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Parents' initial concerns about the development of their children later diagnosed with fragile X syndrome

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Abstract

Background—Retrospective parental reports have often been used to identify the early characteristics of children later diagnosed with a developmental disorder.

Method—We applied this methodology to document 13 parents' initial concerns about the development of their 17 children later diagnosed with fragile X syndrome (FXS). Parents were additionally asked about when they noticed the emergence of behavioural signs related to FXS.

Results—More than half of the parents reported initial concerns prior to the child's first birthday and in most cases it was deviant motor behaviours that caused the first concerns. Behavioural signs related to the FXS phenotype were also reported to be perceptible in the first year of the child's life.

Conclusions—Due to limitations of retrospective parental questionnaires, we suggest that other methodologies, such as home video analysis, are needed to complement our understanding of the pathways of developmental disorders with late clinical onsets.

Keywords

Infants; early signs; fragile X syndrome; parental concerns; parental questionnaire; recall bias

Introduction

In clinical practice and research, retrospective parental reports have often been used to identify the early characteristics and development of children later diagnosed with a developmental disorder. This methodology would seem particularly useful when attempting to identify early signs of disorders that have a late clinical presentation and/or diagnosis

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(e.g., Bailey, Raspa, Olmsted, & Holiday, 2008; Charman et al., 2002; Neul et al., 2014; Roberts, Mirrett, & Burchinal, 2001; Urbanowicz, Downs, Girdler, Ciccone, & Leonard, 2015). The variability and subtlety in the expression of disorders that are not detected until later in development (e.g., autism spectrum disorder [ASD], fragile X syndrome, Rett syndrome) make early identification, and hence provision of early intervention challenging. Participants for prospective studies on prodromal development of rare disorders are not routinely available, and retrospective parental reports have limitations (e.g., recall bias). Still, the latter methodology appears to be a useful tool for researchers interested in exploring the early development of such disorders (Abrams et al., 2012; Bailey, Raspa, Bishop, & Holiday, 2009; Bailey, Skinner, Hatton, & Roberts, 2000; Bailey, Skinner, & Sparkman, 2003; Bailey et al., 2008; Baranek et al., 2008; Goldberg, Thorsen, Osann, & Spence, 2008; Hinton et al., 2013; Johnson, 2008; Marschik et al., 2014; Roberts et al., 2001; Zwaigenbaum, Bryson, & Garon, 2013).

As mentioned before, fragile X syndrome (FXS; OMIM 300624) is one of these disorders and affects approximately 1 in 3,600 males and 1 in 6,000 females (e.g., Hagerman, 2008). Early diagnosis of FXS is often difficult and delayed because the associated physical features (e.g., facial dysmorphia), and other signs of impairment are often very subtle at first (Hagerman, 2002). Indeed, FXS is generally not identified until 3 years of age or older especially in countries other than the United States (US) or United Kingdom (e.g., Bailey et al., 2009; Essop & Krause, 2013; Gabis & Kesner, 2007; Iredale, Turpin, & Bailey, 2009; Lessmann & Sarimski, 2013; Meguid, Ismail, El-Mahdy, Barakat, & El-Awady, 2014; Vuust, Larsen, Grønskov, Nørgaard-Pedersen, & Brøndum-Nielsen, 2006; Yim, Jeon, Yang, & Kim, 2008). Given the limited number of studies into the early development of children with FXS, there is still a lot to learn about the development in the infant and toddler period (Baranek et al., 2005, 2008; Farzin, Rivera, & Whitney, 2011; Hatton et al., 2009; Hinton et al., 2013; Marschik et al., 2014; Mirrett, Bailey, Roberts, & Hatton, 2004; Prouty et al., 1988; Roberts, Tonnsen, Robinson, & Shinkareva, 2012; Roberts et al., 2001; Roberts, Mankowski, et al., 2009; Rogers, Wehner, & Hagerman, 2001; Zingerevich et al., 2009).

Studies of individuals diagnosed with FXS consistently report the presence of moderate to severe intellectual disability and a range of neurobehavioural abnormalities, including behaviour characteristic of ASD, attention-deficit/hyperactivity, sensory hypersensitivity, poor motor coordination, and repetitive behaviours (Boyle & Kaufmann, 2010; Hagerman, 2002; Hagerman & Hagerman, 2002; Hagerman et al., 2009; Hayes & Matalon, 2009; Talisa, Boyle, Crafa, & Kaufmann, 2014). Speech-language and gestural development in individuals with FXS is commonly delayed/limited in terms of forms and functions (Abbeduto, Brady, & Kover, 2007; Finestack, Richmond, & Abbeduto, 2009; Hinton et al., 2013; Marschik et al., 2014; Roberts, Mirrett, Anderson, Burchinal, & Neebe, 2002; Roberts et al., 2001). Atypical socio-communicative behaviours, such as avoidance of eye contact, unease when cuddled, and shyness, are also frequently observed (Bailey et al., 1998; Baranek et al., 2005; Hessl, Glaser, Dyer-Friedman, & Reiss, 2006; Kaufmann et al., 2004; Marschik et al., 2014; Rogers, Hepburn, Stackhouse, & Wehner, 2003).

Similar to other developmental disorders with late onset of the more obvious symptoms, parents of individuals with FXS are commonly the first to notice signs of atypical and/or

delayed development in their child. About 80% of the first parental concerns are related to developmental delay. Other concerns include noticing a variety of peculiar behaviours (Bailey et al., 2000, 2003, 2009). Such parental concerns are usually the initial step that eventually leads to diagnosis (Bailey et al., 2000, 2003, 2009; Carmichael, Pembrey, Turner, & Barnicoat, 1999; Mirrett et al., 2004).

In a recently launched project, we gained support from a German advocacy group comprised of parents of individuals with FXS (Interessensgemeinschaft Fragiles-X e.V.) who consented to fill in a questionnaire focusing on the earliest development of their children. In the current study, we aimed to explore the parental perception on the prodromal development of their child with FXS. In particular we sought to identify (a) the initial parental concerns, (b) the onsets of behavioural signs related to FXS phenotype, (c) how initial parental concerns are influenced by the occurrences of the behavioural signs, (d) the relation between the initial concerns and the age of diagnosis, and (e) the impact of the interval between the occurrence of events and the time of recollection on parental reports.

Methods

Participants

Thirteen parents (P1−P13, Table 1) of 17 individuals diagnosed with FXS (Cases 1−17, Table 1) participated by completing the questionnaire. Of the 17 individuals with FXS, 12 were firstborns. Cases 1, 2, and 3 were from the same family, Cases 1 and 2 being twins. Cases 5 and 6 as well as Cases 13 and 14 were siblings (Table 1). The age of the individuals with FXS at the time when parents filled in the questionnaire (“current age”, from here on) ranged from 2 years 11 months to 48 years 7 months (*Mdn* = 17 years 10 months). The study was approved by the Institutional Review Board of the Medical University of Graz, Austria (24-226 ex 11/12) and the parents gave their informed written consent to participate in the study and to the publication of the results.

Research design and procedure

This is an exploratory retrospective study on the early phenotype of FXS using parental reports. Our FXS − Early Development Questionnaire (FXS-EDQ) consists of 48 questions on the medical history, the familial background, initial parental concerns, the age of diagnosis and comorbidities (e.g., ASD), the child’s early development in different domains (e.g., motor, speech-language), and the child’s current abilities and communicative behaviours (Table 2). With the exception of the questions on the medical history and current abilities, all other questions were closed-ended. Parents could also comment on each question in an open-ended format.

The questionnaires were sent to 14 members of the Interessensgemeinschaft Fragiles-X e.V. (Germany) whose child(ren) had been diagnosed with FXS. Parents were explicitly invited to review medical records and diaries for a better recall of events. Thirteen parents returned the completed questionnaires within 6 months (2012; response rate: 93%). In two cases, the father filled in the questionnaire (P4 and P11), in four cases (P1, P8, P10, P13) both parents did. For the remaining cases only the mother filled in the questionnaire. For this paper, we

exclusively focused on questions related to initial parental concerns and the emergence of behaviours related to the FXS phenotype (Table 2).

Data analysis

Data from the completed questionnaires were analysed using SPSS Version 22.0. Due to small sample size, findings about the areas of initial parental concerns and the behavioural signs were presented in a descriptive manner. Spearman rank order correlation was applied to estimate the association between two variables. When partial correlations were computed, they were based on Spearman rhos. As the PARTIAL CORR procedure in SPSS does not specify rank correlations, the /MATRIX subcommands in NONPAR CORR procedure was combined with the PARTIAL CORR procedure. Two-tailed significance level ($p < .05$) was applied if not otherwise specified. As correlation coefficients are suitable measures of effect sizes, no extra indices for effect sizes have been provided in this manuscript.

Results

Initial parental concerns

As shown in Table 1, parents of nine out of the 17 individuals with FXS had concerns about the child's development before the child's first birthday. Only the parent P1 reported that initial concerns (for Cases 5 and 6) occurred after 2 years of age. By 18 months of age, parental concerns were mostly related to peculiar motor behaviours. Other concerns included noticing that the child avoided eye contact (Case 4); had prolonged crying episodes (Cases 9 and 12); showed limited interest in surroundings, people, and situations (Case 10); and had feeding difficulties (Cases 11 and 12). After the age of 18 months, concerns were also related to conspicuous or delayed speech-language behaviours. Parent P7 (Case 16) also recalled that the child showed excessive shyness, which was of major concern to the parent.

Emergence of early signs

Table 3 provides the age of their child when parents observed the first appearance of behaviours related to the FXS phenotype. Some parents noted the first such signs during the child's first year of life, such as unease when cuddled, avoidance of eye contact, hyperactivity, or hand stereotypies. Shyness, aggression, anxiety, echolalia, and frequent self-biting were noted during the second year of life, whereas panic attacks were reported to appear after 2 years of age. Echolalia (13/17 children), hand stereotypies (12/17), avoidance of eye contact (10/17), and hyperactivity (8/17) were among the most frequently reported signs. Although parents confirmed the occurrence of various early signs, seven of them were not able to recall the age of emergence for at least one of these particular signs.

The parents of Cases 4, 7, 9, 11, and 12 reported the first occurrence of one or more signs coinciding with their initial concerns (Tables 1 and 3). Some parents had obviously recognised first signs before they were concerned (Cases 6, 16, and 17). For example, parents of Case 6 recalled the onset of hand stereotypies between 13 and 18 months of age, yet reported that their initial concerns occurred much later (after 24 months). No significant correlation between the age of initial parental concerns and the first appearance of signs related to FXS was found (rho = .03, $p = .91$). However, the age of initial parental concerns

was associated with the number of signs parents had recalled (rho = -.49, $p < .05$): The more signs that were noted, the earlier was the parent concerned.

Age of diagnosis and its association with initial parental concerns

All individuals were diagnosed before 2010. Their median age at diagnosis was 3 years 5 months (range: 1 year 1 month−16 years 0 months; see Table 1). In the present sample, siblings within the same family were diagnosed at the same time. Individuals born more recently were diagnosed at a younger age (rho = .78, $p < .01$). In order to compare our findings with a previous study that investigated potential changes in diagnosis after the year 2000 (Bailey et al., 2009), we split the subjects into two subgroups based on whether the child was diagnosed before or after 2000 (Table 1). The correlation between the current age and the age of diagnosis remained significant for both groups (for the seven cases diagnosed before 2000, rho = .78, $p < .05$; for the 10 cases diagnosed after 2000, rho = .93, $p < .001$). Although we found no significant correlation between number of signs recalled and the age of diagnosis (rho = -.12, $p = .68$), the earlier the parent was concerned, the earlier the diagnosis was received (rho = .50, $p < .05$).

The impact of interval between the occurrence of events and the time of recollection

To investigate the memory effects on parental recall, we first assessed the correlations between the child's current age and other variables of interest (Table 4). As these correlation coefficients approached significance, we ran the partial correlation procedure taking the current age as the control variable. Neither the partial correlation between the age of first parental concerns and the number of signs ($r = -.36$, $p = .17$) nor the partial correlation between the age of first parental concerns and the age of diagnosis remained significant ($r = .14$, $p = .61$).

Discussion

In line with previous findings (Bailey et al., 2000; Carmichael et al., 1999), more than half of the parents in our study reported initial concerns before the child's first birthday. Unlike previous studies, we did not ask the parents to choose the main reason for concern from a list of problems in our questionnaire (e.g., Bailey et al., 2000, 2003, 2009). Rather, we asked the parents in general *which* developmental *area* made them particularly concerned at first, and *when* was that (Table 2). In most cases, deviant motor behaviours caused the first concerns, whereas concerns related to speech-language development emerged in general after 18 months of age. As the first productive word appears usually within 8 to 18 months of age, it is understandable that most parents were not worried about the child's language development before 18 months, but were indeed worried thereafter. A potential limitation of our questionnaire is that we did not ask the parents to specify the atypical behaviour in the area(s) of initial concern.

In our sample, the median age of FXS diagnosis was 3 years 5 months, which is in line with the literature. Similar to other studies (Bailey et al., 2000; Carmichael et al., 1999), we found that children born more recently were identified at a younger age, suggesting a possible improvement in the diagnostic process in Germany over the last few decades. Bailey and

colleagues (2009), however, found no trend of improvement in the diagnostic age between 2000 and 2007 in the US. Despite concerted efforts by professional organisations and advocacy groups recommending closer links between paediatricians and geneticists – and for any child with unexplained delays to be tested for FXS – the mean age of diagnosis remained stable over this period and was about 3 years 3 months. The discrepancy to our findings could be related to two factors. First, our sample was smaller and had a relatively wide age range. Second, for the comparable period (i.e., diagnoses performed after 2000), the age of diagnosis in our sample had been brought forward from 10 years to 1 year 1 month (Table 1). As the diagnoses were received at a very late age initially, the improvement appeared obvious. In addition, Bailey and colleagues excluded the seven cases diagnosed between 10 and 26 years of age as outliers in their calculations. Thus their sample might be more homogeneous with regard to the current age and the diagnostic age of the individuals with FXS. This was not the case in our study.

To our knowledge, our study is the first to ask parents about the onset of the behavioural signs related to the FXS phenotype. Note that we consider these signs as *related to* but not *specific to* FXS. For example, “avoid eye contact” is also frequently observed in other neurodevelopmental disorders, such as ASD. In our study, we found that some signs (e.g., echolalia, hand stereotypies, and avoidance of eye contact) were observed in more than half of the individuals with FXS. Second, our results suggest that the onset of the behavioural signs varied. Among the 10 listed signs, four (e.g., hand stereotypies) were reported to occur before 12 months of age, the others in the second year of life (5/10, e.g., repetition of self-biting) or even later (1/10, i.e., panic attacks). Panic attacks have been observed in adult individuals with FXS (Roberts, Bailey, et al., 2009) but might not belong to the “early” behavioural signs for FXS. As expected, the parents in our study did not observe it before 24 months of age. Third, we found that the onset of the earliest FXS-related sign(s) did not coincide with the initial parental concerns. A few parents reported that certain peculiar signs (e.g., hand stereotypies) appeared much earlier than their first concerns, which might suggest a recall bias.

Retrospective parental reports are limited and thus our data must be interpreted with caution. Indeed, previous studies have pointed out that retrospective parental reports are inaccurate with respect to event dates (Henry, Moffitt, Caspi, Langley, & Silva, 1994; Yarrow, Campbell, & Burton, 1970) and in our study, many parents (7/13) admitted that they did observe certain signs, but could not remember the age of onset of those signs (Table 3). However, Goldberg et al. (2008) reported that parents were better able to remember behaviours related to expressive language than behaviours related to non-language areas. In our study, for all the 13 children reported to show echolalia, their parents did seem to have confidence in their ability to recall the age of onset: mostly after 24 months (11/13), and no earlier than 19 months. This expressive-language-related parental account coincided with what we know about language development of children with FXS. As shown in a recent study, the first productive word in children with FXS appeared on average at 21 months of age (Hinton et al., 2013). Thus, echolalia would be unlikely to appear earlier than this age, which is consistent with our data.

Still, given that retrospective parental reports are vulnerable to memory bias, we considered the impact of the interval between filling in the questionnaire and the occurrence of events of interest on parents' recollection. According to a previous study, parents had difficulties in remembering the time and frequency of events that occurred in the distant past (Henry et al., 1994). Thus in our study, one might expect that parents of the individuals with FXS who were of an older age would be more likely to be inaccurate about the onset of concerns and behavioural signs. In fact, we found that these parents tended to report the first concerns at a later time, and reported fewer behavioural signs and later onsets of the first signs (see Table 4). It might be true that due to better general awareness of early child development, parents of children born more recently might have been more alert to developmental deviances and thus more likely to raise concerns earlier. However, it is unlikely to be true that the number of signs and the onset of the first signs would be related to the current age of the individuals with FXS. Rather, the results might be suggesting that the parents of older individuals with FXS might not be able to accurately recall the emergence of the signs and consequently reported fewer signs and later onset times for these signs. It has also been reported that when people are asked about a particular event, they tend to report it as having occurred more recently than it did, a memory bias called "forward telescoping" (Loftus & Marburger, 1983; Lord, Shulman, & DiLavore, 2004). This appeared to occur also in our study: The parents of older individuals with FXS reported that their initial concerns, and the onsets of the signs, occurred at a more recent time. One factor that might have attenuated the memory lapse is the intermittent character of these children's development. The appearance of atypical behaviours in very young children with FXS was usually subtle (Hatton et al., 2009; Roberts, Mankowski, et al., 2009). Various developmental delays or atypical development might become noticeable only with time. Accordingly, it is difficult for parents to precisely identify the onset when a certain sign or behaviour became obvious.

While considering the associations among the initial parental concerns, the behavioural signs, and the age of diagnosis, we found two significant correlations. First, the parents who perceived more peculiar signs raised concerns earlier. Second, the earlier the initial parental concerns, the earlier the children were diagnosed. Both results seem reasonable and are consistent with the results of other studies. Bailey and colleagues (2009), for example, reported that children with FXS who had more co-occurring conditions (e.g., autism, hyperactivity, aggressiveness, anxiety) were diagnosed earlier, and that the delay between the first parental concerns and the diagnosis was shorter. In addition, Kozlowski, Matson, Horovitz, Worley, and Neal (2011) studied children with ASD and reported that the earlier the parental concerns, the earlier the diagnosis was sought. However, since we found that the number of reported signs and the age of the first parental concerns were both correlated to the current age of the individuals with FXS, we re-examined the above-mentioned results, taking the current age of the individuals as the control variable. Both correlations turned out to be nonsignificant. In other words, these correlations might be artifacts of memory bias. Unfortunately, we cannot draw any conclusion on whether and how the initial parental concerns, the behavioural signs, and the age of diagnosis were associated with each other because the effects, if any, of memory bias cannot be determined from our data.

Conclusion

To study early development of individuals with a rare disorder such as FXS, which is typically not diagnosed until toddler or preschool age, researchers often have to rely on retrospective information reported. Such data, given inherent limits, should not be disregarded, since they provide us with insights that could improve the understanding of the earliest development of rare diseases. Although the relatively small sample is a limitation, FXS is a rare condition, which makes it logistically difficult to obtain large samples in European countries. Given that our sample was small and had a wide age range, our results should be interpreted with caution. Retrospective parental data alone will not be able to build up the full picture of our knowledge and further research on the prodromal period of FXS is warranted. Future efforts might be improved by inclusion of other data sources, such as the analysis of home videos of the child's early development and prospective observations. These data sources could complement our current understanding of the pathways of developmental disorders with late clinical onsets.

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References

Abbeduto L, Brady N, Kover ST. Language development and fragile X syndrome: profiles, syndrome-specificity, and within-syndrome differences. Mental Retardation and Developmental Disabilities Research Reviews. 2007; 13:36–46. DOI: 10.1002/mrdd.20142 [PubMed: 17326110]

Abrams L, Cronister A, Brown WT, Tassone F, Sherman SL, Finucane B, McConkie-Rosell A, Hagerman RJ, Kaufmann WE, Picker J, Coffey SM, et al. Newborn, carrier, and early childhood screening recommendations for fragile X. Pediatrics. 2012; 130:1126–1135. DOI: 10.1542/peds.2012-0693 [PubMed: 23129072]

Bailey DB, Mesibov GB, Hatton DD, Clark RD, Roberts JE, Mayhew L. Autistic behavior in young boys with fragile X syndrome. Journal of Autism and Developmental Disorders. 1998; 28:499–508. DOI: 10.1023/A:1026048027397 [PubMed: 9932236]

Bailey DB, Raspa M, Bishop E, Holiday D. No change in the age of diagnosis for fragile x syndrome: findings from a national parent survey. Pediatrics. 2009; 124:527–533. DOI: 10.1542/peds.2008-2992 [PubMed: 19581269]

Bailey DB, Raspa M, Olmsted M, Holiday DB. Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey. American Journal of Medical Genetics. Part A. 2008; 146A:2060–2069. DOI: 10.1002/ajmg.a.32439 [PubMed: 18570292]

Bailey DB, Skinner D, Hatton D, Roberts J. Family experiences and factors associated with the diagnosis of fragile X syndrome. Journal of Developmental and Behavioral Pediatrics. 2000; 21:315–321. DOI: 10.1097/00004703-200010000-00001 [PubMed: 11064958]

Bailey DB, Skinner D, Sparkman KL. Discovering fragile X syndrome: family experiences and perceptions. Pediatrics. 2003; 111:407–416. DOI: 10.1542/peds.111.2.407 [PubMed: 12563071]

Baranek GT, Danko CD, Skinner ML, Bailey DB, Hatton DD, Roberts JE, Mirrett PL. Video analysis of sensory-motor features in infants with fragile X syndrome at 9-12 months of age. Journal of Autism and Developmental Disorders. 2005; 35:645–656. DOI: 10.1007/s10803-005-0008-7 [PubMed: 16172809]

Baranek GT, Roberts JE, David FJ, Sideris J, Mirrett PL, Hatton DD, Bailey DB. Developmental trajectories and correlates of sensory processing in young boys with fragile X syndrome. Physical &

Occupational Therapy in Pediatrics. 2008; 28:79–98. DOI: 10.1300/J006v28n01_06 [PubMed: 18399048]

Boyle L, Kaufmann WE. The behavioral phenotype of FMR1 mutations. American Journal of Medical Genetics. Part C, Seminars in Medical Genetics. 2010; 154C:469–476. DOI: 10.1002/ajmg.c.30277

Carmichael B, Pembrey M, Turner G, Barnicoat A. Diagnosis of fragile-X syndrome: the experiences of parents. Journal of Intellectual Disability Research. 1999; 43:47–53. DOI: 10.1046/j.1365-2788.1999.43120157.x [PubMed: 10088968]

Charman T, Cass H, Owen L, Wigram T, Slonims V, Weeks L, Wisbeach A, Reilly S. Regression in individuals with Rett syndrome. Brain & Development. 2002; 24:281–283. DOI: 10.1016/S0387-7604(02)00058-X [PubMed: 12142064]

Essop FB, Krause A. Diagnostic, carrier and prenatal genetic testing for fragile X syndrome and other FMR-1-related disorders in Johannesburg, South Africa: a 20-year review. South African Medical Journal. 2013; 103:994–998. DOI: 10.7196/samj.7144 [PubMed: 24300646]

Farzin F, Rivera SM, Whitney D. Resolution of spatial and temporal visual attention in infants with fragile X syndrome. Brain. 2011; 134:3355–3368. DOI: 10.1093/brain/awr249 [PubMed: 22075522]

Finestack LH, Richmond EK, Abbeduto L. Language development in individuals with fragile X syndrome. Topics in Language Disorders. 2009; 29:133–148. DOI: 10.1097/tld.0b013e3181a72016 [PubMed: 20396595]

Gabis L, Kesner Y. Behavioral characteristics of children with Fragile X syndrome. Harefuah. 2007; 146:469–474. [PubMed: 17760403]

Goldberg WA, Thorsen KL, Osann K, Spence MA. Use of home videotapes to confirm parental reports of regression in autism. Journal of Autism and Developmental Disorders. 2008; 38:1136–1146. DOI: 10.1007/s10803-007-0498-6 [PubMed: 18058010]

Hagerman PJ. The fragile X prevalence paradox. Journal of Medical Genetics. 2008; 45:498–499. Erratum in: *Journal of Medical Genetics, 45, 768*. DOI: 10.1136/jmg.2008.059055 [PubMed: 18413371]

Hagerman, RJ. The physical and behavioral phenotype. Fragile X syndrome: diagnosis, treatment, and research. Hagerman, RJ., Hagerman, PJ., editors. Baltimore: Johns Hopkins University Press; 2002. p. 3-109.

Hagerman RJ, Berry-Kravis E, Kaufmann WE, Ono MY, Tartaglia N, Lachiewicz A, Kronk R, Delahunty C, Hessl D, Visootsak J, Picker J, et al. Advances in the treatment of fragile X syndrome. Pediatrics. 2009; 123:378–390. DOI: 10.1542/peds.2008-0317 [PubMed: 19117905]

Hagerman, RJ., Hagerman, PJ., editors. Fragile X syndrome: diagnosis, treatment, and research. (3rd ed.). Baltimore: Johns Hopkins University Press; 2002.

Hatton DD, Wheeler A, Sideris J, Sullivan K, Reichardt A, Roberts J, Clark R, Bailey DB. Developmental trajectories of young girls with fragile x syndrome. American Journal on Intellectual and Developmental Disabilities. 2009; 114:161–171. DOI: 10.1352/1944-7558-114.3.161 [PubMed: 19374463]

Hayes EW, Matalon R. Fragile X syndrome. Pediatrics. 2009; 124:790–792. DOI: 10.1542/peds.2009-0569 [PubMed: 19581265]

Henry B, Moffitt TE, Caspi A, Langley J, Silva PA. On the "remembrance of things past": a longitudinal evaluation of the retrospective method. Psychological Assessment. 1994; 6:92–101. DOI: 10.1037//1040-3590.6.2.92

Hessl D, Glaser B, Dyer-Friedman J, Reiss AL. Social behavior and cortisol reactivity in children with fragile X syndrome. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 2006; 47:602–610. DOI: 10.1111/j.1469-7610.2005.01556.x

Hinton R, Budimirovic DB, Marschik PB, Talisa VB, Einspieler C, Gipson T, Johnston MV. Parental reports on early language and motor milestones in fragile X syndrome with and without autism spectrum disorders. Developmental Neurorehabilitation. 2013; 16:58–66. DOI: 10.3109/17518423.2012.704414 [PubMed: 23249372]

Iredale, R., Turpin, T., Bailey, D. The Australian and New Zealand fragile X family survey. Sydney, Australia: Fragile X Association of Australia; 2009.

Johnson VA. Checklist assessments of the FMR1 gene mutation phenotypes. Journal of Cultural Diversity. 2008; 15:117–131. [PubMed: 19025200]

Kaufmann WE, Cortell R, Kau AS, Bukelis I, Tierney E, Gray RM, Cox C, Capone GT, Stanard P. Autism spectrum disorder in fragile X syndrome: communication, social interaction, and specific behaviors. American Journal of Medical Genetics. Part A. 2004; 129A:225–234. DOI: 10.1002/ajmg.a.30229 [PubMed: 15326621]

Kozlowski AM, Matson JL, Horovitz M, Worley JA, Neal D. Parents' first concerns of their child's development in toddlers with autism spectrum disorders. Developmental Neurorehabilitation. 2011; 14:72–78. DOI: 10.3109/17518423.2010.539193 [PubMed: 21410398]

Lessmann J, Sarimski K. Diagnosemitteilung beim Fragilen-X-Syndrom – retrospektive Befragung von Eltern [Family experiences with the diagnosis of fragile X syndrome – results of a retrospective parental survey]. Praxis der Kinderpsychologie und Kinderpsychiatrie. 2013; 62:420–434. DOI: 10.13109/prkk.2013.62.6.420 [PubMed: 23901619]

Loftus EF, Marburger W. Since the eruption of Mt. St. Helens, has anyone beaten you up? Improving the accuracy of retrospective reports with landmark events. Memory & Cognition. 1983; 11:114–120. DOI: 10.3758/bf03213465 [PubMed: 6865744]

Lord C, Shulman C, DiLavore P. Regression and word loss in autistic spectrum disorders. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 2004; 45:936–955. DOI: 10.1111/j.1469-7610.2004.t01-1-00287.x

Marschik PB, Bartl-Pokorny KD, Sigafoos J, Urlesberger L, Pokorny F, Didden R, Einspieler C, Kaufmann WE. Development of socio-communicative skills in 9- to 12-month-old individuals with fragile X syndrome. Research in Developmental Disabilities. 2014; 35:597–602. DOI: 10.1016/j.ridd.2014.01.004 [PubMed: 24480609]

Meguid NA, Ismail MF, El-Mahdy RS, Barakat MA, El-Awady MK. Simple molecular diagnostic method for fragile X syndrome in Egyptian patients: pilot study. Acta Biochimica Polonica. 2014; 61:259–263. [PubMed: 24936518]

Mirrett PL, Bailey DB, Roberts JE, Hatton DD. Developmental screening and detection of developmental delays in infants and toddlers with fragile X syndrome. Journal of Developmental and Behavioral Pediatrics. 2004; 25:21–27. DOI: 10.1097/00004703-200402000-00004 [PubMed: 14767352]

Neul JL, Lane JB, Lee HS, Geerts S, Barrish JO, Annese F, Baggett LM, Barnes K, Skinner SA, Motil KJ, Glaze DG, et al. Developmental delay in Rett syndrome: data from the natural history study. Journal of Neurodevelopmental Disorders. 2014; 6:20.doi: 10.1186/1866-1955-6-20s [PubMed: 25071871]

Prouty LA, Rogers RC, Stevenson RE, Dean JH, Palmer KK, Simensen RJ, Coston GN, Schwartz CE. Fragile X syndrome: growth, development, and intellectual function. American Journal of Medical Genetics. 1988; 30:123–142. DOI: 10.1002/ajmg.1320300111 [PubMed: 3177438]

Roberts JE, Bailey DB, Mankowski J, Ford A, Sideris J, Weisenfeld LA, Heath TM, Golden RN. Mood and anxiety disorders in females with the FMR1 premutation. American Journal of Medical Genetics Part B, Neuropsychiatric Genetics. 2009; 150B:130–139. DOI: 10.1002/ajmg.b.30786

Roberts JE, Mankowski JB, Sideris J, Goldman BD, Hatton DD, Mirrett PL, Baranek GT, Reznick JS, Long AC, Bailey DB. Trajectories and predictors of the development of very young boys with fragile X syndrome. Journal of Pediatric Psychology. 2009; 34:827–836. DOI: 10.1093/jpepsy/jsn129 [PubMed: 19074489]

Roberts JE, Mirrett P, Anderson K, Burchinal M, Neebe E. Early communication, symbolic behavior, and social profiles of young males with fragile X syndrome. American Journal of Speech-Language Pathology. 2002; 11:295–304. DOI: 10.1044/1058-0360(2002/034)

Roberts JE, Mirrett P, Burchinal M. Receptive and expressive communication development of young males with fragile X syndrome. American Journal of Mental Retardation. 2001; 106:216–230. DOI: 10.1352/0895-8017(2001)106%3C0216:raecdo%3E2.0.co;2s [PubMed: 11389664]

Roberts JE, Tonnsen B, Robinson A, Shinkareva SV. Heart activity and autistic behavior in infants and toddlers with fragile X syndrome. American Journal on Intellectual and Developmental Disabilities. 2012; 117:90–102. DOI: 10.1352/1944-7558-117.2.90 [PubMed: 22515825]

Rogers SJ, Hepburn SL, Stackhouse T, Wehner E. Imitation performance in toddlers with autism and those with other developmental disorders. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 2003; 44:763–781. DOI: 10.1111/1469-7610.00162

Rogers SJ, Wehner DE, Hagerman R. The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. Journal of Developmental and Behavioral Pediatrics. 2001; 22:409–417. DOI: 10.1097/00004703-200112000-00008 [PubMed: 11773805]

Talisa VB, Boyle L, Crafa D, Kaufmann WE. Autism and anxiety in males with fragile X syndrome: an exploratory analysis of neurobehavioral profiles from a parent survey. American Journal of Medical Genetics. Part A. 2014; 164A:1198–1203. DOI: 10.1002/ajmg.a.36468 [PubMed: 24664669]

Urbanowicz A, Downs J, Girdler S, Ciccone N, Leonard H. Aspects of speech-language abilities are influenced by MECP2 mutation type in girls with Rett syndrome. American Journal of Medical Genetics. Part A. 2015; 167A:354–362. DOI: 10.1002/ajmg.a.36871 [PubMed: 25428820]

Vuust J, Larsen LA, Grønskov K, Nørgaard-Pedersen B, Brøndum-Nielsen K. Screening for fragile X syndrome. International experiences. Ugeskrift for Laeger. 2006; 168:3704–3709. [PubMed: 17069733]

Yarrow MR, Campbell JD, Burton RV. Recollections of childhood. A study of the retrospective method. Monographs of the Society for Research in Child Development. 1970; 35:1–83. DOI: 10.2307/1165649

Yim SY, Jeon BH, Yang JA, Kim HJ. Fragile X syndrome in Korea: a case series and a review of the literature. Journal of Korean Medical Science. 2008; 23:470–476. DOI: 10.3346/jkms.2008.23.3.470 [PubMed: 18583885]

Zingerevich C, Greiss-Hess L, Lemons-Chitwood K, Harris SW, Hessl D, Cook K, Hagerman RJ. Motor abilities of children diagnosed with fragile X syndrome with and without autism. Journal of Intellectual Disability Research. 2009; 53:11–18. DOI: 10.1111/j.1365-2788.2008.01107.x [PubMed: 18771512]

Zwaigenbaum L, Bryson S, Garon N. Early identification of autism spectrum disorders. Behavioural Brain Research. 2013; 251:133–146. DOI: 10.1016/j.bbr.2013.04.004 [PubMed: 23588272]

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Table 1

Characteristics of 17 individuals with FXS reported by parents (*N* = 13)

Parent code	Case number	Gender	Current age (in completed years)	Age of first parental concern (in months)	Area of first parental concern	Age of diagnosis	Diagnosed after 2000	Number of signs
P1	6[b]	M	48	> 24	MB+SL	16 years 0 months	No	2
P1	5[b]	M	47	> 24	MB+SL	15 years 0 months	No	4
P2	8	M	21	19-24	MB+SL	3 years 0 months	No	1
P3	13[b]	F	19	19–24	MB+SL	10 years 0 months	Yes	1
P3	14[b]	F	18	19–24	MB+SL	8 years 6 months	Yes	1
P4	3[b]	M	19	< 12	MB	4 years 11 months	No	5
P4	1[b]	M	17	< 12	MB	3 years 5 months	No	6
P4	2[b]	M	17	< 12	MB	3 years 5 months	No	4
P5	10[a]	M	18	< 12	MB+O	10 years 0 months	Yes	7
P6	12	M	16	< 12	O	1 years 10 months	No	6
P7	16	F	14	19–24	SL+O	3 years 2 months	Yes	7
P8	17	M	10	19–24	SL	3 years 9 months	Yes	6
P9	11	M	10	< 12	MB+O	7 years 1 month	Yes	5
P10	7	M	10	13–18	MB	2 years 0 months	Yes	4
P11	9	M	7	< 12	MB+O	1 years 6 months	Yes	6
P12	4[a]	M	5	< 12	MB+SL+O	1 years 1 month	Yes	6
P13	15	M	2	< 12	MB	1 years 1 month	Yes	3

Note. Individuals with FXS (Cases 1–17) are sorted in descending order according to the current age. MB = motor behaviours; SL = speech/language; O = others.

[a]These cases were additionally diagnosed with ASD.

[b]Cases 5 and 6, Cases 13 and 14 as well as Cases 1, 2, and 3 are siblings, Cases 1 and 2 being twins.

Table 2

List of questions in the FXS-EDQ on initial parental concerns and the emergence of FXS-related behaviours used for the present study

When did you get concerned for the first time suspecting a developmental disorder?[a]
Which developmental area (e.g., motor, speech/language, others) made you particularly concerned at first?
Did your child feel uncomfortable when being cuddled? If yes, when did you observe it for the first time?
Did your child avoid eye contact? If yes, when did you observe it for the first time?
Was your child exceptionally shy? If yes, when did you observe it for the first time?
Was your child particularly aggressive? If yes, when did you observe it for the first time?
Was your child particularly anxious? If yes, when did you observe it for the first time?
Did your child have panic attacks? If yes, when did you observe it for the first time?
Did your child consistently repeat words not suitable for the situation? If yes, when did you observe it for the first time?
Was your child constantly in motion (or hyperactive)? If yes, when did you observe it for the first time?
Did your child have hand stereotypies, e.g., waggling his/her hands? If yes, when did you observe it for the first time?
Did your child repeatedly bite his/her hand? If yes, when did you observe it for the first time?

Note. FXS-EDQ = Fragile X Syndrome – Early Development Questionnaire.

[a]Except for the second question listed in this table, the participants were provided with the following options: (a) between the 1st and the 6th month; (b) between the 7th and the 12th month; (c) between the 13th and the 18th month; (d) between the 19th and the 24th month; (e) later than 24 months; (f) I cannot remember the age. For each question, extra space was also assigned for any additional comment.

Table 3
First occurrence of signs related to the FXS phenotype in 17 individuals

	Sign (not) observed for *n* cases		Age					
	Yes	No	1–6 m	7–12 m	13–18 m	19–24 m	> 24 m	Age not remembered
Unease when cuddled	6	11	9 11				10 16	1 13
Avoidance of eye contact	10	7	9	4	15 17		10 12 16	1 2 3
Shyness	5	12				10	7 16	3 17
Aggression	5	12			1		4 11 14	5
Anxiety	7	10				10 17	4 7 11 12 16	
Panic attacks[a]	4	12					5 12	9 17
Echolalia	13	4				7 12	1 2 3 4 5 6 9 10 11 16 17	
Hyperactivity	8	9	9 11 12		4			1 2 3 5
Hand stereotypies	12	5	9	4 12	6		8 10	1 2 3 15 16
Repetition of self-biting	5	12			7 15 16		10	17

Note. The number in the circle refers to the case number.

[a]Parent of Case 17 (P8) did not answer this question

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Table 4

Correlation coefficients between the current age and the other variables

Variable(s)		Age of the initial parental concerns	Age of the first occurrence of sign(s)	Number of signs
Current age	Spearman's rho	.44	.48	-.44
	p value	*.08*	*.06*	*.08*
	N	17	16	17