

# A Complex Chromosome 7q Rearrangement Identified in a Patient With Mental Retardation, Anxiety Disorder, and Autistic Features

Johannes G. Dauwerse,<sup>1\*</sup> Claudia A. Ruivenkamp,<sup>1</sup> Kerstin Hansson,<sup>1</sup> Godfried M. Marijnissen,<sup>2</sup> Dorien J.M. Peters,<sup>1</sup> Martijn H. Breuning,<sup>1</sup> and Yvonne Hilhorst-Hofstee<sup>1</sup>

<sup>1</sup>Center for Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands

<sup>2</sup>Academic Center Curium, Oegstgeest, The Netherlands

Received 20 April 2009; Accepted 2 November 2009

We have characterized a *de novo* complex rearrangement of the long arm of chromosome 7 in a female patient with moderate mental retardation (MR), anxiety disorder, and autistic features. G-banding suggested a *de novo* paracentric inversion 46,XX,inv-(7)(q31.3q34). However, SNP-array analysis, showed a  $\pm 10$  Mb, 7q21.11–q21.3 deletion in the paternal chromosome. Subsequent FISH analysis with BAC/PAC clones in the 7q21–q35 region confirmed this deletion. However, the expected paracentric inversion turned out to be an intra-chromosomal insertion of the 7q31.31–q35 fragment into band 7q21.3, disrupting the predicted gene *C7orf58* in band 7q31.31. Seven other patients have been previously reported with a deletion of 7q21.1–q21.3. Although there is an overlap in phenotype between our patient and these patients, none of them has been described with anxiety disorder and/or autistic features. Therefore we suggest that disruption of the *C7orf58* gene might contribute to the anxiety disorder, and autistic features in our patient. © 2010 Wiley-Liss, Inc.

**Key words:** mental retardation; anxiety disorder; autistic features; 7q; deletion; intra-chromosomal insertion

## INTRODUCTION

Interstitial deletions in different parts of the proximal long arm of chromosome 7 are frequently reported and have been associated with various clinical manifestations. Deletions in band 7q11.23 have been found in patients with Williams–Beuren syndrome (WBS [OMIM 194050]) deleting a contiguous set of genes resulting in a characteristic phenotype. A subset of these patients, with a severe form of WBS, including infantile spasms, carry larger deletions at 7q11.23–q21.11. These deletions hemizygotously disrupt the *MAGI2* gene [Marshall et al., 2008]. In the neighboring chromosomal region, 7q21.2–q22.1, deletions have been found in patients with split hand/split foot malformation (SHFM1 [OMIM 183600]) with or without sensorineural hearing loss (SHFM1D [OMIM 220600]).

In addition, a third group of patients with deletions partly overlapping with the deletions found in WBS and SHFM1 patients

### How to Cite this Article:

Dauwerse JG, Ruivenkamp CA, Hansson K, Marijnissen GM, Peters DJM, Breuning MH, Hilhorst-Hofstee Y. 2010. A complex chromosome 7q rearrangement identified in a patient with mental retardation, anxiety disorder, and autistic features.

Am J Med Genet Part A 152A:427–433.

has been presented in the literature. To date seven patients with similar clinical features with deletions in 7q21.1–21.3 have been reported [Ostrer et al., 1984; Fryns et al., 1987; Nunes et al., 1994; Haberlandt et al., 2001; DeBerardinis et al., 2003; Courtens et al., 2005; Manguoglu et al., 2005]. The features include mental retardation, pre- and postnatal growth deficiency, early infancy feeding problems, hypotonia, mild facial dysmorphism, hernia, high cleft palate, abnormal EEG, and/or seizures, microcephaly and hearing loss. Two of the patients also presented with split hand/split foot malformation and another patient [DeBerardinis et al., 2003] has been reported with myoclonic dystonia (DYT11 [OMIM 159900]), carrying a deletion of 9–15 Mb, deleting the  $\epsilon$ -sarcoglycan gene (*SGCE*). In addition Asmus et al. [2007] reported on two DYT11 patients with deletions of 1.63 and 4.99 Mb including the *SGCE* gene.

In this study we report on a girl with a *de novo* interstitial deletion at 7q21.1–q21.3 together with an intra-chromosomal insertion, detected with single nucleotide polymorphism (SNP) array and fluorescence in situ hybridization (FISH) analysis. The

\*Correspondence to:

Johannes G. Dauwerse, Department of Human Genetics, Center for Human and Clinical Genetics, Leiden University Medical Center (LUMC), P.O. Box 9600, 2300 RC Leiden, The Netherlands.

E-mail: dauw@lumc.nl

Published online 15 January 2010 in Wiley InterScience (www.interscience.wiley.com)

DOI 10.1002/ajmg.a.33203

genotype and phenotype of this patient are compared with previously reported patients with a comparable 7q21.1–q21.3 deletion.

## CLINICAL REPORT

The index patient is a now 14 years old girl. She is the second child of a 33-year-old healthy mother and the first child of a 32-year-old healthy father. Her 7-year older half sister was healthy. The pregnancy was complicated by vaginal bleeding from week 7 till 34 and amnion leakage at 32 weeks of gestation. Breech delivery found place at 42 weeks of gestation. Although the amniotic fluid was meconium stained the APGAR score was 10 after 1 min and there were no signs of asphyxia. Her birth weight was 3,040 g. Feeding problems occurred during the first weeks of life for which she was hospitalized for 1 week.

She was referred to our department for dysmorphic features at the age of 11 weeks. At that time her development was adequate. Neurologic examination was normal. She made good contact and had no head lag. She was treated by splints for hip dysplasia. Her length was 60 cm (mean) and skull circumference was 37 cm ( $-2$  SD). Her weight was on the  $-1.5$  SD and she had a tented mouth, high palate, a simple formed left lop ear and dysplastic right ear (Fig. 1A,B). The thumbs were proximally implanted (Fig. 1C), she had bilateral single palmar creases and a sacral dimple. She also had small palpebral fissures, scoliosis and long halluxes (Fig. 1D).

On follow-up at 10.5 years of age her length and skull circumference were on the  $-1$  and  $-2.5$  SD, respectively. The girl had moderate mental retardation with autistic features; ritualized and repetitive behavior, and periods of extreme stillness. She could not be tested with the common autism behavior tests (Autism Diagnostic Interview-Revised (ADI-R), Childhood Autism Rating Scale (CARS), Pre-Linguistic Autism Diagnostic Observation Schedule (PL-ADOS)) due to her emotional state. She had delayed speech and suffered from a severe anxiety disorder, more precisely described as a disturbance in the anxiety regulation, with introverted, still, fearfully and panicky behavior outdoors, and intense grief and anger indoors. She had a coordination disorder with jerky movements and hypotonia. Her mean IQ was 48. An EEG revealed an abnormally slow background with frequent spikes and spike and wave complexes especially in the occipital region without clinical epileptic seizures.

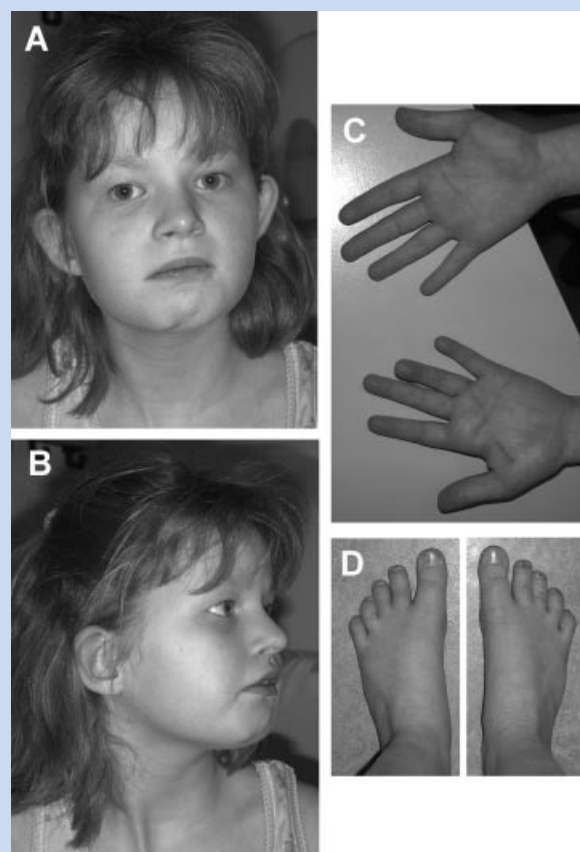
## MATERIALS AND METHODS

### Cytogenetic Analysis

Conventional chromosome analysis was performed on phytohemagglutinin stimulated lymphocytes from peripheral blood cultures using GTG-banding according to standard protocols.

### FISH Analysis

One and two color fluorescence in situ hybridization (FISH) analysis was performed on metaphase spreads of the patient according to standard techniques [Dauwerse et al., 1992]. Bacterial artificial clones (BAC) and P1 artificial clones (PAC) were selected



**FIG. 1.** The patient at the age of 10 years. **A:** Frontal view. **B:** Lateral view showing the tented mouth, low set ears, a simple formed lop ear on the left site, dysplastic ear on the right site, and small palpebral fissures. **C:** Patient's hands with proximally implanted thumbs. **D:** Patient's feet showing the long halluxes.

from the Human 1 Mb spaced and tile path clone set of the Ensembl chromosome 7 map (<http://www.ensembl.org>). The BAC and PAC clones were obtained from the Sanger Institute (<http://www.sanger.ac.uk>) and the BACPAC Resource Center (<http://bacpac.chori.org/order.php>). DNA was isolated from the clones using Nucleobond AX100 columns (Machery and Nagel GmbH, Düren, Germany), according to the manufacturer's instructions.

### SNP Array

The Affymetrix GeneChip Human Mapping 262K *NspI* array (Affymetrix, Santa Clara, CA) was used as described previously [Gijsbers et al., 2009].

## RESULTS

### Karyotyping

The results of conventional chromosome analysis on lymphocytes of the patient suggested a de novo paracentric inversion in the long

arm of chromosome 7; 46,XX,inv(7)(q31.3q34), while the parental chromosomes were normal.

## FISH Analysis of the Long Arm of the Derivative Chromosome 7

We performed a detailed FISH analysis with BAC and PAC clones of 7q (Fig. 2). To map the exact breakpoints of the inversion in chromosome 7q, BAC and PAC clones in chromosome bands 7q34–35 and 7q31 were selected for FISH analysis on metaphase chromosomes of the patient (Fig. 2). FISH analysis with clones in band 7q34–35, that is, RP11-282G13 (red) and RP5-819O4 (green), showed the red and green signal in close proximity near the telomere on the normal chromosome 7. On the derivative 7 (der(7)) the green signal was still close to the telomere, but the red signal was repositioned to the middle of the q-arm, suggesting that the breakpoint was situated between these two clones in band 7q34–35 (Fig. 3(3.1A)). FISH analysis with clones in band 7q31, that is, RP11-560I19 and RP5-866N18, resulted in an unexpected hybridization pattern (Fig. 3(3.1B)) compared to the results of conventional karyotyping. On the normal chromosome 7, RP11-560I19 (green) was localized distally from RP5-866N18 (red). Unexpectedly, on the der(7) RP5-866N18 was located closer to the telomere, while RP11-560I19 hybridized closer to the centromere. This result implied that the aberrant banding pattern on the der(7) did not originate from a paracentric inversion because then the 7q31.3–q34 region in the der(7) should have been inverted, changing the order of the clones within this fragment. To test this hypothesis, two probe pairs, RP11-224A1 and RP11-36B6, and RP11-358A10 and RP11-563O5, were hybridized. An identical order of clones was observed on both the normal chromosome 7 and the der(7) (Fig. 3(3.1C,D)) excluding a paracentric inversion and suggesting a more complex rearrangement at der(7).

Additional breakpoint mapping in the 7q31.31–q31.32 region revealed one PAC clone, RP5-1047E14, that showed split signals on the der(7) only, thus spanning the breakpoint in band 7q31 (Figs. Fig. 3(3.2A) and Fig. 4(4.1)). This breakpoint disrupted the predicted gene *C7orf58* that has a transcript of 5,271 bp, consists of 23 exons spanning a genomic region of 310 kb, and codes for a protein of 1,026 aa. This protein is predicted to be a cytoplasmic protein containing a signal peptide and one transmembrane domain (<http://www.ensembl.org>).

In addition, more clones were tested in the 7q34–q35 region to identify the breakpoint. The PAC clone RP4-545C24 encompassed the breakpoint in band 7q35 (Figs. Fig. 3(3.2B) and Fig. 4(4.1)). This PAC clone showed signals near the telomere and in the middle of the long arm of the der(7). Another clone RP11-464H1 also spanned the 7q35 breakpoint. The remaining signal of this clone at the telomeric region of the der(7) was very weak indicating that the breakpoint was in the region between the *NOBOX* and *TPK1* genes (not shown). From this we conclude that no gene seemed to be disrupted by the 7q35 breakpoint.

We could conclude that the der(7) chromosome was not the result of a paracentric inversion but of an intra-chromosomal insertion of fragment 7q31.31–q35 into band 7q21.3 with a deletion of 7q21.11–21.3 at the insertion site (Figs. 3 and Fig. 4(4.1)).

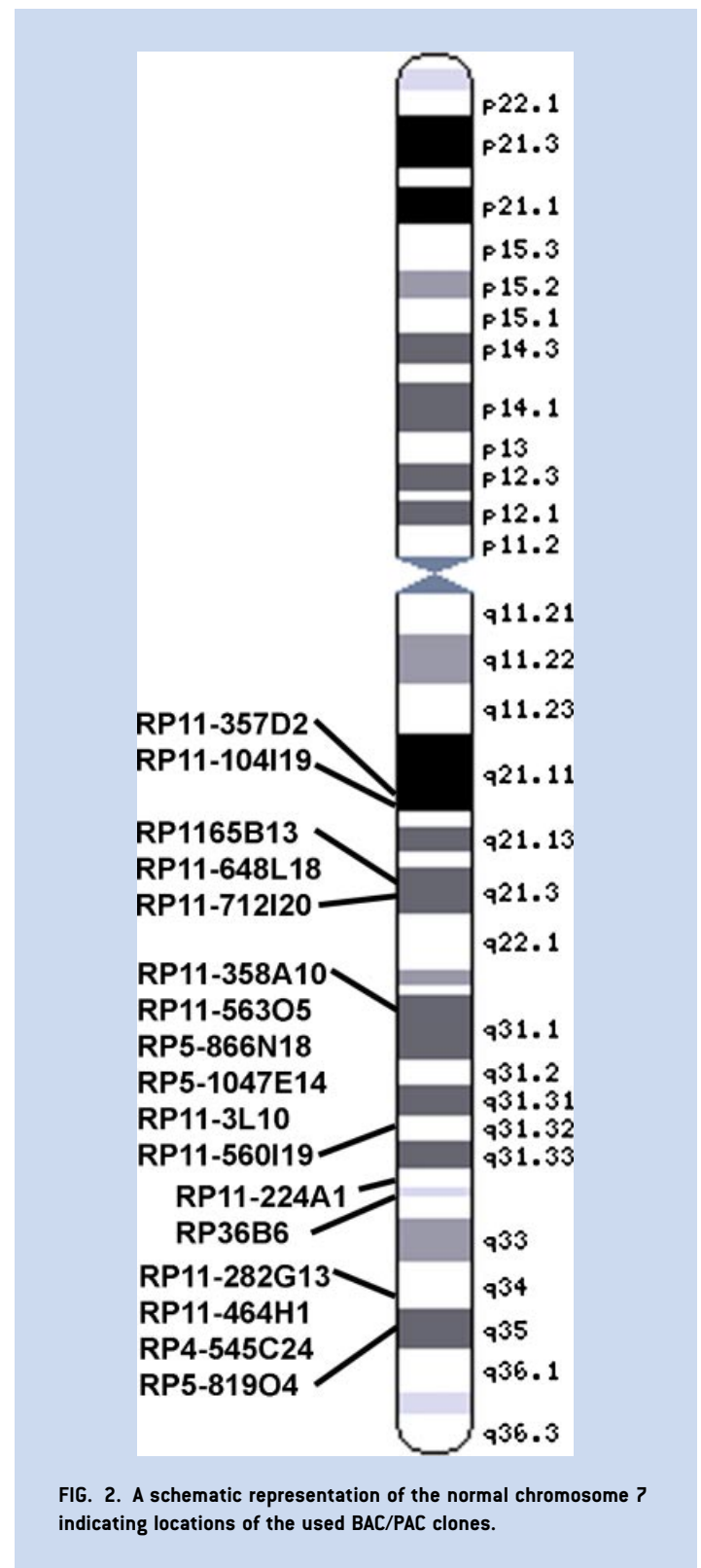
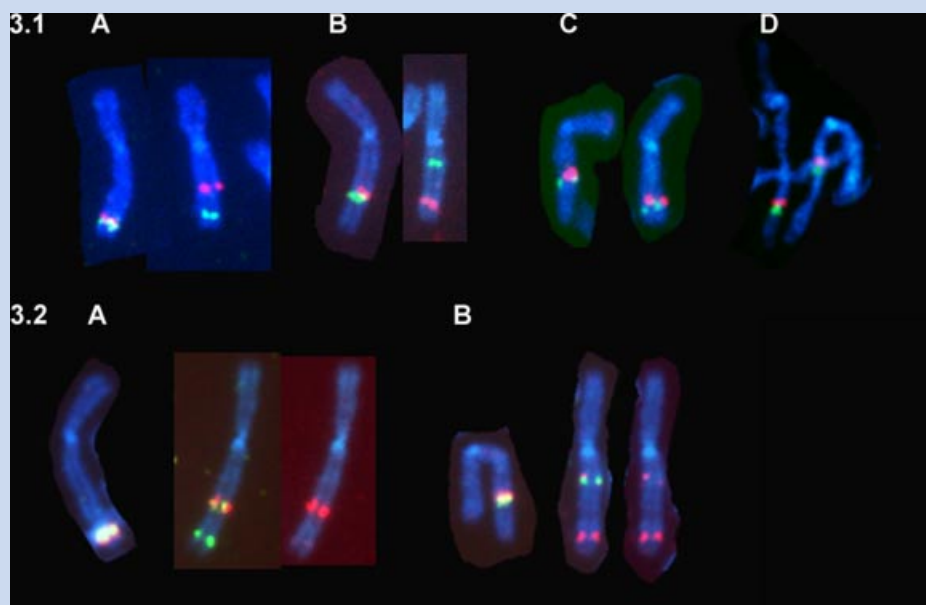


FIG. 2. A schematic representation of the normal chromosome 7 indicating locations of the used BAC/PAC clones.

## SNP-Array Analysis

The Affymetrix GeneChip Human Mapping 262K *NspI* SNP array detected a  $\pm 10$  Mb deletion in the long arm of chromosome 7, from band 7q21.11 to band 7q21.3 (Fig. 4(4.2)). The breakpoint



**FIG. 3.** >3.1: Two color FISH analysis on metaphase chromosomes of the patient. At the left side the normal chromosome 7 and at the right side the der(7), with; (A) RP11-282G13 (red) and RP5-81904 (green), in band 7q34–35, showing on the der(7) the green signal near the telomere and the red signal is repositioned to a more proximal position, indicating that the breakpoint is located between these two clones, (B) RP5-866N18 (red) and RP11-560I19 (green), in band 7q31, RP11-560I19, on the normal chromosome 7, is localized distally from RP5-866N18 on 7q. On the der(7), however, RP11-560I19 hybridizes closer to the centromere and RP5-866N18 more towards the telomere, (C) RP11-224A1 (red) and RP11-36B6 (green) hybridizing on the normal chromosome 7 in band 7q32. The order of the clones is the same for the normal chromosome 7 and der(7), but on the der(7) they are positioned more distally, (D) RP11-358A10 and RP11-56305 hybridizing on the normal chromosome 7 in band 7q31. The order of clones is the same for the normal chromosome 7 and the der(7), but on the der(7) they are positioned more proximally. 3.2: Two color FISH analysis on metaphase chromosomes of the patient. A: RP5-1047E14 (red) and RP11-3L10 (green) with only RP5-1047E14 spanning the 7q31.31 breakpoint. Left, the normal chromosome 7, middle, the der(7) with signals for both clones, right the der(7) with only the red signal of RP5-1047E14 with clear splitting of the signal. B: RP11-464H1 (red) and RP4-545C24 (green) clones that both span the 7q35 breakpoint. Left, the normal chromosome 7, middle, the der(7) with signals for both clones with clear splitting of the green signal, right, the der(7) with only the red signal for RP11-464H1 showing very weak signals near the telomere. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

in band 7q21.11 was located between the last present SNP rs12540580 (85,813,502 bp) and the first deleted SNP rs7384064 (85,838,435 bp), and the breakpoint in band 7q21.3 was located between the last deleted SNP rs17166393 (94,106,189 bp) and the first present SNP rs6465422 (94,149,236 bp). The deleted region contained approximately 49 genes.

Array analysis of the parents showed no abnormalities. The SNP genotype data revealed that the deletion occurred in the paternal chromosome 7 (data not shown). The deletion was confirmed by FISH analysis with BAC clones (Fig. 2).

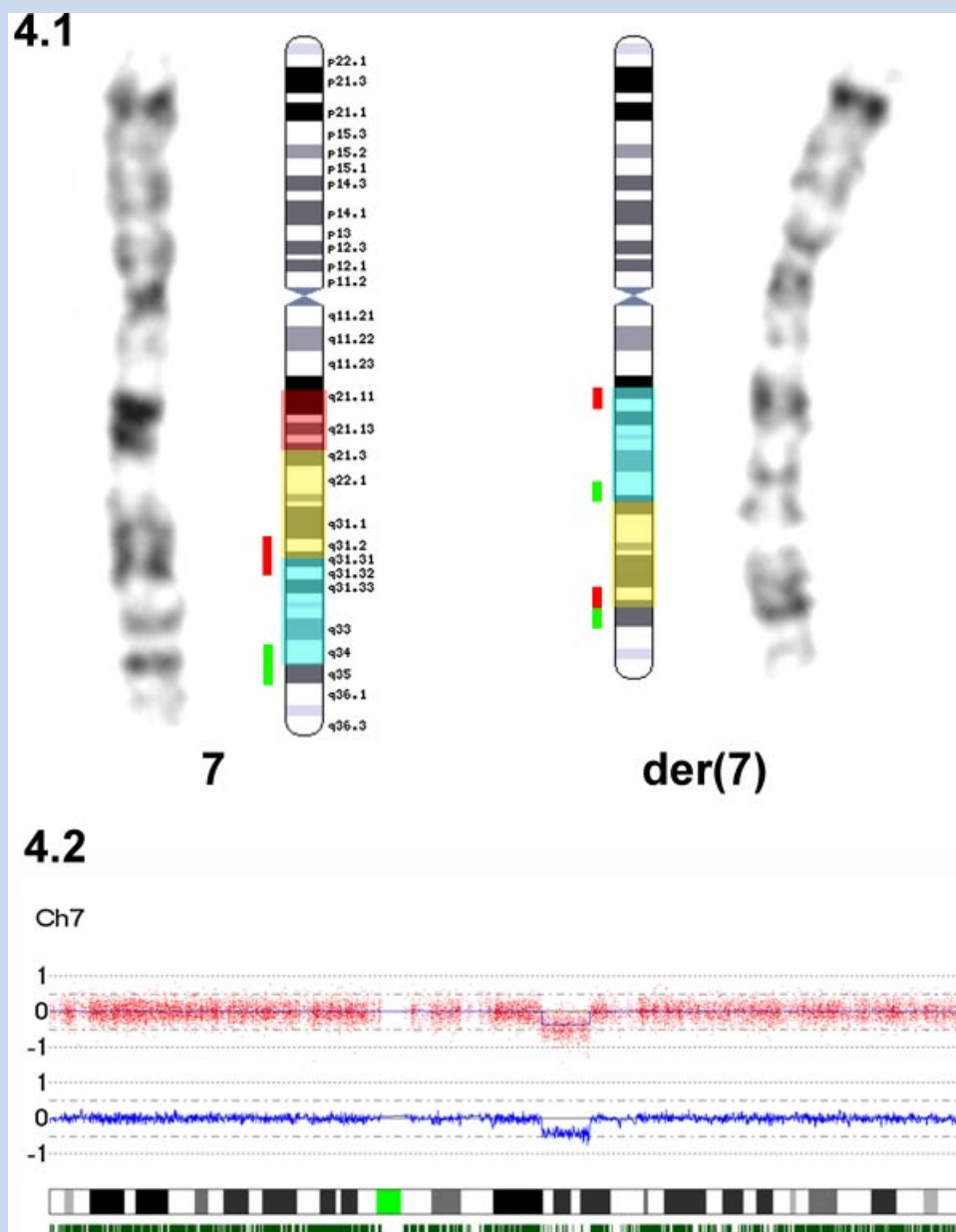
## DISCUSSION

We present a patient with mental retardation and autistic behavior complicated by a severe anxiety disorder and dysmorphic features. Initial karyotyping suggested a de novo paracentric inversion in the long arm of chromosome 7, with the breakpoints in q31.3 and q34. FISH analysis with BAC and PAC clones revealed however a more complex rearrangement of 7q. Clones were detected spanning two breakpoints in bands 7q31.31 and 7q35. Additional SNP

array- and FISH analysis demonstrated a deletion of the region 7q21.11–7q21.3.

The proposed mechanism for formation of the der(7) chromosome is an intra-chromosomal insertion of fragment 7q31.31–q35 into band 7q21.3, followed by a deletion of 7q21.11–q21.3 at the insertion site. The der(7) is depicted in Figure 4 (Fig 4.1). The revised karyotype is 46,XX,der(7)del(7)(q21.11q21.3)ins(7)(q21.3q31.31q35).

To our knowledge this is the eighth case with a de novo interstitial deletion of 7q21.1–q21.3 [Ostrer et al., 1984; Fryns et al., 1987; Nunes et al., 1994; Haberlandt et al., 2001; DeBerardinis et al., 2003; Courtens et al., 2005; Manguoglu et al., 2005]. Two smaller deletions within this region, from 7q21.2 to 7q21.3, have been reported in two patients with myoclonic dystonia (DYT11) [Asmus et al., 2007]. In four of these previously reported cases (reviewed by Courtens et al. [2005], DeBerardinis et al. [2003]) the origin of inheritance of the deletion chromosome was investigated and was paternal, as in our patient. Parental imprinting of genes on chromosome 7 is often found. It has been associated with Silver-Russell syndrome (SRS [OMIM180860]), 7p11.2, and maternal uniparental disomy for chromosome 7 (matUPD7). Courtens et al. [2005] found resemblance between the clinical characteristics of patients



**FIG. 4.** 4.1: A schematic representation of the chromosome 7 rearrangement. A partial karyogram and ideogram of both chromosomes 7 of the patient, with the der(7) on the right. The red box depicts the deleted 7q21.1–q21.3 region. The yellow box depicts the 7q31.31–q35 fragment, which is inserted in 7q21.3. The blue box delineates the 7q21.3–q31.31 region. The red bar depicts RP5-1047E14, spanning the 7q31.31 breakpoint and therefore giving two signals on the der(7). The green bar depicts RP4-545C24 spanning the 7q35 breakpoint and therefore giving two signals on the der(7). 4.2: Partial molecular karyotype of the imbalance on chromosome 7 in our patient detected with the GeneChip Human Mapping 262K *NspI* SNP array. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

with a maternal monosomy for the 7q21.1–q21.3 region and patients with Silver–Russell syndrome and matUPD7 suggesting that imprinting of one or more genes in the 7q21.1–q21.3 region contributes to these phenotypes.

The best documented case that was examined with molecular techniques is the one described by Courtens et al. [2005]. The authors report on a female with a de novo 16.77 Mb deletion of 7q21.1–q21.3 of paternal origin. We here describe a female patient,

with a de novo  $\pm 10$  Mb deletion of 7q21.1–q21.3, also of paternal origin. Both patients have approximately the same distal deletion breakpoint. The proximal breakpoint in our patient however is  $\pm 6.5$  Mb more distal to the proximal breakpoint of the patient described by Courtens et al. [2005]. Phenotypically these two patients also have much in common. Overlapping clinical features are mental retardation, hypotonia, abnormal EEG, microcephaly, low set ears, small palpebral fissures, sacral dimple, and a high

palate. Our patient, however, has had no pre- or postnatal growth retardation, which is together with MR and microcephaly, one of the three most important characteristics of the group of seven reported patients with a 7q21.1–q21.3 deletion. Another striking difference with our patient is that for none of these seven patients, with a de novo 7q21.1–q21.3 deletion, autistic features and/or anxiety disorder were reported. This suggests an involvement of a gene or genes disrupted by the breakpoints of the intra-chromosomal insertion, in bands 7q31.31 and 7q35, in the phenotype of our patient. Only the breakpoint in band 7q31.31 disrupts a gene, the *C7orf58* gene. Disruption of the *C7orf58* gene might contribute to the anxiety disorder and the autistic features of our patient.

A number of genetic studies have provided evidence for a susceptibility to autism locus (AUTS) on chromosome 7. Linkage and association studies depict numerous loci at 7q31 (AUTS9) [International Molecular Genetic Study of Autism Consortium, 1998; Folstein and Mankoski, 2000; Gutknecht, 2001; Bonora et al., 2005] and at 7q35 (AUTS15) [Alarcon et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008]. Although chromosome 7 rearrangements in autistic patients involving band 7q31 and 7q35 are rare, one autistic patient with a complex rearrangement t(7;13)(q31.3;q21.3), inv(11)(p15.3p15.5) has been reported [Gribble et al., 2005] for which the 7q breakpoint falls in BAC clone RP11-384A20. This clone maps around 700 kb distally to our patients' 7q31.31 breakpoint, indicating that in contrast to our patient, the breakpoint does not disrupt the *C7orf58* gene. Other autistic individuals have been described with a t(7;13)(q31.2;q21), that disrupts the *ST7* gene (*RAY1*) [Vincent et al., 2000] and an inv(7)(p12.2q31.3) [Warburton et al., 2000] with the 7q breakpoint between CFTR and D7S643, a marker inside *C7orf58*, both breakpoints within 4 Mb of the position where *C7orf58* is situated. Other 7q31 breakpoints and interstitial deletions involving this region are described in patients with speech-language disorder (SPCH1 [OMIM 602081]) also called developmental verbal dyspraxia (DVD). In these patients, absence of a paternally inherited *FOXP2* gene plays an important role [Fisher et al., 1998; Zeeman et al., 2006], but only some of them present with autistic features, and none of them are reported with anxiety disorder. Therefore, not all patients with a deletion of *C7orf58* show autistic features or anxiety disorder.

Another possible explanation for the anxiety disorder in our patient is the deletion of the *SGCE* gene, which was reported to be involved in DYT11, and although our patient did not present with a typical DYT11 phenotype including dystonia, but jerky movements have been observed. A small number of DYT11 patients, however, have been reported with anxiety and/or panic attacks [Klein and Ozelius, 2002; Saunders-Pullman et al., 2002]. Asmus et al. [2002], for example, reported on five affected members of three families that had a history of panic attacks, depression, and agoraphobia. Therefore, we cannot exclude that the severe anxiety in our patient is caused by the deletion of the *SGCE* gene.

With the introduction of high-resolution genome analysis techniques, like SNP arrays, genotype-phenotype correlations will further improve. Analysis of 7q21.1–q21.3 deletion patients with these techniques will lead to a more precise mapping of the deletion boundaries. The differences in presence or absence of particular genes within the deletions in these patients and

their differences in phenotype could then be more accurately correlated.

With further investigations into the role of the *C7orf58* gene in autism and anxiety disorder, the role of this gene in autistic features and/or anxiety disorder phenotype of our patient might be more clear cut.

## ACKNOWLEDGMENTS

We express our sincere gratitude to the patient's parents for their participation in this study. We also thank W.M.C. van Roon-Mom for critical review of the manuscript.

## REFERENCES

- Alarcon M, Abrahams BS, Stone JL, Duvall JA, Perederiy JV, Bomar JM, Sebat J, Wigler M, Martin CL, Ledbetter DH, Nelson SF, Cantor RM, Geschwind DH. 2008. Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. *Am J Hum Genet* 82:150–159.
- Arking DE, Cutler DJ, Brune CW, Teslovich TM, West K, Ikeda M, Rea A, Guy M, Lin S, Cook EH, Chakravarti A. 2008. A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. *Am J Hum Genet* 82:160–164.
- Asmus F, Zimprich A, Tezenas Du MS, Kabus C, Deuschl G, Kupsch A, Ziemann U, Castro M, Kuhn AA, Strom TM, Vidailhet M, Bhatia KP, Durr A, Wood NW, Brice A, Gasser T. 2002. Myoclonus-dystonia syndrome: Epsilon-sarcoglycan mutations and phenotype. *Ann Neurol* 52:489–492.
- Asmus F, Hjermland LE, Dupont E, Wagenstaller J, Haberlandt E, Munz M, Strom TM, Gasser T. 2007. Genomic deletion size at the epsilon-sarcoglycan locus determines the clinical phenotype. *Brain* 130: 2736–2745.
- Bakkaloglu B, O'Roak BJ, Louvi A, Gupta AR, Abelson JF, Morgan TM, Chawarska K, Klin A, Ercan-Sencicek AG, Stillman AA, Tanriover G, Abrahams BS, Duvall JA, Robbins EM, Geschwind DH, Biederer T, Gunel M, Lifton RP, State MW. 2008. Molecular cytogenetic analysis and resequencing of contactin associated protein-like 2 in autism spectrum disorders. *Am J Hum Genet* 82:165–173.
- Bonora E, Lamb JA, Barnby G, Sykes N, Moberly T, Beyer KS, Klauck SM, Poustka F, Bacchelli E, Blasi F, Maestrini E, Battaglia A, Haracopos D, Pedersen L, Isager T, Eriksen G, Viskum B, Sorensen EU, Brondum-Nielsen K, Cotterill R, Engeland H, Jonge M, Kemner C, Stegghuis K, Scherpenisse M, Rutter M, Bolton PF, Parr JR, Poustka A, Bailey AJ, Monaco AP. 2005. Mutation screening and association analysis of six candidate genes for autism on chromosome 7q. *Eur J Hum Genet* 13:198–207.
- Courtens W, Vermeulen S, Wuyts W, Messiaen L, Wauters J, Nuytinck L, Peeters N, Storm K, Speleman F, Nothen MM. 2005. An interstitial deletion of chromosome 7 at band q21: A case report and review. *Am J Med Genet Part A* 134A:12–23.
- Dauwerse JG, Jumelet EA, Wessels JW, Saris JJ, Hagemeyer A, Beverstock GC, Van Ommen GJB, Breuning MH. 1992. Extensive cross-homology between the long and short arm of chromosome 16 may explain leukemic inversions and translocations. *Blood* 79:1299–1304.
- DeBerardinis RJ, Conforto D, Russell K, Kaplan J, Kollros PR, Zackai EH, Emanuel BS. 2003. Myoclonus in a patient with a deletion of the epsilon-sarcoglycan locus on chromosome 7q21. *Am J Med Genet Part A* 121A:31–36.

- Fisher SE, Vargha-Khadem F, Watkins KE, Monaco AP, Pembrey ME. 1998. Localisation of a gene implicated in a severe speech and language disorder. *Nat Genet* 18:168–170.
- Folstein SE, Mankoski RE. 2000. Chromosome 7q: Where autism meets language disorder? *Am J Hum Genet* 67:278–281.
- Fryns JP, Kleczkowska A, Van den Berghe H. 1987. Moderate mental retardation and mild dysmorphic syndrome in proximal 7q interstitial deletion. *Ann Genet* 30:111–112.
- Gijsbers AC, Lew JY, Bosch CA, Schuurs-Hoeijmakers JH, van Haeringen A, den Hollander NS, Kant SG, Bijlsma EK, Breuning MH, Bakker E, Ruivenkamp CA. 2009. A new diagnostic workflow for patients with mental retardation and/or multiple congenital abnormalities: Test arrays first. *Eur J Hum Genet* 17:1394–1402.
- Gribble SM, Prigmore E, Burford DC, Porter KM, Ng BL, Douglas EJ, Fiegler H, Carr P, Kalaitzopoulos D, Clegg S, Sandstrom R, Temple IK, Youings SA, Thomas NS, Dennis NR, Jacobs PA, Crolla JA, Carter NP. 2005. The complex nature of constitutional de novo apparently balanced translocations in patients presenting with abnormal phenotypes. *J Med Genet* 42:8–16.
- Gutknecht L. 2001. Full-genome scans with autistic disorder: A review. *Behav Genet* 31:113–123.
- Haberlandt E, Loffler J, Hirst-Stadlmann A, Stockl B, Judmaier W, Fischer H, Heinz-Erian P, Muller T, Utermann G, Smith RJ, Janecke AR. 2001. Split hand/split foot malformation associated with sensorineural deafness, inner and middle ear malformation, hypodontia, congenital vertical talus, and deletion of eight microsatellite markers in 7q21.1-q21.3. *J Med Genet* 38:405–409.
- International Molecular Genetic Study of Autism Consortium. 1998. A full genome screen for autism with evidence for linkage to a region on chromosome 7q. *Hum Mol Genet* 7:571–578.
- Klein C, Ozelius LJ. 2002. Dystonia: Clinical features, genetics, and treatment. *Curr Opin Neurol* 15:491–497.
- Manguoglu E, Berker-Karauzum S, BAumer A, Mihci E, Tacoy S, Luleci G, Schinzel A. 2005. A case with de novo interstitial deletion of chromosome 7q21.1-q22. *Genet Couns* 16:155–159.
- Marshall CR, Young EJ, Pani AM, Freckmann ML, Lacassie Y, Howald C, Fitzgerald KK, Peippo M, Morris CA, Shane K, Priolo M, Morimoto M, Kondo I, Manguoglu E, Berker-Karauzum S, Edery P, Hobart HH, Mervis CB, Zuffardi O, Reymond A, Kaplan P, Tassabehji M, Gregg RG, Scherer SW, Osborne LR. 2008. Infantile spasms is associated with deletion of the MAGI2 gene on chromosome 7q11.23-q21.11. *Am J Hum Genet* 83:106–111.
- Nunes ME, Pagon RA, Distechi CJ, Evans JP. 1994. A contiguous gene deletion syndrome at 7q21-q22 and implications for a relationship between isolated ectrodactyly and syndromic ectrodactyly. *Clin Dysmorphol* 3:277–286.
- Ostrer H, Stamberg J, Perinchief P. 1984. Two chromosome aberrations in the child of a woman with systemic lupus erythematosus treated with azathioprine and prednisone. *Am J Med Genet* 17:627–632.
- Saunders-Pullman R, Ozelius L, Bressman SB. 2002. Inherited myoclonus-dystonia. *Adv Neurol* 89:185–191.
- Vincent JB, Herbrick JA, Gurling HM, Bolton PF, Roberts W, Scherer SW. 2000. Identification of a novel gene on chromosome 7q31 that is interrupted by a translocation breakpoint in an autistic individual. *Am J Hum Genet* 67:510–514.
- Warburton P, Baird G, Chen W, Morris K, Jacobs BW, Hodgson S, Docherty Z. 2000. Support for linkage of autism and specific language impairment to 7q3 from two chromosome rearrangements involving band 7q31. *Am J Med Genet* 96:228–234.
- Zeesman S, Nowaczyk MJ, Teshima I, Roberts W, Cardy JO, Brian J, Senman L, Feuk L, Osborne LR, Scherer SW. 2006. Speech and language impairment and oromotor dyspraxia due to deletion of 7q31 that involves FOXP2. *Am J Med Genet Part A* 140:509–514.