

Joubert Syndrome Is Not a Cause of Classical Autism

T.N. Takahashi,^{1*} J.E. Farmer,¹ K.K. Deidrick,¹ B.S. Hsu,¹ J.H. Miles,¹ and B.L. Maria²

¹The Children's Hospital at the University of Missouri-Columbia, Columbia, Missouri

²Children's Research Institute at the Medical University of South Carolina, Charleston, South Carolina

A previous report noted a 27% prevalence of autism in Joubert syndrome (JS), raising the question of overlapping etiologies. Family studies have shown that autism is characterized by family loading for a number of specific behavioral and psychiatric disorders and that the sib recurrence risk is around 4%. The purpose of this study is to determine whether children with Joubert and their families show behavioral or genetic characteristics similar to autism. Thirty-one volunteer Joubert families were identified. Parents completed a semi-structured family history interview and the Autism Behavioral Checklist. Rates of family loading for neuropsychiatric disorders in the JS families were compared to autism family history data and Down syndrome (DS) controls. The JS families had significantly lower rates of autism, alcoholism, cognitive, and language disorders than the autism families. Their rate of depression was lower, but not significantly different from that found in autism families. None of the JS children met the clinical cut-off for autism based on parental symptom report and the sib recurrence risk was 32% for the JS families compared to 4% for the autism and 0% for DS families. These data indicate that JS is a genetically distinct disorder from autism. Different genes with different inheritance patterns that affect neurodevelopment of the cerebellum could explain the clinical similarities previously reported in JS and autism. © 2005 Wiley-Liss, Inc.

KEY WORDS: Joubert; autism; recurrence risks

INTRODUCTION

Joubert syndrome (JS) is a rare neurodevelopmental disorder characterized by hypoplasia of the cerebellar vermis, hypotonia, ocular motor apraxia, and global developmental delays. The reported male to female ratio is about 2:1. Though the inheritance pattern is considered autosomal recessive based on the number of affected siblings and consanguineous parents, the recurrence risk is often less than 25%, suggesting etiologic heterogeneity [Cantani, 1989; Saraiva and Baraitser, 1992].

Grant sponsor: Missouri Department of Mental Health; Grant sponsor: Division of Mental Retardation and Developmental Disabilities; Grant sponsor: Leda J. Sears Trust.

*Correspondence to: T.N. Takahashi, Division of Medical Genetics, The Children's Hospital, University of Missouri-Columbia, #1 Hospital Drive, Columbia, MO 65212.
E-mail: takahashin@missouri.edu

Received 18 August 2004; Accepted 11 October 2004

DOI 10.1002/ajmg.a.30500

Autism is a complex neurodevelopmental disorder characterized by social and language deficits, and repetitive and stereotypic behaviors. Autism has a 4:1 male to female sex ratio and the average sibling recurrence risk is about 4% [Ritvo et al., 1989; Bolton et al., 1994], leading many to consider idiopathic autism to be a multifactorial disorder. There have been reports of several children with JS being diagnosed with autism [Holroyd et al., 1991; Ozonoff et al., 1999]. Holroyd et al. reported two siblings with JS, one meeting full DSM-III-R autism diagnostic criteria and the other with autistic behaviors. Ozonoff and colleagues reported a 27% prevalence of autism in 11 children with JS using DSM-IV criteria.

Genetic studies have consistently noted family loading for neuropsychiatric disorders including depression, alcoholism, and anxiety disorders in families of children with autism [Piven et al., 1991; Smalley et al., 1995; Bolton et al., 1998; Piven and Palmer, 1999; Miles et al., 2003], but to date there has been no systematic pedigree analysis of families of individuals with JS. Thus, the first purpose of this study was to analyze family histories from a large uniformly diagnosed population of children with JS to determine whether their families had an increased rate of autism, depression, alcoholism, and other neurodevelopmental disorders compared to families of children with autism. The second purpose was to examine the behavioral phenotype of the JS children to determine how many might meet criteria for autism. Based on previous research suggesting a relationship between autism and JS, we hypothesized autistic symptoms in JS might be high, though that alone would not confer any information about overlapping genetic etiologies. On the other hand, if JS families had high genetic loading for the neuropsychiatric disorders found in autism families, it would support the hypothesis that JS, or at least a significant fraction of cases, was caused by genes that also caused autism and conferred milder behavioral phenotypes in gene carriers.

MATERIALS AND METHODS

Participants

Participants included children with JS (N = 47) and their parents, who were attending a national conference sponsored by the Joubert Syndrome Foundation and the National Institute of Neurologic Disease and Stroke. Of the 44 families attending the conference, 98% (N = 43) agreed to participate in the research study. Inclusion criteria included chronologic age less than 18 years old and a medical diagnosis of JS. One family declined to participate and three children were ineligible because they were over 18 years old.

Children ranged in age from 0.4 to 16.2 years with a mean age of 6.6 years (SD = 5.3 years) (Table I). The male to female sex ratio was 1.6:1 (29:19). With the exception of one African-American child, participants were Caucasian. Mean age of mothers was 36.7 years (SD = 5.1 years; n = 32) and for fathers was 39.8 years (SD = 5.5 years; n = 31). With the exception of one father, information was available regarding the educational level of these parents. More than half of mothers (63%) and fathers (57%) had achieved a bachelor's or graduate degree. Of the remaining parents, most were high school

TABLE I. Demographics

	Joubert syndrome (N = 43)	Autism (N = 157)	Down syndrome (N = 22)
Mean age (SD)	6.6 (5.3)	8.3 (6.8)	2.4 (4.5)
Age range	0.4–16.2	0.97–41.2	0.003–16.3
Mean age of mothers (SD)	36.7 (5.1)	34.8 (8.7)	32.9 (8.9)
Mean age of fathers (SD)	39.8 (5.5)	37.2 (8.4)	35.4 (10.1)
Ethnicity			
Caucasian	42/43 (98%)	146/157 (93%)	21/22 (95%)
African American	1/43 (2%)	7/157 (4%)	0/22 (0%)
Asian	0/43 (0%)	2/157 (13%)	0/22 (0%)
Other (biracial)	0/43 (0%)	12/157 (8%)	1/22 (4%)
Education of parents			
Mothers college/graduate training ($P = 0.006^*$)	20/32 (63%)	36/103 (35%)	9/22 (41%)
Mothers high school only ($P = 0.002^*$)	11/32 (34%)	67/103 (65%)	12/22 (54%)
Mothers less than high school	1/32 (3%)	10/103 (10%)	1/22 (5%)
Fathers college/graduate training	16/30 (53%)	46/115 (40%)	8/22 (36%)
Fathers high school only ($P = 0.03^*$)	12/30 (40%)	71/115 (62%)	11/22 (50%)
Fathers less than high school	2/30 (7%)	3/115 (3%)	3/22 (14%)

* P -values are for comparisons between Joubert syndrome and autism.

graduates (34% of mothers and 37% of fathers), but some had not completed high school (3% of mothers and 6% of fathers).

Autism family histories were obtained from 157 unrelated autism families referred to the Autism Center at the University of Missouri-Columbia from 1994 to 2000. All autism patients were evaluated using our center-based version of the ADI and ADOS scoring protocol and all met autism diagnostic criteria specified by DSM-IV [American Psychiatric Association, 2000] and CARS criteria [Schopler et al., 1986]. Patients with a recognized genetic syndrome were excluded from the study group. The autism group had a male to female sex ratio of 4.4:1 (128:29) and ranged in age from 0.97 to 41.2 years with a mean age of 8.3 years ($SD = 6.8$ years). The majority of subjects in the autism group were Caucasian (93%) with the remainder being Asian (13%), biracial (8%), and African-American (4%). The mean age of mothers was 34.8 years ($SD = 5.1$) and 37.2 years for fathers ($SD = 8.4$). Approximately one-third of mothers (35%) and fathers (40%) in the autism group had achieved a bachelor's or graduate degree and over half of mothers (65%) and fathers (62%) obtained a high school education only. The remaining mothers (10%) and fathers (3%) had not completed high school.

The Down syndrome (DS) information was obtained from 22 families of children with DS who have received care through the DS clinic at the University of Missouri and who have agreed to participate in family studies as part of an autism research study. Their participation was approved by the Health Sciences Institutional Review Board. The DS group had a male to female sex ratio of 4.5:1 (18:4) and ranged in age from 0.003 to 16.3 years with a mean age of 2.4 years ($SD = 4.5$). The mean age of mothers was 32.9 years ($SD = 8.9$) and 35.4 years for fathers ($SD = 10.1$). With the exception of one biracial patient in the DS group, subjects were Caucasian (95%). Less than half of mothers (41%) and fathers (36%) had obtained a bachelor's or graduate degree, and 54% of mothers and 50% of fathers obtained a high school education only. The remaining mothers (5%) and fathers (14%) had less than a high school education.

Procedures

As part of the larger multidisciplinary study at the JS conference, parents were interviewed by one of the two authors (J.H.M., T.N.T.) using a direct semi-structured family history interview. They also responded to a set of questionnaires regarding their child's behavior and their current level of stress and coping. The number of children and parents who

completed the different measures used in this study varied slightly. Researchers conducted the study according to a protocol approved by the Health Sciences Institutional Review Board.

Measures

Family history. Complete family histories were obtained from 31 families. For multiplex families, the oldest sibling with JS was designated the proband. Family history was obtained by direct semi-structured interviews using the family history method [Orvaschel et al., 1982; Thompson et al., 1982; Andreasen et al., 1986; Rice et al., 1995; Davies et al., 1997]. A "significant family history of a disorder" was defined as either (1) the diagnosis in a first-degree relative, (2) the same diagnosis in a second degree relative plus at least two additional relatives related in an apparent Mendelian pattern, or (3) the same diagnosis in at least four family members in the same branch of the family. Other family histories were considered non-significant. Pedigrees were created and stored in the Cyrillic 2.1.3 database [Chapman, 2000].

Autism behavior checklist (ABC). The ABC asks parents to rate the presence or absence of 57 characteristics related to autism [Krug et al., 1993]. Parents of children ages 3 years and older completed the ABC ($n = 32$). Items are grouped into five subscales: sensory, relating, body and object use, language, and social/self-help. Each item is assigned a weight on the basis of its strength as a predictor of an autism diagnosis. A total score is derived by summing the weighted items endorsed by parents. Despite some controversy in the literature regarding clinical cut-off criteria, it appears that children with previous diagnoses of autism typically receive ABC scores that are 1–1.5 standard deviations above the mean of scores for children with no diagnosis [Krug et al., 1993; Miranda-Linne and Melin, 2002]. Classifications of autism derived from the ABC are consistent with those derived from other measures (e.g., Pervasive Developmental Disorders Rating Scale Phi coefficient = 0.68) [Eaves et al., 2000]. Adequate split-half reliability is reported by the author ($r = 0.87$) and others report satisfactory internal consistency for the total scale score (Cronbach's alpha = 0.87) [Sturmeijer et al., 1992].

Data Analysis

Autistic symptoms on the ABC among children with JS were compared to the measure's normative data for children

who are typically developing, for those with autism, and for those with mental retardation. Prevalence of neuropsychiatric disorders in families of children with JS was compared to our extensive autism family history data ($N=157$) that was collected using the same family history approach. We have used this method successfully in a large study of families with autism and have documented increased family histories of autism, affective disorders, alcoholism, and cognitive disorders [Miles et al., 2003]. Frequency comparisons were also made with a control population of 22 families ascertained through a child with DS.

RESULTS

Autism Diagnostic Studies

When screened using the ABC, no child met the clinical cut-off for autism. Only 4 of 32 children (13%) exhibited borderline clinically significant symptoms of autism. As shown in Figure 1, children with JS displayed more total symptoms of autism compared to the ABC normative sample, but were more like the ABC comparison sample of children with mental retardation than children with autism.

Family History of Autism and Other Behavioral and Psychiatric Disorders

None of the 31 Joubert families with available histories met criteria for a significant family history of autism or autism symptoms compared to 18% in autism families (29/157, $P=0.02$) and 0% in the DS control group (Table II).

The JS families also had significantly reduced family histories of alcoholism, cognitive, and language disorders. Familial alcoholism was reported by 13% (4/31) of Joubert families compared to 39% (65/167, $P=0.005$) of autism families versus 0% of DS families (0/22, $P=0.22$). In the Joubert families, alcoholism was reported in 1.6% (1/62) of first-degree relatives compared to 13.5% (45/334, $P=0.007$) in the autism group and 0.0% in the DS control group (0/44, $P=0.755$). Rates of cognitive disorder and language disorder in Joubert families were also much lower than in autism families ($P=0.0004$, 0.007).

Though the JS families reported less familial depression than the autism families (19% (6/31) versus 34% (54/157), the difference was not statistically significant ($P=0.10$). Only familial depression was not significantly lower in the JS than the autism families. Depression among first-degree relatives was, however, significantly less in the JS families 6% (4/62) compared to 17% (54/314, $P=0.03$) in autism families and not significantly different from the DS controls 0% (0/44, $P=0.2$).

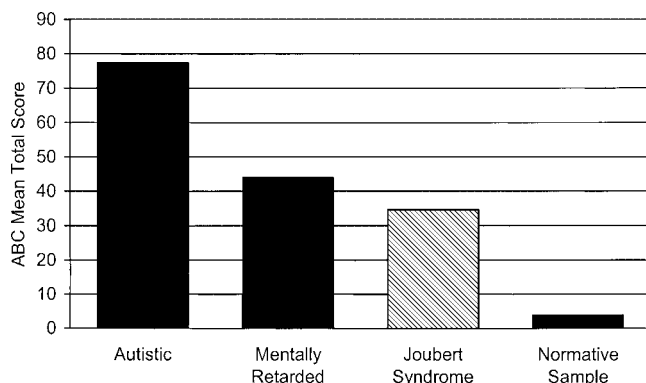


Fig. 1. Mean total score on the Autism Behavior Checklist for children with Joubert syndrome compared to previously reported samples of children with autism, severe mental retardation, and no diagnosis [Krug et al., 1993].

Sibling Recurrence Risks

In this population, the JS sibling recurrence risk was 32% (9/28) for all sibs and 60% (9/15) for latter born sibs. Twenty-six percent (8/31) of families that completed the family history interview were multiplex (had more than one child affected with JS). The autism recurrence risk was 3.8% (8/209) for all sibs and 4.4% (4/90) for latter born sibs. In the DS control group, there were no affected sibs.

DISCUSSION

When the Joubert families were compared to autism families, we found different male to female sex ratios, different recurrence risks, and different family history profiles. This indicates that JS and autism are genetically distinct disorders with no evidence for a shared genetic liability. The greater than 25% affected sib pairs are felt to represent the bias of ascertainment for multiplex families since families with more than one affected child are more likely to be diagnosed and are more likely to attend a national conference.

Autism is considered to be a multifactorial disorder, caused by the actions of many genes contributed from both parents. Evidence for multiple genes each with small effects comes from family studies that demonstrate family loading for an array of neuropsychiatric disorders and mild autism spectrum symptoms [DeLong and Dwyer, 1988; Smalley et al., 1995; Piven and Palmer, 1999; Miles et al., 2003]. The genetic profile for JS is consistent with an autosomal recessive disorder with no effects in the heterozygotes.

Since JS is a neurologic disorder with its primary defects in the brain stem and cerebellum, it is not surprising that children with Joubert have been noted to have autism symptoms in the past [Ozonoff et al., 1999]. While none of the children in this study met the clinical cut-off for autism using the ABC, 13% exhibited borderline clinically significant symptoms; it would not be unexpected for some children with JS to meet ADI-R criteria for a behavioral diagnosis of autism. These children would be considered to have secondary autism, that is, secondary to another genetic or medical diagnosis. Between 5% and 10% of children diagnosed with autism have another genetic disorder, most commonly a chromosome disorder, fragile X syndrome, tuberous sclerosis, or Soto's syndrome, which is felt to be the primary cause of their behavioral symptoms [Ritvo et al., 1990; Rutter et al., 1994; Gillberg and Coleman, 1996; Barton and Volkmar, 1998; Gillberg, 1998].

The prevalence of autistic symptoms in this sample of Joubert patients is similar to that found in a comparison sample of children with mental retardation. Several large-scale studies have shown the rate of autism to be elevated in individuals with severe intellectual disability. An epidemiologic study conducted in Scotland found that 36% of severely to profoundly retarded and 16% of moderately retarded individuals met DSM-III-R criteria for autistic disorder [Deb and Prasad, 1994]. In a study from Sweden, 14% of children with severe mental retardation met DSM-III-R criteria for autistic disorder and another 16% met diagnostic criteria for a more broadly defined autism spectrum disorder [Nordin and Gillberg, 1996].

Different genes affecting neurodevelopment of the cerebellum could explain the clinical similarities between Joubert and autism. Joubert is caused by hypoplasia of the cerebellar vermis and is frequently associated with a complex brain stem malformation represented as the molar tooth sign on MRI [Maria et al., 1997, 1999]. Autism has also been associated with defects in cerebellar development including structural malformations, atrophy, and vermal hypoplasia [Courchesne et al., 1988, 1994; Hashimoto et al., 1995; Miles and Hillman,

TABLE II. Genetic Characteristics of Joubert Syndrome Compared to Controls

	Joubert syndrome (N = 47)	Autism (N = 157)	Down syndrome (N = 22)
Male to female ratio ($P = 0.005^*$)	1.6:1 (29:18)	4.4:1 (128:29)	4.5:1 (18:4)
Sib recurrence risk ($P = 0.000004^*$)	9/28 (32%)	8/209 (4%)	0/27 (0%)
Families with significant history of:			
Autism ($P = 0.02^*$)	0/31 (0%)	29/157 (18%)	0/22 (0%)
Cognitive disorder ($P = 0.0004^*$)	0/31 (0%)	48/157 (31%)	0/22 (0%)
Language disorder ($P = 0.007^*$)	1/31 (3%)	39/157 (25%)	0/22 (0%)
Alcoholism ($P = 0.005^*$)	4/31 (13%)	61/157 (39%)	1/22 (4%)
Depression ($P = 0.1^*$)	6/31 (19%)	54/157 (34%)	0/22 (0%)

None of the comparisons between Joubert syndrome and Down syndrome were statistically significant.
* P -values are for comparisons between Joubert syndrome and autism.

2000], indicating that cerebellar abnormalities, and perhaps more specifically vermal defects, can cause autistic symptoms. Thus, it is not unexpected that other cerebellar malformation disorders including JS may be associated with autistic symptoms. However, other studies have been unable to replicate the findings of vermal hypoplasia in different autism populations [Holttum et al., 1992; Kleiman et al., 1992; Piven et al., 1997]. Schaefer et al. [1996] found no difference in the rate of vermal hypoplasia in various neurogenetic syndromes that present both with and without associated autistic features, which contradicts a direct etiologic relationship between vermal hypoplasia and autistic behavior and suggests that vermal hypoplasia may be a non-specific characteristic of many neurodevelopmental disorders.

The data presented here provide several important pieces of information. First, we were able to describe the family structure of a large, reliably diagnosed population of children with JS, documenting the genetic features, including the male to female ratio, sib recurrence risks, and incidence of other neurodevelopmental and neuropsychiatric disorders. Second, comparing these results to comparably studied autism and DS populations allowed us to conclude that JS is an autosomal recessive disorder and is not a significant cause of autism.

There are a number of limitations of the study that must be acknowledged. The JS population was strongly biased by its selection at a Joubert Foundation Meeting, which undoubtedly accounts for the large number of multiplex families. Moreover, the JS population size is too small to explore questions of heterogeneity within JS. Nevertheless, our data indicate quite strongly that the genetic bases of JS and autism do not etiologically overlap, and that JS is not a frequent cause of autism. Further studies to characterize the clinical phenotype and neuropsychological features of JS are needed to clarify any heterogeneity within the JS diagnosis and facilitate more focused clinical, epidemiologic, therapeutic, and gene-finding studies.

ACKNOWLEDGMENTS

Research was supported by a grant from the Missouri Department of Mental Health, Division of Mental Retardation and Developmental Disabilities and a grant from the Leda J. Sears Trust.

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