Journal of Autism and Developmental Disorders, Vol. 33, No. 2, April 2003 (© 2003)

Partial Tetrasomy of Chromosome 3q and Mosaicism in a Child with Autism

Guiomar Oliveira,[1,6] Eunice Matoso,[2] Astrid Vicente,[3] Patricia Ribeiro,[2] Carla Marques,[1] Assunção Ataíde,[4] Teresa Miguel,[4] Jorge Saraiva,[5] Isabel Carreira[2]

In this report we describe the case of an 11-year-old male with autism and mental retardation, presenting a tetrasomy of chromosome 3q. Cytogenetic analysis showed a mosaic for an unbalanced karyotype consisting of mos46,XY,add(12)(p13.3)(56)/46,XY(45). FISH using WCP and subtelomeric probes identified the extra material on 12p to be an inverted duplication of the distal segment of chromosome 3q. Anomalies in chromosome 3q have not been previously described in association with autism, although association with psychomotor delays and behavior problems has been frequently reported and are here further discussed. This chromosomal 3q segment is therefore likely to include genes involved in specific neurodevelopment pathways, and further analysis of the region is warranted for the identification of the molecular alterations that lead to the autistic features described.

KEY WORDS: Autism; chromosome 3: partial tetrasomy 3q; mosaicism.

INTRODUCTION

Infantile autism is currently viewed as a behaviorally defined neurodevelopment disorder of early childhood. It has become accepted that autism is a constellation of behavioral symptoms (disturbance of reciprocal social interaction, disturbance of communication, disturbance of normal variation in behavior), that expresses the atypical function of an affected individual's brain.

A large number of specific medical disorders/organic conditions (chromosomal abnormalities, tuberous sclerosis, neurofibromatosis, Moebius syndrome, infectious agents, and metabolic disorders) have been found to be associated with autism or autistic-like conditions. Gillberg and Coleman refer to such disorders as PARMDs (Possibly Autism Related Medical Disorders). The estimated rate of PARMDs varies from 11% to 12% in population-based studies, that did not include comprehensive neurological and medical investigation, to 37% in studies that include such investigation (Gillberg & Coleman, 1996).

The possible causes of autism have been under debate for many years. The disorder was once thought to have a psychogenic base, but it is now recognized that multiple biological processes probably lay in its origin (Gillberg & Coleman, 1992). Family and twin studies show that autistic disorder is in large measure genetically determined (Bailey, Philips, & Rutter, 1996). However, the inheritance pattern is not well defined, indicating that the genetic contribution is likely to be polygenic rather than result from a single gene defect. There have now been reports of autism associated with abnormalities in almost every chromosome, varying in frequency from 1% to 15% (Carratalá *et al.*, 1998; Ghaziuddin & Burmeister, 1999; Gillberg, 1998; Goizet

[1] Centro de Desenvolvimento da Criança, Hospital Pediátrico Coimbra Portugal.
[2] Unidade Citogenética, Faculdade de Medicina—Universidade de Coimbra Portugal.
[3] Instituto Gulbenkian de Ciência, Oeiras, Portugal.
[4] Direcção Regional da Educação do Centro, Portugal.
[5] Serviço de Genética, Centro Hospitalar Coimbra, Portugal.
[6] Correspondence should be addressed to Guiomar Oliveira, Consulta de Autismo—Centro de Desenvolvimento da Criança, Hospital Pediátrico Coimbra, Av Bissaya Barreto, 3000-076-Coimbra, Portugal; e-mail:guiomar@hpc.chc.min-saude.pt

0162-3257/03/0400-0177

et al., 2000; Lauritsen, Mors, Mortesen, & Ewald, 1999; Smith *et al.*, 2000). The most frequently reported chromosomal aberrations are found on the long arm of chromosome 15, including deletions, duplications, and inversions in the 15q11–q13 region, near the Prader-Willi–Angelman gene region (Bundey, Hardy, Vickers, Kilpatrick, & Corbett, 1994; Gillberg, 1998). A defect on the FMR-1 gene, in the fragile X region on chromosome Xq27.3, is also frequently associated with autistic behavior, although this abnormality defines specifically the fragile X syndrome and is a relatively uncommon cause of autism (Filipek *et al.*, 1999; Gillberg, 1998; Lauritsen *et al.*, 1999; Wassink *et al.*, 1999). Abnormalities in almost all other chromosomes have been reported to be associated with autism, but generally occur with a low frequency (Gillberg, 1998). Such findings are particularly important for the identification of susceptibility genes: by examining chromosomal abnormalities associated with autism, such as translocations and deletions, it is possible to identify breakpoints that are indicative of loci involved in autism and therefore spot candidate sites for molecular investigation (Bristol *et al.*, 1996).

In the following report we describe the occurrence of autism in a child with partial tetrasomy in mosaic of a distal chromosome 3q segment, involving a translocation to the short arm of chromosome 12. The extra material on chromosome 12p was identified by fluorescent in situ hybridization (FISH) as a segment of the long arm of chromosome 3 that is present in an inverted duplicated form.

CASE REPORT

A.P. is a Caucasian male born on 12/3/88. He is the first child of healthy unrelated Portuguese parents, aged 30 and 32 at evaluation, and has a 6-year-old sister who is a healthy, normal girl. A.P. was born by forceps at term, weighing 2850 g and with an Apgar score of 10 at 5 minutes. There were no neonatal problems, but he was born with a clubfoot, which was surgically corrected at 18 months. Between 9 and 24 months he suffered from simple fever convulsion. EEG was normal at the age of 1 year. All of his developmental milestones were delayed: he walked independently at 3 years old and started to speak at 4. At the age of 3 years he was referred by his family doctor to a child psychiatrist, with suspicion of a pervasive developmental disorder of autistic type.

A.P. was assessed in our Autism Unit in 1997 and subsequently in 1999, at the age of 9 and 11 years, respectively. He was found to have general delay in his development; his social relation and communication skills were impaired and associated with stereotyped and ritualistic behavior. Most aspects of the abnormal behavior had been noticed by the parents before the age of 3 years.

Neurodevelopment Evaluation

Based on clinical history and examination, A.P. met 10 DSM IV (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition), (American Psychiatric Association, 1994) criteria for pervasive developmental disorder of the autistic subtype. Specifically, he showed marked impairment in social interaction (impairment in the use of nonverbal behavior such as eye contact and facial expression, failure to establish proper peer relationships for his developmental level and lack of adequate social or emotional reciprocity). His spoken language was delayed, stereotyped, and repetitive, with marked impairment in the ability to initiate or sustain a conversation with others. He also showed marked impairment of nonverbal communication and restricted repetitive and stereotyped patterns of behavior, interests, and activities (hand-flapping, “pulling faces” and persistent preoccupation with parts of cars and other objects that make noises).

The total Childhood Autism Rating Scale (CARS) (Schopler, Reichler, & Renner, 1988) score for A.P. was 32 points indicating mild to moderate autism. A.P. was assessed using the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & LeCouteur, 1994) and satisfied the cutoff for autistic disorder. His scores on the three domains of social interaction, communication, and repetitive behaviors were 30, 24, and 4, respectively (Table I).

The general physical examination did not show any focal neurological or sensorial deficits or neurocutaneous lesions. His height at 11 years was 142 cm

Table I. Algorithm Scores for the Autism Diagnostic Interview

Domains	AP score	Autism cutoff*
Qualitative impairment in reciprocal social interaction	30	10
Impairment in communication	24	8
Repetitive behaviors and stereotyped patterns	4	3
Abnormality of development evident at or before 36 months	5	1

* Scores at or above the cutoff indicate autism.

(between the 25th and 50th centiles), weight was 47.5 kg (90th centile), and head circumference was 53.5 cm (50th centile). There were some minor dysmorphic features, specifically, round face, mild obesity, high palate, and ear length 7cm ($> +2SD$).

Multidisciplinary Assessment

The multidisciplinary assessment consisted of a developmental evaluation by a psychologist, a learning disabilities specialist, and a developmental paediatrician. The tests used were the Psycho-Educational Profile-Revised (PEP-R) (Schopler, Reichler, Bashford, Lansing, & Marcus, 1990), the Vineland Adaptative Behaviour Scale Interview-survey form (VABS) (Sparrow, Balla, & Cicchetti, 1984), the Ruth Griffiths Mental Development Scale II (Griffiths, 1984), and the Leiter International Performance Scale–Revised (Leiter, 1997).

The PEP-R is used to assess the abilities of autistic and developmentally disabled children who often have idiosyncratic and uneven developmental profiles. The PEP-R also provides an assessment of behavioral pathology within the following four areas: relations and affects, play and interest in materials, sensory responses, and language. Results of the PEP-R at age 11 indicated a developmental score of 101, equivalent to an age score of 46 months. The best areas were perception and fine motor and gross motor skills. The worst areas were imitation, eye-hand integration, cognitive performance, and cognitive verbal skills. The PEP-R Behavioural Scale showed abnormal behavioral patterns in the four areas, which is characteristic of autism.

Results of the VABS-Survey Form, which assesses personal and social sufficiency of individuals from birth to adulthood, indicated that the adaptative behavior composite skills of A.P. were at the 30-month age level (-4 to -5 *SD*).

The Ruth Griffiths Mental Development Scale II showed a General Developmental Quotient (GDQ) of 39, corresponding to moderate mental retardation, with a cognitive profile characteristic of autistic children. The best results emerged on the performance subscale (DQ of 43) and the poorest on the hearing and speech subscale (DQ of 37), as well as on practical reasoning subscales (DQ of 33). The Leiter-R test yielded a result of nonverbal IQ of 61, corresponding to a mild delay.

A.P. attends a Treatment and Education of Autistic and related Communication Handicapped Children (TEACCH) classroom, located in a public school.

Laboratory and Other Tests

Urine and blood amino acid screen was normal. MRI scan showed brainstem atrophy.

Cytogenetic Analysis

Peripheral blood was set up at 72 hours for synchronized cultures, and metaphase spreads were prepared for high-resolution G banding using standard techniques. Initial analysis of the proband showed a mosaic with a normal cell line 46,XY in approximately 45% of the cells, and another one with an unbalanced karyotype with additional material on the terminal end of the short arm of chromosome 12: 46,XY,add(12)(p13.3) (Fig. 1). The karyotypes of both parents were normal. Skin fibroblast culture of the proband confirmed the mosaic with the abnormal cell line in 14% of the cells.

To identify the extra material on the der12, FISH was performed using Whole Chromosome Paint (WCP), M-multiprobe system (Cytocell), for all chromosomes. Three positive hybridizations were obtained when WCP3 was used: both chromosomes 3 were fully painted, as well as the extra material on the terminal segment of one of the 12p (Fig. 2). The WCP12 probe did not paint any chromosome segment other than the

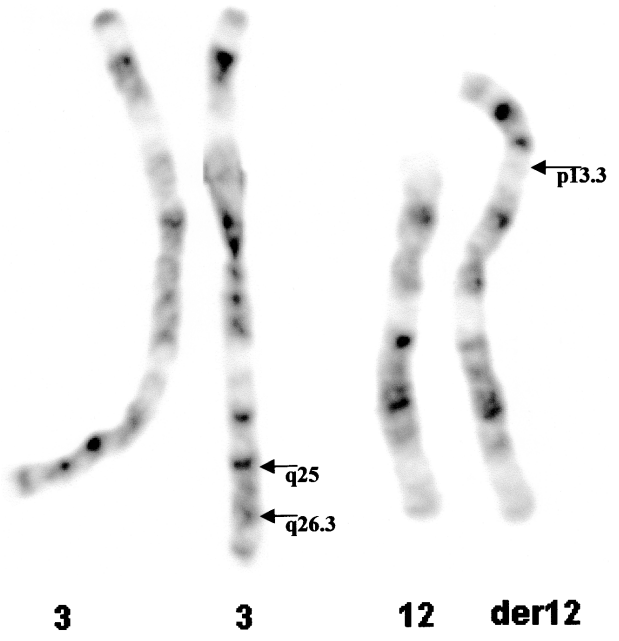

Fig. 1. Partial karyotype of the normal chromosome 3 pair and the chromosome 12 pair with the derivative. The arrows indicate the possible breakpoints.

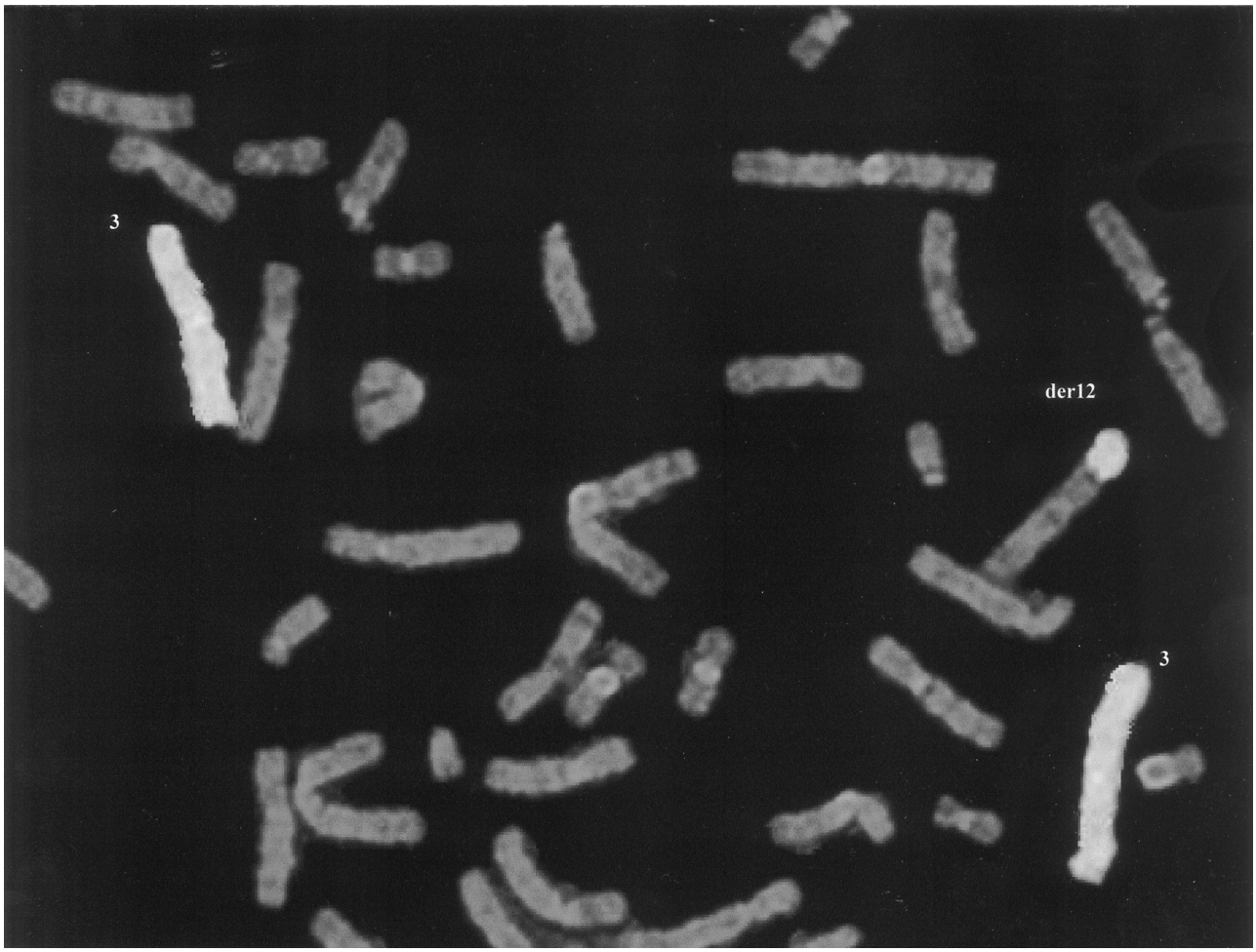

Fig. 2. Whole Chromosome 3 Paint (WCP3) showing the additional signal on chromosome der 12.

pair 12. The extra material on 12 did not paint with the WCP12, ruling out the hypothesis that this extra material could have originated from chromosome 12 (figure not shown). The possibility of a reciprocal translocation was equally ruled out. The combined results of G banding and FISH indicated that only the distal part of 3q was involved in the rearrangement, suggesting initially a partial trisomy of 3q25→qter (see Fig. 1). Further FISH analysis was performed using specific probes for the subtelomeric regions of chromosome 3 (D3S4559; D3S4560) and 12ptel (Vysis). The probe 12ptel showed that there was no deletion of the tip of 12p on the der12 (Fig. 3). The 3q subtelomeric probes hybridized on both normal chromosomes 3 and, unexpectedly, also at the two ends of the extra segment on 12p (Fig. 4, arrows). This suggested the occurrence of an inverted duplication of the terminal 3q. This end result showed that this child is tetrasomic for the region 3q26.3→3qter, with the following karyotype:

Mos46,XY,add12(p13.3).ishinvdup3(q29→q26.3::q26.3→q29)(WCP3+,D3S4560++,12ptel+)[56]/46, XY[45].

DISCUSSION

We report the case of a boy with typical autistic behavior associated with mild to moderate mental retardation, without obvious physical stigmata, and that revealed, upon cytogenetic study, a previously unreported chromosomal abnormality. Complementary evaluation did not reveal any abnormalities, except for an atrophy of the brainstem, which has been described in autism by other authors and related to a developmental anomaly (Hashimoto *et al.*, 1993, 1995).

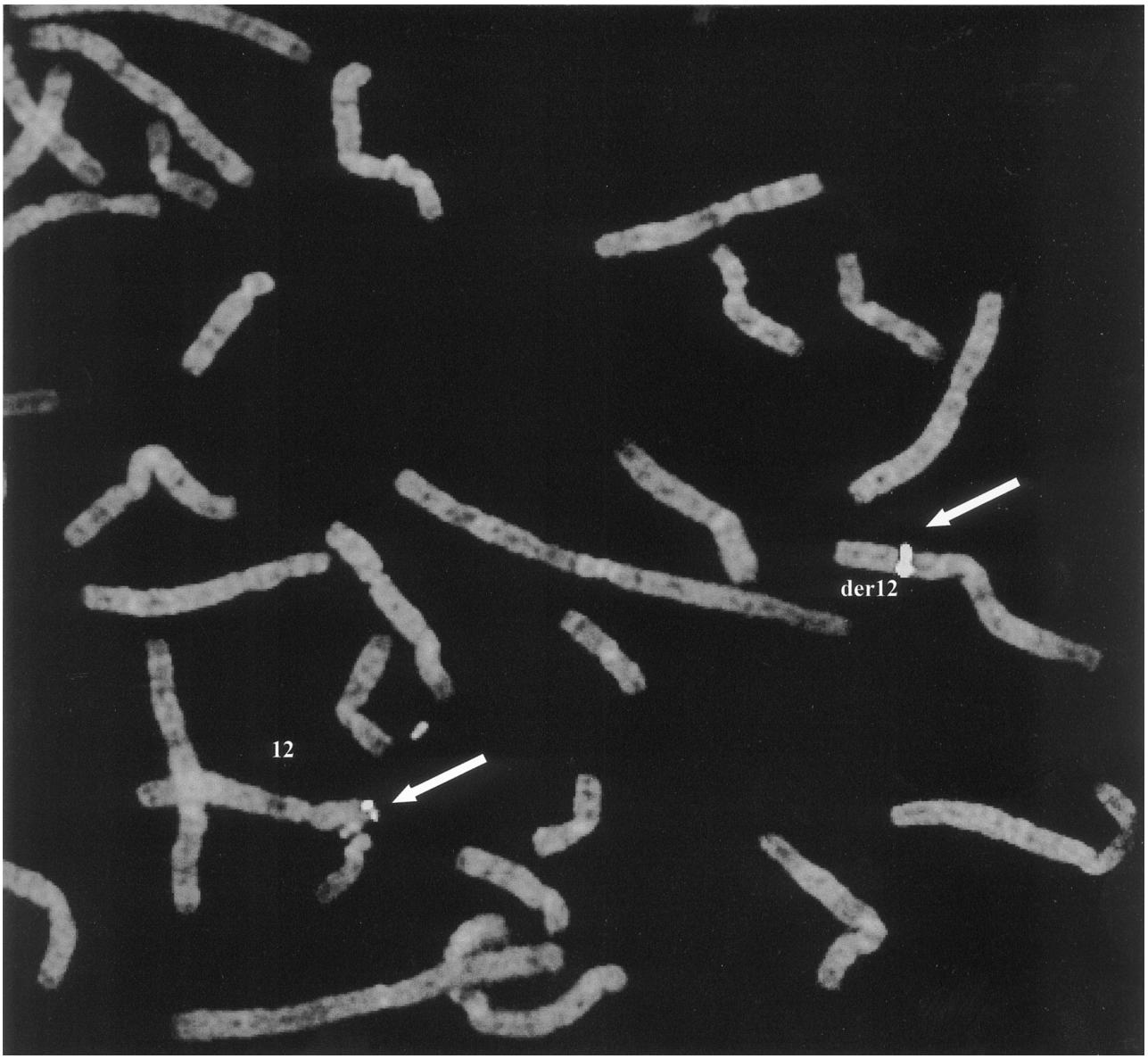

Fig. 3. Partial metaphase showing the hybridization signals of the subtelomeric probe 12ptel on the normal chromosome 12 and the derivative (der12) (⇦)

Chromosomal aberrations in many chromosomes have been described associated with autistic symptoms. However, the specific regions implicated on the rearrangement here described, involving the regions 3q26–29 and 12p13.3, have not yet, to our knowledge, been reported. The mechanism for this rearrangement is unusual. The FISH probes used in this study suggest that there was no disruption of the terminal region of chromosome 12p, although the hypothesis can only be ruled out by further analysis with additional subtelomeric probes. The most likely possibility is that the translocated segment of chromosome 3q, which is found duplicated and inverted, is responsible for the abnormal phenotype, because it is present in four copies. If this is the case, the identification of the translocation breakpoints may give important information regarding disrupted genes mapping to that precise location. Other genes in the duplicated segment are also possible etiological factors for the occurrence of autism with mental retardation in A.P., because they are present in four copies, two of which are in abnormal location and orientation.

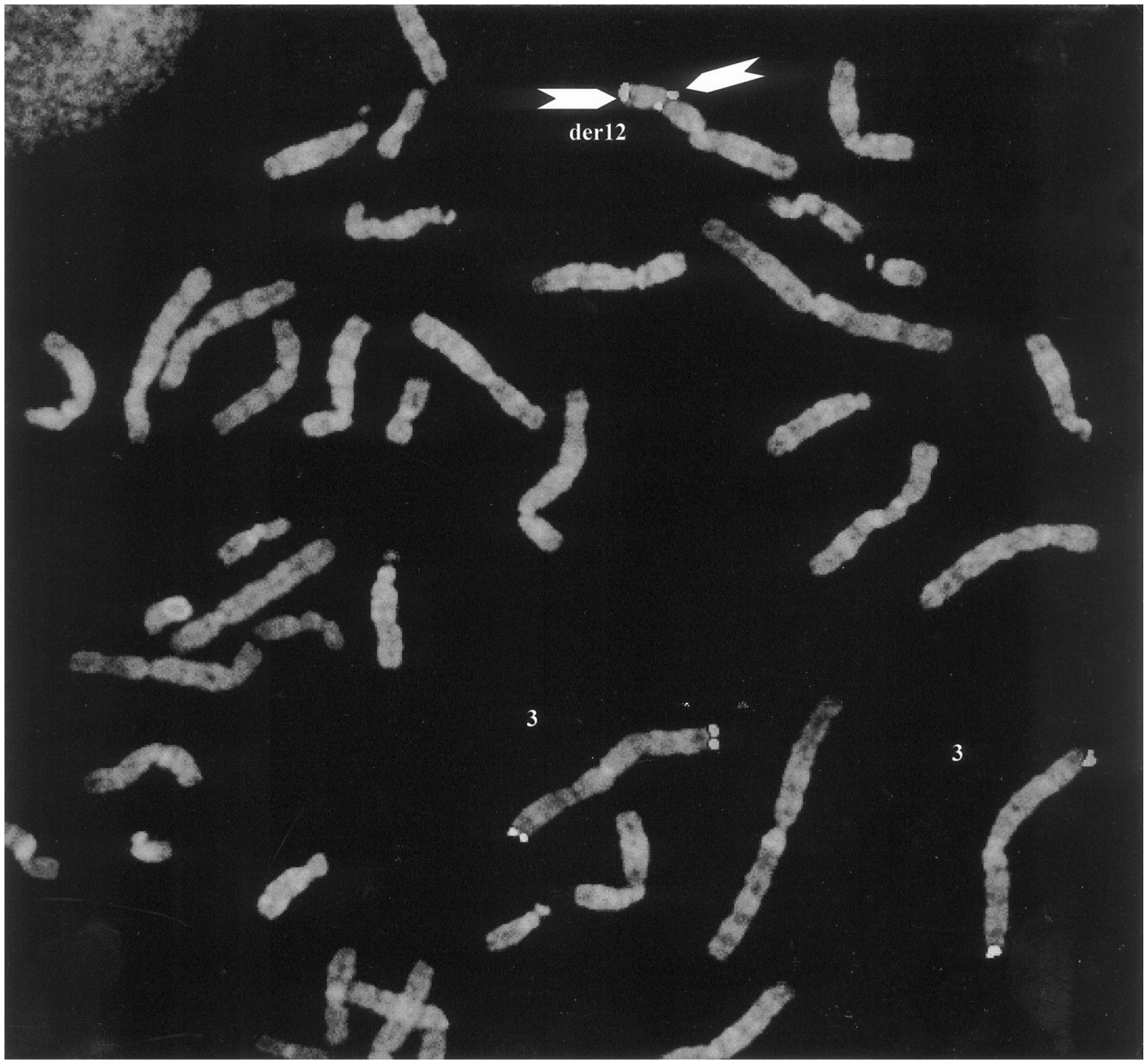

Fig. 4. Hybridization results obtained with D3S4559(3ptel)/D3S4560(3qtel). Both chromosomes 3 present clear signals. The der 12 shows, on the extra material, two hybridization signals with 3qtel ( ), demonstrating an inverted duplicated segment.

Several abnormalities in the 3q region have been described associated with psychomotor delay, behavior problems, and typical physical features, defining a 3q syndrome (Azar, Conte, Kleyman, Logush, & Verma, 1999). Azar *et al.* described a patient with these characteristics and a nonreciprocal translocation of segment 3q26.3-qter to chromosome 4, whereas other authors previously reported cases of trisomy of 3q segments of variable length with many common phenotypic features (reviewed by Azar *et al.,* 1999). Similarities of clinical features, including psychomotor delay, between the trisomy 3q syndrome and Cornelia de Lange syndrome have been found; the latter syndrome can be caused by chromosomal abnormalities involving the 3q26.3–3q27 segment (reviewed by Azar *et al.*, 1999). Mosaicism for tetrasomy of 3q27.1-qter has also been associated to skin pigmentary anomalies with and without psychomotor delay, and this can be associated to the degree of mosaicism in the patient (Kroisel, Petek, & Wagner, 2000; Portnoi *et al.*). Taken together, these

reports evidence the involvement of the 3q distal segment in phenotypic features, including general developmental delay and behavior problems, compatible with the autistic syndrome. A.P. does not present any of the physical stigmata described in other cases of 3q abnormalities. However, the phenotype associated with abnormalities in this chromosomal region is somewhat heterogeneous, possibly reflecting the effects of the particular abnormality, a duplication, inversion, or deletion of a segment, with boundaries that are not yet clearly defined and that therefore may include specific sets of genes. This heterogeneity may also be associated with the presence or absence of mosaicism, which can strongly influence the global phenotype.

We cannot rule out the hypothesis that the chromosomal abnormality found in A.P. is principally responsible for the mental retardation and not for the autistic phenomenology. It is a fact that in most reports of chromosomal abnormalities found in patients with autism, mental retardation is present in a more or less severe degree (Gillberg, 1998; Konstantareas & Homatidis, 1999). Although a wide range of IQ levels are found in autism [the majority of patients with autism have IQ under 70, while high-functioning patients may have very high IQ levels (Gillberg & Coleman, 1992, Fombonne, 1998)], even children from opposite ends of the IQ spectrum do not differ fundamentally from the classical autism definition. On the other hand, autism is not commonly present in patients with mental retardation [5–10% in the middle range to 30% or higher in the moderately to severely disabled (O'Brien, 2000)], indicating that mental retardation is common as a comorbidity of autism, whereas the reverse is not true. The primary diagnosis in this patient is autism: The results obtained with the Griffiths test for A.P. are very characteristic of the pattern found in autistic children (Carpentieri & Morgan, 1996; Sandberg, Nydén, & Hjelnquist, 1993) and indicate, with the Leiter test, a mild to moderate mental retardation. We therefore find it likely that the chromosomal abnormality reported in this case is responsible for a physiological alteration leading to autism associated with mental retardation.

At present there are a few genes that, given their central nervous system (CNS) patterns of expression, the role of their encoded proteins in CNS development or function, or their involvement in other CNS pathologies, may be candidate genes for the reported phenotypes associated with the 3q segment, including its autistic features. For instance, the DLG1 gene on 3q29 encodes a prosynaptic protein, SAP97, which interacts with the cytoplasmic tail of the NMDA receptor and is involved in neuronal cell signaling (Azim *et al.*, 1995; Lue, Marfatia, Branton, & Chishti, 1994). The HRY gene encodes a transcription factor that may suppress neuronal differentiation and maps to 3q28–29 (Feder, Li, Jan, & Jan, 1994). The PLXNA1 gene was located to 3q21-qter, and encodes Plexin A1, a membrane protein involved in neurogenesis (Tamagnone *et al.*, 1999). The CLDN11 gene, mapping to 3q26.2–26.3, encodes a tight junction–associated protein, claudin, which is a major component of myelin (Bronstein *et al.*, 1996, 2000). The gene for neuroserpin maps to 3q26 and encodes a serine protease inhibitor, a protein secreted from axons and expressed in the late stages of neurogenesis during synapse formation (Schrimpf *et al.*, 1997). Mutations in the neuroserpin gene are responsible for familial encephalopathy, an autosomal dominant neurodegenerative disorder (Davis *et al.*, 1999). Finally, it is intriguing that the FRX1 gene, a fragile X mental retardation autosomal homologue, maps to 3q28 (Coy *et al.*, 1995). This gene is highly homologous to the FMR1 gene, which causes fragile X mental retardation, sometimes with autistic symptoms, and the protein encoded is equally an RNA binding protein (Siomi *et al.*, 1995, 1996).

The co-occurrence of infantile autism and specific chromosomal abnormalities may be a determinant factor in the identification of candidate gene regions for the disease or for specific clinical features of the disease, which can then be tested in linkage and association studies (Lauritsen *et al.*, 1999). A good example of this approach is the identification of a translocation breakpoint on 7q31 in an autistic individual, which allowed the finding of a novel gene that is interrupted by the translocation (Vincent *et al.*, 2000). The 7q31 region had been previously associated to autism in several genome-wide screenings (IMGSAC, 1998; IMGSAC, 2001; Philippe *et al.*, 1999), and it is probably of significance that a locus for a severe disorder of speech and language also maps to 7q31 (Folstein & Mankoski, 2000; Lai *et al.*, 2000). Further characterization of the 3q distal segment boundaries will likely bring more insight into the genes located in the region that may be responsible for the described phenotype and for the related alterations reported by other authors.

We believe that our case is the first reported with this chromosomal abnormality. Physical stigmata in chromosomal disorders associated with autism range from severe to mild, and may actually not be evident (Gillberg, 1998; Konstantareas *et al.*, 1999; Seshadri, Wallerstein, & Burack, 1992). The absence of obvious physical features should therefore not prevent clinicians

evaluating children with autistic disorders from performing karyotypes. Finding chromosomal abnormalities may in fact provide a valuable contribution for genetic counseling of the families and also improve our understanding of the genetic basis of autism.

REFERENCES

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, D. C.: Author.

Azar, G. M., Conte, R. A., Kleyman, S. M., Logush, A. Z., & Verma, R. S. (1999). Probing the human genome in search for a new 3q syndrome. *Annales de Génétique, 42,* 95–100.

Azim, A. C., Knoll, J. H., Marfatia, S. M., Peel, D. J., Bryant, P. J., & Chishti, A. H. (1995). DLGI: Chromosome location of the closest human homologue of the drosophila discs large tumor supressor gene. *Genomics, 30,* 613–6.

Bailey, A., Philips, W., & Rutter, M. (1996). Autism: Towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. *Journal of Child Psychology and Psychiatry, 37,* 89–126.

Bristol, M., Cohen, J., Castello, J., Denzla, M., Eckberg, J., Kallen, R., Kraemer, C., Lord, C., Maurer, R., Mcilvane, J., Miushew, N., Sigman, M., & Spencer, M. (1996). State of the Science in autism: Report to the National Institutes of Health. *Journal of Autism and Developmental Disorders, 26,* 121–154.

Bronstein, J. M., Kozak, C. A., Chen, X.-N., Wu, S., Danciger, M., Korenberg, J. R., & Farber, D. B. (1996). Chromosomal localization of murine and human oligodendrocyte-specific protein genes. *Genomics, 34,* 255–257.

Bronstein, J. M., Tiwari-Woodruff, S., Buznikov, A. G., & Stevens, D. B. (2000). Involvement of OSP/claudin-11 in oligodendrocyte membrane interactions: Role in biology and disease. *Journal of Neuroscience Research, 59,* 706–711.

Bundey, S., Hardy, C., Vickers, S., Kilpatrick, M. W., & Corbett, J. A. (1994). Duplication of the 15q11–13 region in a patient with autism, epilepsy and ataxia. *Developmental Medicine and Child Neurology, 36,* 736–742.

Carpentieri, S., Morgan, B. S. (1996). Adaptative and intelectual functioningh in autistic and nonautistic retarded children. *Journal of Autism and Developmental Disorders, 26,* 611–620.

Carratalá, F., Galán, F., Moya, M., Estivill, X., Pritchard, M., Llevadot, R., Nada, M., & Gratacós, M. (1998). A patient with autistic disorder and a 20/22 chromosomal translocation. *Developmental Medicine and Child Neurology, 40,* 492–495.

Coy, J. F., Sedlacek, Z., Bachner, D., Hameister, H., Joos, S., Lichter, P., & Delius, H. (1995). Highly conserved 3′ UTR and expression pattern of FXR1 points to a divergent gene regulation of FXRI and FMRI. *Human Molecular Genetics, 4,* 2209–2218.

Davis, R. L., Shrimpton, A. E., Holohan, P. D., Bradshaw, C., Feiglin, D., Collins, G. H., Sonderegger, P., Kinter, J., Becker, L. M., Lacbawan, F., Krasnewich, D., Muenke, M., Lawrence, D. A., Yerby, M. S., Shaw, C. M., Gooptu, B., Elliott, P. R., Finch, J. T., Carrell, R. W., & Lomas, D. A. (1999). Familial dementia caused by polymerisation of mutant neuroserpin. *Nature, 401,* 376–379.

Feder, J. N., Li, L., Jan, L. Y., & Jan, Y. N. (1994). Genomic cloning and chromosomal localization of HRY, the human homolog of the *Drosophila* segmentation gene, *hairy*. *Genomics, 20,* 56–61.

Filipek, A. P., Accardo, P. J., Baranek, G. T., Cook, E. H., Dawson, G., Gordon, B., Gravel, J. S., Johnson, C. P., Kallen, R. J., Levy, S. E., Minshew, N. J., Prizant, B. M., Rapin, I., Rogers, S. J., Stone, W. L., Teplin, S., Tuchman, R. F., & Volkmar, F. R. (1999). The screening and diagnosis of autistic spectrum disorders. *Journal of Autism and Developmental Disorders, 29,* 439–484.

Folstein, S. E., & Mankoski, R. E. (2000). Chromosome 7q: Where autism meets language disorders? *American Journal Human Genetics, 67,* 278–281.

Fombonne, E. (1998). Epidemiological surveys of autism. In F. R. Volkmar (Ed.), *Autism and Pervasive Developmental Disorders,* (pp. 32–63). Cambridge, Cambridge University Press.

Gillberg, C. (1998). Chromosomal disorders and autism. *Journal of Autism and Developmental Disorders, 28,* 415–425.

Gillberg, C., & Coleman, M. (1992). *The biology of autistic syndromes* (2nd ed). London: Mackeith Press

Gillberg, C., & Coleman, M. (1996). Autism and medical disorders: A review of the literature. *Developmental Medicine and Child Neurology, 38,* 191–202.

Ghaziuddin, M., & Burmeister, M. (1999). Deletion of chromosome 2q37 and autism: A distinct subtype? *Journal of Autism and Developmental Disorders, 29,* 259–263.

Goizet, C., Excoffier, E., Taine, L., Taupiac, E., Moneim, A., Arveiler, B., Bouvard, M., & Lacomb, D. (2000). Case with autistic syndrome and chromosome 22q13.3 deletion detected by FISH. *American Journal of Medical Genetics (Neuropsychiatric Genetics), 96,* 839–844.

Griffiths, R. (1984). *The abilities of young children*. London: University of London Press.

Hashimoto, T., Tayama, M., Miyazaki, M., Murakawa, K., & Kuroda, Y. (1993). Brainstem and cerebellar vermis involvement in autistic children. *Journal Child Neurol, 8,* 149–153.

Hashimoto, T., Tayama, M., Murakawa, K., Yoshimoto, T., Miyazaki, M., Harada, M., & Kuroda, Y. (1995). Developmental of brainstem and cerebellum in autistic patients. *Journal of Autism and Developmental Disorders, 25,* 1–18.

IMGSAC (1998). A full genome screen for autism with evidence for linkage to a region on chromosome 7q. *Human Molecular Genetics, 7,* 571–578.

IMGSAC (2001). Further characterization of the autism susceptibility locus AUTSI on chromosome 7q. *Human Molecular Genetics, 10,* 973–982.

Konstantareas, M. M., & Homatidis, S. (1999). Chromosomal abnormalities in a series of children with autistic disorder. *Journal of Autism and Developmental Disorders, 29,* 275–285.

Kroisel, P. M., Petek, E., & Wagner, K. (2000). Skin pigmentary anomalies in a mosaic form of partial tetrasomy 3q. *Journal of Medical Genetics, 37,* 723–725.

Lai, C., Fisher, S. E., Hurst, J. A., Levy, E. R., Hodgson, S., Fox, M., Jeremiah, S., Povey, S., Jamison, C., Green, E. D., Vargha-Khadem, F., & Monaco, A. P. (2000). The SPCHI region on human 7q31: Genomic characterization of the critical interval and localization of translocations associated with speech and language disorders. *American Journal Human Genetics, 67,* 357–368.

Lauritsen, M., Mors, O., Mortesen, B. P., & Ewald, H. (1999). Infantile autism and associated autosomal chromosome abnormalities: A register-based study and a literature survey. *Journal of Child Psychology and Psychiatry, 40,* 335–345.

Leiter, R. (1997). *The Leiter International Performance Scale-Revised*. Chicago: Stoeling.

Lord, C., Rutter, M., & LeCouteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 24,* 659–685.

Lue, R. A., Marfatia, S. M., Branton, D., & Chishti, A. H. (1994). Cloning and characterization of hdlg: The human homologue of the *Drosophila* discs large tumor suppressor binds to protein 4.1. *Proceedings of the National Academy of Sciences, 91,* 9818–9822.

O'Brien, G. (2000) Learning disability. In C. Gillberg & G. O'Brien (Eds.), *Developmental Disabilities and Behaviour* (pp. 12–26). London.

Philippe, A., Martinez, M., Guilloud-Bataille, M., Gillberg, C., Rastam, M., Sponheim, E., Coleman, M., Zappella, M., Aschauer,

H., Malldergerme, L., Penet, C., Feingold, J., Brice, A., Leboyer, M., & PARISS (1999). Genome-wide scan for autism susceptibility genes. *Human Molecular Genetics, 8,* 805–812.

Portnoi, F., Boutchnet, S., Bouscarat, F., Morlier, G., Nizard, S., Dersatkissian, H., Crickx, B., Nouchy, M., Taillemite, J. L., & Belaich, S. (1998). Skin pigmentary anomalies and mosaicism for an accentric marker chromosome originating from 3q. *Journal of Medical Genetics, 36,* 246–250.

Sandberg, D. A., Nydén, A., & Hjelmquist, E. (1993). The cognitive profile in infantile autism: A study of 70 children and adolescents using the Griffiths Mental Development Scale. *British Journal of Psychology, 84,* 365–373.

Schopler, E., Reichler, R. J., Renner, B. R. (1988). The Childhood Autism Rating Scale (CARS). Los Angeles: Western Psychological Services.

Schopler, E., Reichler, R. J., Bashford, A., Lansing, M. D., Marcus, L. M. (1990). Psychoeducational Profile revised. Austin, TX: Pro- Ed.

Schrimpf, S. P., Bleiker, A. J., Brecevic, L., Kozlov, S. V., Berger, P., Osterwalder, T., Krueger, S. R., Schinzel, A., & Sonderegger, P. (1997). Human neuroserpin (PI12): cDNA cloning and chromosomal location to 3q26. *Genomics, 40,* 55–62.

Seshadri, K., Wallerstein, R., & Burack, G. (1992). 18q-Chromosomal abnormality in a phenotypically normal 21/2 year old male with autism. *Developmental Medicine and Child Neurology, 34,* 1005–1009.

Siomi, M. C., Siomi, H., Sauer, W. H., Srinivasan, S., Nussbaum, R. L., & Dreyfuss, G. (1995). FXR1, an autosomal homolog of the fragile X mental retardation gene. *EMBO Journal, 14,* 2401–2408.

Siomi, M. C., Zhang, Y., Siomi, H., & Dreyfuss, G. (1996). Specific sequences in the fragile X syndrome protein FMRI and the FXR proteins mediate their binding to 60S ribosomal subunits and the interactions among them. *Molecular Cell Biology, 16,* 3825–3832.

Smith, M., Filipek, A. P., Wu, C., Bocian, M., Hakim, S., Modahl, C., & Spence, M. A. (2000). Analysis of a I-megabase deletion in 15q22-q23 in an autistic patient: Identification of candidate genes for autism and of homologous DNA segments in 15q22-q23 and 15q11-q13. *American Journal of Medical Genetics (Neuropsychiatric Genetics), 96,* 765–770.

Sparrow, S. S., Balla, D. A., & Cicchetti, D. V. (1984). Vineland adaptative Behaviour Scales: Interview edition, Survey form. Circle pines, MN: American Guidance Service.

Tamagnone, L., Artigiani, S., Chen, H., He, Z., Ming, G., Song, H., Chedotal, A., Winberg, M. L., Goodman, C. S., Poo, M., Tessier-Lavigne, M., & Comoglio, P. M. (1999). Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vertebrates. *Cell, 99,* 71–80.

Vincent, J. B., Herbrick, J. A., Gurling, H. M. D., Bolton, P.F., Roberts, W., & Scherer, S. W. (2000). Identification of a novel gene on chromosome 7q31 that is interrupted by a translocation breakpoint in an autistic individual. *American Journal of Human Genetics, 67,* 510–514.

Wassink, T. H., Piven, J., Sheffield, V. C., Folstein, S. E., Haines, J. L., & Patil, S. R. (1999). Chromosomal abnormalities in autism. *The American Journal of Human Genetics, 65,* A362.