AAO. For instance, in the Cross National Epidemiology of OCD (Weissman *et al.* 1994), mean AAO was $26·2 \pm 11·6$ in the USA, $21·9 \pm 7·2$ in Edmonton, and $35·5 \pm 13·6$ in Puerto Rico. Thus, the apparent unimodality may cover a mixture of different Gaussian distributions. Moreover, the observed distribution of AAO in our study is consistent with previous studies suggesting a bimodal distribution, with one peak in childhood and another in adulthood. Adult OCD studies have reported a mean AAO of 21 years (Karno *et al.* 1988; Rasmussen & Eisen, 1992), while juvenile OCD studies have consistently documented a mean

https://doi.org/10.1017/S0033291704003253 Published online by Cambridge University Press

AAO around 10 years (Geller *et al*. 1996). In addition, the large proportion of patients who develop OCD before age 21 in our sample is in agreement with previous reports (Hollander & Stein, 1997; DeSilva & Rachman, 1998). For instance, Hollander and Stein (1997) reported that 65% of OCD patients have an AAO before age 25 years. Taken together, these arguments reinforce the hypothesis of a potential bimodal distribution of AAO with one peak in childhood and another in adulthood.

Further evidence of the existence of two OCD subgroups according to AAO is provided by our findings that these subgroups have different clinical profiles. The association between early-onset OCD (first distribution), Tourette's syndrome, and familial history of OCD observed in our study has also been described in previous studies (Pauls *et al*. 1995; Nestadt *et al*. 2000; Eichstedt & Arnold, 2001; Grados *et al*. 2001). In addition, we observed a higher proportion of major depressive disorder and general anxiety disorder in late-onset OCD, independently of age at interview. This finding is corroborated by that obtained recently by Nestadt *et al*. (2003) using latent class analysis to identify OCD-related subgroups based on co-morbidity. These authors showed that patients with OCD, major depressive disorder, and general anxiety disorder appear to constitute a well defined subgroup, suggesting that these three disorders could share a genetic susceptibility factor. Taken together, these results suggest that early-onset and late-onset OCD could be different in terms of their genetic backgrounds. Early-onset OCD could share genetic vulnerability factors with Tourette's syndrome and constitute a specific subgroup of OCD families, whereas late-onset OCD could share genetic vulnerability factors with major depressive disorder and general anxiety disorder.

No gender difference between the early- and late-onset subgroups was found in the present sample, in agreement with previous studies (Sobin *et al*. 2000; Rosario-Campos *et al*. 2001; Millet *et al*. 2004). However, boys have been reported to outnumber girls, often by as much as 1·5–2·5 times in studies investigating childhood OCD in clinically referred samples (Swedo *et al*. 1989; Hanna, 1995) as well as in early-onset OCD (Geller *et al*. 2001; Fontenelle *et al*. 2003). These discrepancies could be due to age at interview and to the cut-off used to distinguish early- and late-onset subgroups.

A number of methodological limitations in the study should be noted. The evaluation of AAO was retrospective and thus subject to recall bias (Masia *et al*. 2003). It is also possible that AAO reporting is less accurate for adults than for children, given the longer period of elapsed time from onset to interview. Although such recall bias is unlikely to account for the pattern of results reported in this study, studies with longitudinally ascertained samples may help to clarify this issue. Furthermore, since the sample used in this study consisted of children and adults recruited in OCD university-based programs, the results need to be confirmed in community samples or in other mental health clinic samples. Finally, although the size of our sample provides sufficient power for Gaussian mixture analysis, it is possible that with a larger sample, the cut-off between the two Gaussian distributions could vary slightly. In addition, because of the relatively low number of patients with a late-onset OCD (12·5%), the clinical features found to be specific of each distribution should be replicated in larger samples. In particular, the lack of significant increase of family history of Tourette's syndrome in the early-onset group could be the consequence of the unequal number of patients in both distributions ($n=141$ and $n=20$ in the first and second distributions respectively), and the small number of patients who had a family history of Tourette's syndrome ($n=12$ and $n=0$ in the first and second distributions respectively).

Confirmation of our hypothesis would need external validators of the existence of two subgroups using genetic, cognitive, biochemical or neurophysiological probes. If confirmed, these findings may assist in clarifying the relation between genetic factors and OCD and may enhance the discriminative capacity of linkage and association studies. Working with subgroups defined according to AAO may facilitate the identification of more specific etiopathogenic features underlying each of the AAO subgroups as well as factors implicated in the onset of the disorder. Our results based on a statistically validated AAO cut-off and those of previous studies on AAO in OCD suggest that AAO is a crucial phenotypic characteristic in understanding the genetic basis of this disorder.

https://doi.org/10.1017/S0033291704003253 Published online by Cambridge University Press

ACKNOWLEDGEMENTS

We thank the patients and their families who made this research possible and Dr Catalina Betancur for helpful comments on the manuscript. This research was supported by INSERM (National Institute of Health and Medical Research). Richard Delorme was supported by a fellowship from the Fondation pour la Recherche Médicale and Nadia Chabane by a fellowship from INSERM.

DECLARATION OF INTEREST

None.

REFERENCES

Andrew, S. E., Goldberg, Y. P., Kremer, B., Telenius, H., Theilmann, J., Adam, S., Starr, E., Squitieri, F., Lin, B., Kalchman, M. A., Graham, R. K. & Hayden, M. R. (1993). The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nature Genetics* **4**, 398–403.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM-IV). American Psychiatric Association: Washington, DC.

Bellivier, F., Golmard, J. L., Henry, C., Leboyer, M. & Schurhoff, F. (2001). Admixture analysis of age at onset in bipolar I affective disorder. *Archives of General Psychiatry* **58**, 510–512.

Bellivier, F., Golmard, J. L., Rietschel, M., Schulze, T. G., Malafosse, A., Preisig, M., McKeon, P., Mynett-Johnson, L., Henry, C. & Leboyer, M. (2003). Age at onset in bipolar I affective disorder: further evidence for three subgroups. *American Journal of Psychiatry* **160**, 999–1001.

Busatto, G. F., Buchpiguel, C. A., Zamignani, D. R., Garrido, G. E., Glabus, M. F., Rosario-Campos, M. C., Castro, C. C., Maia, A., Rocha, E. T., McGuire, P. K. & Miguel, E. C. (2001). Regional cerebral blood flow abnormalities in early-onset obsessive-compulsive disorder: an exploratory SPECT study. *Journal of the American Academy of Child and Adolescent Psychiatry* **40**, 347–354.

Canino, G. J., Bird, H. R., Shrout, P. E., Rubio-Stipec, M., Bravo, M., Martinez, R., Sesman, M. & Guevara, L. M. (1987). The prevalence of specific psychiatric disorders in Puerto Rico. *Archives of General Psychiatry* **44** (Suppl.), 727–735.

Celeux, G. & Diebolt, J. (1990). The EM and the SEM algorithms for the mixtures: statistical and numerical aspects. *Cahier CERO* **32**, 135–151.

DeSilva, P. & Rachman, S. (1998). *Obsessive Compulsive Disorder: The Facts*. Oxford: Oxford University Press.

Eichstedt, J. A. & Arnold, S. L. (2001). Childhood-onset obsessive-compulsive disorder: a tic-related subtype of OCD? *Clinical Psychology Review* **21**, 137–157.

Fleiss, J. L. (1972). Classification of the depressive disorders by numerical typology. *Journal of Psychiatric Research* **9**, 141–153.

Fontenelle, L. F., Mendlowicz, M. V., Marques, C. & Versiani, M. (2003). Early- and late-onset obsessive-compulsive disorder in adult patients: an exploratory clinical and therapeutic study. *Journal of Psychiatric Research* **37**, 127–133.

Geller, D. A., Biederman, J., Faraone, S. V., Bellordre, C. A., Kim, G. S., Hagermoser, L., Cradock, K., Frazier, J. & Coffey, B. J. (2001). Disentangling chronological age from age of onset in children and adolescents with obsessive-compulsive disorder. *International Journal of Neuropsychopharmacology* **4**, 169–178.

Geller, D. A., Biederman, J., Griffin, S., Jones, J. & Lefkowitz, T. R. (1996). Comorbidity of juvenile obsessive-compulsive disorder with disruptive behaviour disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* **35**, 1637–1646.

Geller, D., Biederman, J., Jones, J., Park, K., Schwartz, S., Shapiro, S. & Coffey, B. (1998). Is juvenile obsessive-compulsive disorder a developmental subtype of the disorder? A review of the pediatric literature. *Journal of the American Academy of Child and Adolescent Psychiatry* **37**, 420–427.

Gibbons, R. D., Dorus, E., Ostrow, D. G., Pandey, G. N., Davis, J. M. & Levy, D. L. (1984). Mixture distributions in psychiatric research. *Biological Psychiatry* **19**, 935–961.

Goate, A., Chartier-Harlin, M. C., Mullan, M., Brown, J., Crawford, F., Fidani, L., Giuffra, L., Haynes, A., Irving, N., James, L., Mant, R., Newton, P., Rooke, K., Roques, P., Talbot, C., Pericak-Vance, M., Roses, A., Williamson, R., Rossor, M., Owen, M. & Hardy, J. (1991). Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* **349**, 704–706.

Grados, M. A., Riddle, M. A., Samuels, J. F., Liang, K. Y., Hoehn-Saric, R., Bienvenu, O. J., Walkup, J. T., Song, D. & Nestadt, G. (2001). The familial phenotype of obsessive-compulsive disorder in relation to tic disorders: the Hopkins OCD family study. *Biological Psychiatry* **50**, 559–565.

Hall, D., Dhilla, A., Charalambous, A., Gogos, J. A. & Karayiorgou, M. (2003). Sequence variants of the brain-derived neurotrophic factor (BDNF) gene are strongly associated with obsessive-compulsive disorder. *American Journal of Human Genetics* **73**, 370–376.

Hanna, G. L. (1995). Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* **34**, 19–27.

Hoffman, E. P. & Kunkel, L. M. (1989). Dystrophin abnormalities in Duchenne/Becker muscular dystrophy. *Neuron* **2**, 1019–1029.

Hollander, E. & Stein, D. (1997). *Obsessive compulsive disorder: diagnosis, etiology, treatment*. New York: Dekker.

Karno, M., Golding, J. M., Sorenson, S. B. & Burnam, M. A. (1988). The epidemiology of obsessive-compulsive disorder in five US communities. *Archives of General Psychiatry* **45**, 1094–1099.

Kolada, J. L., Bland, R. C. & Newman, S. C. (1994). Epidemiology of psychiatric disorders in Edmonton. Obsessive-compulsive disorder. *Acta Psychiatrica Scandinavica* **376**, 24–35.

Masia, C. L., Storch, E. A., Dent, H. C., Adams, P., Verdeli, H., Davies, M. & Weissman, M. M. (2003). Recall of childhood psychopathology more than 10 years later. *Journal of the American Academy of Child and Adolescent Psychiatry* **42**, 6–12.

Miguel, E. C., Rosario-Campos, M. C., Shavitt, R. G., Hounie, A. G. & Mercadante, M. T. (2001). The tic-related obsessive-compulsive disorder phenotype and treatment implications. *Advances in Neurology* **85**, 43–55.

Millet, B., Kochman, F., Gallarda, T., Krebs, M. O., Demonfaucon, F., Barrot, I., Bourdel, M. C., Olie, J. P., Loo, H. & Hantouche, E. G. (2004). Phenomenological and comorbid features associated in obsessive-compulsive disorder: influence of age of onset. *Journal of Affective Disorders* **79**, 241–246.

Nestadt, G., Addington, A., Samuels, J., Liang, K. Y., Bienvenu, O. J., Riddle, M., Grados, M., Hoehn-Saric, R. & Cullen, B. (2003). The identification of OCD-related subgroups based on comorbidity. *Biological Psychiatry* **53**, 914–920.

Nestadt, G., Samuels, J., Riddle, M., Bienvenu, O. J., Liang, K. Y., LaBuda, M., Walkup, J., Grados, M. & Hoehn-Saric, R. (2000). A family study of obsessive-compulsive disorder. *Archives of General Psychiatry* **57**, 358–363.

Nurnberger, J. J., Blehar, M., Kaufman, C., York-Cooler, C., Simpson, S., Harkavy-Friedman, J., Severe, J., Malaspina, D. & Reich, T. (1994). Diagnostic interview for genetic studies: rationale, unique features, and training: NIMH Genetics Initiative. *Archives of General Psychiatry* **51**, 849–864.

Orvaschel, H., Puig-Antich, J., Chambers, W., Tabrizi, M. A. & Johnson, R. (1982). Retrospective assessment of prepubertal major

https://doi.org/10.1017/S0033291704003253 Published online by Cambridge University Press

depression with the Kiddie-SADS-E. *Journal of the American Academy of Child and Adolescent Psychiatry* **21**, 392–397.

Pauls, D. L., Alsobrook, J. P., II, Goodman, W., Rasmussen, S. & Leckman, J. F. (1995). A family study of obsessive-compulsive disorder. *American Journal of Psychiatry* **152**, 76–84.

Polymeropoulos, M. H., Lavedan, C., Leroy, E., Ide, S. E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E. S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W. G., Lazzarini, A. M., Duvoisin, R. C., Di Iorio, G., Golbe, L. I. & Nussbaum, R. L. (1997). Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* **276**, 2045–2047.

Rasmussen, S. A. & Eisen, J. L. (1992). The epidemiology and differential diagnosis of obsessive compulsive disorder. *Journal of Clinical Psychiatry* **53** (Suppl.), 4–10.

Rosario-Campos, M. C., Leckman, J. F., Mercadante, M. T., Shavitt, R. G., Prado, H. S., Sada, P., Zamignani, D. & Miguel, E. C. (2001). Adults with early-onset obsessive-compulsive disorder. *American Journal of Psychiatry* **158**, 1899–1903.

Scott, C. L., Jenkins, M. A., Southey, M. C., Davis, T. A., Leary, J. A., Easton, D. F., Phillips, K. A. & Hopper, J. L. (2003). Average age-specific cumulative risk of breast cancer according to type and site of germline mutations in BRCA1 and BRCA2 estimated from multiple-case breast cancer families attending Australian family cancer clinics. *Human Genetics* **112**, 542–551.

Skoog, G. & Skoog, I. (1999). A 40-year follow-up of patients with obsessive-compulsive disorder. *Archives of General Psychiatry* **56**, 121–127.

Sobin, C., Blundell, M. L. & Karayiorgou, M. (2000). Phenotypic differences in early- and late-onset obsessive-compulsive disorder. *Comprehensive Psychiatry* **41**, 373–379.

Swedo, S. E., Rapoport, J. L., Leonard, H., Lenane, M. & Cheslow, D. (1989). Obsessive-compulsive disorder in children and adolescents. Clinical phenomenology of 70 consecutive cases. *Archives of General Psychiatry* **46**, 335–341.

Weissman, M. M., Bland, R. C., Canino, G. J., Greenwald, S., Hwu, H. G., Lee, C. K., Newman, S. C., Oakley-Browne, M. A., Rubio-Stipec, M., Wickramaratne, P. J., Wittchen, H. U. & Yeh, E. K. (1994). The cross-national epidemiology of obsessive compulsive disorder. The Cross-National Collaborative Group. *Journal of Clinical Psychiatry* **55** (Suppl.), 5–10.

Zohar, A. H., Pauls, D. L., Ratzoni, G., Apter, A., Dycian, A., Binder, M., King, R., Leckman, J. F., Kron, S. & Cohen, D. J. (1997). Obsessive-compulsive disorder with and without tics in an epidemiological sample of adolescents. *American Journal of Psychiatry* **154**, 274–276.

https://doi.org/10.1017/S0033291704003253 Published online by Cambridge University Press