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ARTICLE

Familial pericentric inversion of chromosome 18: behavioral abnormalities in patients heterozygous for either the dup(18p)/del(18q) or dup(18q)/del(18p) recombinant chromosome

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We describe a family in which the largest hitherto reported pericentric inversion of chromosome 18, inv(18)(p11.22q23), segregates. Individuals heterozygous for the nonrecombinant inversion were unaffected. However, those heterozygous for either the dup(18p)/del(18q) or dup(18q) /del(18p) recombinant exhibited mild learning difficulty, personality disorders and deficient social behavior in the absence of mental retardation. Of the three family members tested, the behavioral abnormalities were more prominent in the two individuals with the dup(18p)/del(18q) recombinant than in the one with the dup(18q)/del(18p) recombinant. Genetic counseling issues for this family, in particular for the affected, include the enhanced probability of reduced fertility as well as the recurrence risk of the parental inversion equaling 1/2 in surviving offspring. This observation kindles the interest in determining the frequency of subtelomeric rearrangements in individuals with learning difficulty and deficiency in social interaction, phenotypic features often considered to be of multifactorial causation.
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Introduction

Partial duplication–deletion aneusomy of the subtelomeric ends of chromosome 18 due to meiotic recombination within a pericentric inversion remains a rare observation in human beings. Most reports have involved recombinant terminal duplications and deletions large enough to be readily detectable in standard G-banded metaphases, and many have not included any higher-resolution molecular cytogenetic studies.[1–13] The majority of families were ascertained through the familial occurrence of patients with mental retardation/multiple congenital anomaly (MR/MCA) syndromes with features similar to the 18p and/or 18q terminal deletion syndromes. In some of the more severely affected patients, malformations such as lethal congenital adenomatoid malformation of the lung[13] and alobar holoprosencephaly[11] have been reported.

We report the clinical, psychological, cytogenetic and molecular findings in a family in which three members are heterozygous for dup/del-derivative chromosomes resulting from a large pericentric inversion, inv(18)(p11.22q23). The phenotypic consequences in the inversion recombinants were learning deficits, anxiety, depression and

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difficulties in social interaction. It is also interesting to note that the patients exhibited no MR or dysmorphic features.

Materials and methods

Subjects

The proband (see electronic supplementary information, eFigure 1a; Figure 1, VI.1) was the 16-year-old daughter and first child of healthy nonconsanguineous parents. The parents requested clinical and genetic counseling regarding a learning difficulty encountered in her first year of high school and the teachers' recommendation of future vocationally oriented training. She had finished regular grade school with difficulty and delay. The parents were also concerned about the putative cognitive and behavioral resemblance of their daughter to her paternal uncle. Except for a high degree of myopia, for which she wore corrective glasses, the proband had not previously had any significant health problems.

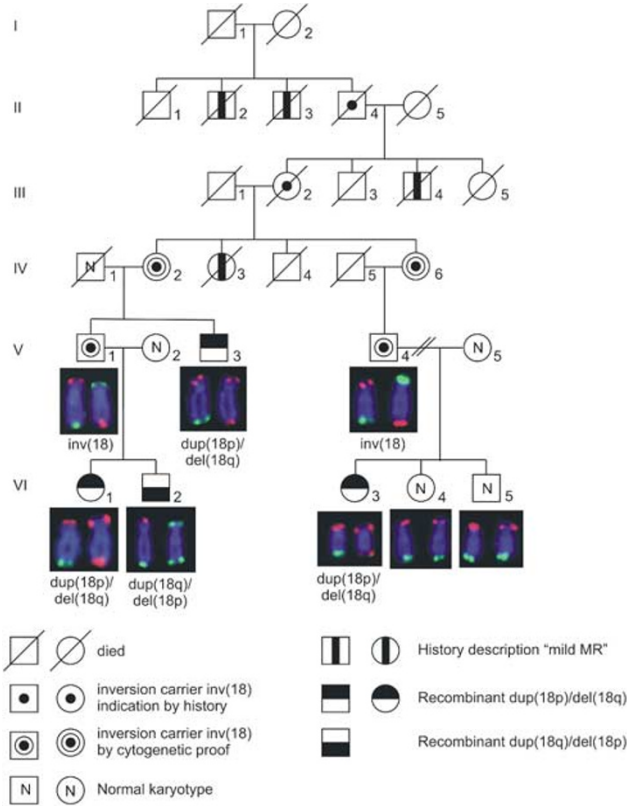

Figure 1 Family pedigree and representative partial FISH karyotypes. FISH performed using locus specific PAC probes: GS-52-M11 (18pter, spectrum orange) and GS-964-M9 (18qter, spectrum green). The normal chromosome 18 is depicted on the left, the aberrant chromosome 18 on the right. Inv(18); V.1 and V.4, recombinant dup(18p)/del(18q) in VI.1, V.3 and VI.3 and dup(18q)/del(18p) in VI.2. The karyotype is normal in VI.4 and VI.5.

The proband's brother, aged 14 years, was physically healthy (see electronic supplementary information, eFigure1b; Figure 1, VI.2). He had consistently obtained near-average overall results in school, albeit with much help from the parents. His parents expressed concern about his social interaction skills. The proband and her brother approved the reproduction of their pictures.

Information provided mainly by the parents (Figure 1, V.1 and V.2) and by the proband's paternal grandaunt (Figure 1, IV.6) allowed construction of the family pedigree. Physical abnormalities were not recorded in any family member in any generation except for a moderate degree of myopia in the proband's brother and paternal uncle (V.3). High-degree myopia had also been present in IV.3, but was absent in IV.6 and her descendants. The individuals III.3, III.5 and IV.4 died in early childhood from unknown causes. The individuals II.2, II.3 and III.4 were known in the family as 'mildly retarded' persons. All informants agreed that III.2, who had died in her 80s, was a physically and cognitively normal person. Her daughter (IV.3) had a weak, withdrawn and anxious personality and was thought to have mild MR. She was dependent on her mother's care and support, and died within 6 months after the passing of her mother. All descendants of IV.6 were at least college level graduates, except VI.3 who had learning difficulties and variant behavior. Fluorescence *in situ* hybridization (FISH) studies were performed in all surviving family members.

Psychometric and personality testing

As a quantitative psychometric test instrument the Dutch version of the Wechsler Adult Intelligence Scale, edition III (WAIS-III) was used (see supplementary information). In addition, a number of qualitative behavior and personality test instruments were used: the Symptom Checklist 90 (SCL-90), the Nijmegen Personality Questionnaire (NPQ), the State Trait Anxiety Inventory (STAI), the Social Anxiety Inventory (SAI), the Utrecht Coping Questionnaire (UCQ) and the revised Beck Depression Inventory (BDI) (see supplementary information).

Cytogenetic and molecular investigations

Analysis of G-banded prometaphase chromosomes was performed on short-term lymphocyte cultures using standard procedures.[14] FISH, microsatellite analysis and breakpoint mapping were performed essentially as described in the supplementary information.

Results

Clinical examinations

At the age of 16 years, the proband's height was 165 cm (p50–p75) (see electronic supplementary information, eFigure 1a; Figure 1, VI.1). Her occipetal frontal circumfer-

ence (OFC) was 51.3 cm (about p3). She weighed 45.3 kg (p3–p10). She wore corrective glasses for high-grade myopia (−12 D), but otherwise showed neither physical nor neurological abnormalities. Her cooperation was excellent. Both parents were clinically normal and healthy. Neither had any grade of myopia. The OFC was 54.3 cm in the mother and 57.5 cm in the father.

The proband's brother (see electronic supplementary information, eFigure 1b; Figure 1, VI.2) was examined at the age of 14 years. His height was 167 cm (p50–p75), OFC was 55.0 cm and he weighed 50.3 kg (p50). Except for adequately corrected mild myopia, he was found to be physically normal. Although the parents did not compare his personality to that of his paternal uncle, they expressed concern mainly about his less than adequate skills in social interaction with his peers.

The paternal uncle (Figure 1, V.3) had an OFC of 56.5 cm but was not fully examined clinically. He had no physical or neurological abnormalities. All other subjects available for study were found to be physically and cognitively normal by at least one of the authors (JGL). None of the patients showed any dysmorphic features; in particular, proximally implanted thumbs and narrow ear canals were not observed.

Characterization of chromosome 18 rearrangements

Upon G-banding the proband (see electronic supplementary information, eFigure 1a; Figure 1, VI.1) was found to have a small additional band at the distal end of 18q (Figure 2e). In order to determine the nature of the rearrangement and the origin of the additional material in 18qter, karyotyping of both parents was performed. The mother's (Figure 1, V.2) karyotype was normal, while in the father (Figure 1, V.1; Figure 2B) the banding analysis suggested the presence of a large, and apparently balanced, pericentric inversion of chromosome 18. Hence, his karyotype was tentatively described as 46,XY, inv(18)(p11.22q23). Subsequent FISH analyses using chromosome 18 paint, the subtelomeric YAC probe HTY3045 (Figure 2c) and PAC probes from the subtelomeric regions of 18p and 18q confirmed the inversion in the father.

In the proband, the derivative chromosome 18 was shown to bear a duplication of the distal 18p segment and a deletion of the distal 18q region. For an overview of all karyotypes, see Table 1. In order to assess the size of the noninverted distal segments of chromosome 18 FISH was performed with a 1 Mb probe set. Probe RP11-146G7 (bp 6752909–6933645 on 18p) was found to be present at both ends of the proband's chromosome 18, and is therefore

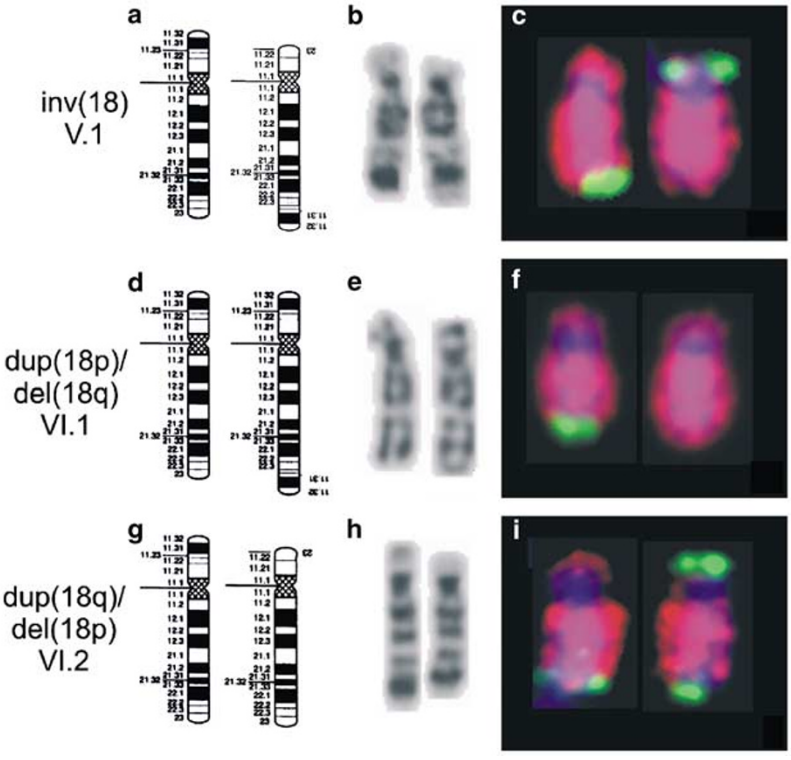

Figure 2 Ideograms of chromosome 18 (**a**, **d**, **g**), representative G-banded partial karyotypes (**b**, **e**, **h**) and FISH results (**c**, **f**, **i**) with the use of the YAC probe HTY3045 (18qter, spectrum green) and a chromosome paint (spectrum red). The normal chromosome 18 is depicted on the left, the aberrant chromosome 18 on the right in each instance. Inv(18) in subject V.1 (**a**–**c**); dup(18p)/del(18q) in proband VI.1 (**d**–**f**); dup(18q)/del(18p) in VI.2 (**g**–**i**).

Table 1 Clinical and cytogenetic data in selected subjects in family with pericentric inversion chromosome 18: Karyotype–phenotype correlation.

Pedigree #	*Relation to proband*	*Karyotype*	*Cytogenetic designation*	*Clinical Phenotype*[a]
VI.1 (proband)	—	46,XX,rec(18)dup(18p)inv(18)(p11.22q23)	dup(18p)/del(18q)	V
VI.2	Brother	46,XY,rec(18)dup(18q)inv(18)(p11.22q23)	dup(18q)/del(18p)	V!
V.1	Father	46,XY,inv(18)(p11.22q23)	inv(18)	nl
V.2	Mother	46,XX	nl	nl
V.3	Pat uncle	46,XY,rec(18)dup(18p)inv(18)p11.22q23)	dup(18p)/del(18q)	V
IV.1	Pat grandfather	46,XY	nl	nl[b]
IV.2	Pat grandmother	46,XX,inv(18)(p11.22q23)	inv(18)	nl
IV.6	Pat grandaunt	46,XX,inv(18)(p11.22q23)	inv(18)	nl
V.4	Pat third degree relative	46,XY,inv(18)(p11.22q23)	inv(18)	nl
VI.3	Pat second cousin	46,XX,rec(18)dup(18)inv(18)(p11.22q23)	dup(18p)/del(18q)	V^{nt}
VI.4	Pat second cousin	46,XX	nl	nl
VI.5	Pat second cousin	46,XY	nl	nl

nl: clinically normal; V: variant behavior; Pat.: paternal.
[a]For description of phenotypes, see text.
[b]Deceased since karyotyping. V!: phenotype not discernable objectively from V by psychologic study; V^{nt}: not available for either psychometric and personality testing.

distal to the inversion breakpoint. Probe RP11-51B9 (bp 7878630–8036438 on 18p) was present in one copy only in the rec(18), on the short arm, and is therefore proximal to the inversion breakpoint.

The 18q23 breakpoint was mapped distal to probe RP11-234N1 (bp 72264534–72443247 on 18qter) and proximal to RP11-118I2 (bp 73602957–73762161 on 18qter). RP11-118I2 was found at neither end of the proband's recombinant chromosome 18, but was detected at both ends of the recombinant chromosome 18 in her brother. From these results, the size of the 18p subtelomeric fragment involved in the recombination was estimated to be approximately 8 Mb, whereas the 18q subtelomeric fragment was estimated to be approximately 3 Mb in size. Similar investigations (Figure 1 and Table 1) showed subsequently that the paternal uncle's (V.3) karyotype harbored the same recombinant dup(18p)/del(18q) chromosome as was found in the proband. A 'non-recombinant' inversion chromosome 18 was subsequently found in the proband's paternal grandmother (IV.2) and in her paternal grandaunt (IV.6) and also in the only son (V.4) of the latter. Upon the request of the paternal grandaunt (IV.6) the three offspring of her son, subject V.4, were also studied. In the oldest daughter (VI.3) the recombinant chromosome dup(18p)/del(18q) was found. In the two younger sibs, the karyotype was normal (Figure 1 and Table 1).

Microsatellite analysis confirmed the findings of the cytogenetic studies (see electronic supplementary information, eFigure 2).

Psychometric testing (see also electronic supplementary information)

Scores on all tests were noticeably lower in the two individuals with the dup(18p)/del(18q) recombinant chromosome than in the subject with the dup(18q)/del(18p) recombinant (see electronic supplementary information, eTable 1). The parents both scored within normal limits in the psychometric and personality tests applied to the affected.

In both the proband and her uncle, FSIQ, VIQ and PIQ were within the normal range. Working memory, processing speed scored significantly below average as was the case in both subject accumulation and verbal arithmetic subtests. The PSI score of the proband's uncle was the only cognitive score that fell below the normal range. Attention deficit and often failing audiogenic memory were also recorded for the uncle. In addition, some subtest scores as well as direct observation suggested that the uncle was dyslexic. The proband's brother had FSIQ and VIQ scores close to the population average. However, like his sister and uncle, his PIQ was significantly below his VIQ score. In some verbal arithmetic subtests (results not shown) he scored much below his FSIQ profile. Thinking in logical sequence was often problematic and logical thinking using numbers often insurmountable.

Information obtained by family history pointed to similar learning difficulty in the proband's second cousin (Figure 1, VI.3), who also has the dup(18p)/del(18q) recombinant chromosome but was not available for psychometric testing.

Behavioral and personality testing

The proband's behavioral phenotype is marked by significant anxiety and intense stress associated with social interactions. On the STAI, she scored in the seventh decile on the trait anxiety scale and the ninth decile on the state anxiety scale. The test results schowed a further increase in her anxiety level in the face of social interactions and other

external events. Consistent with this, she scored high on the social incompetence scale and very high on the hostility/mistrust scale of the NPQ. On the IOA, she scored high to very high on the social anxiety subscales related to initiating conversation, giving compliments and asking attention for one's own opinion, and scored in the midrange on the subscale pertinent to giving critical remarks to others.

In addition the proband also scored high on the SCL-90 depression scale and indicated a high incidence of depressive reactions when coping with stressful events by the UCQ. It should be noted that these scores contradict her mild score on the BDI. However, in all three individuals the BDI scores were consistently lower than the other indices of depression. In addition to anxiety and depression related to social interaction significant mental disorganization was revealed in the personality profile. She scored high on scales of psychoneurosis and mental disorganization in the SCL-90, and very high on the mental instability scale of the NPQ.

The proband's uncle's personality was marked most prominently by depression and to a lesser degree by moderate anxiety. In stressful events, his score on the BDI indicated less depression than his score on other instruments. However, his BDI score (moderate depression) was significantly higher than those of his niece and nephew.

The uncle's personality testing scores indicated moderate to high levels of anxiety, but little if any increased stress in the face of social interactions. Irrespective of the high score of the several tests applied, this person had almost no subjective difficulty upon engaging in social interactions. In spite of the relative ease with which this subject engaged in social interaction, he had a history also of dysfunctional relationships with coworkers, acquaintances and relatives. His lack of success in social interactions may have been due to his high level of psychoneurosis and mental disorganization. The SCL-90 indicated very high levels of both these traits, and he scored high on the mental instability scale of the NPQ.

Mental organization was better in the proband's brother, who was more at peace with himself than his sister or uncle. Unlike the latter, the brother's score on the personal inadequacy scale of the NPQ was average and his level of self-contentment was high. However, the results of the personality tests were somewhat inconsistent in him. Although he scored high on the depression and anxiety scales of the SCL-90, he showed minimal depression according to the BDI, and obtained a midrange score regarding the incidence of depressive coping reactions in the face of stressful events.

In spite of this relative self-contentment, the brother's feelings of social incompetence were strong. In addition, he was highly agoraphobic and scored very high on the hostility and mistrust scales of the SCL-90 and the NPQ. Inconsistent scores for the level of stress in the face of social interactions were obtained. According to the SAI, initiating conversation, requesting attention for his own opinion and criticizing others were only mildly stressful. In contrast, expressing appreciative thoughts of himself or of others was very stressful. His coping with stressful events was often highly emotional (UCQ). In spite of his apparently adequate level of mental organization, high overall levels of psychoneurosis were detected by the SCL-90.

Discussion

This report describes the largest pericentric inversion of chromosome 18 reported to date. It segregated through at least four generations and was transmitted by the normal inversion carriers either as the unaltered inversion or as one of two alternate recombinants. The phenotype observed is of interest for two reasons. First, the mild phenotype would not have satisfied the current criteria put forward in order to select patients for subtelomeric FISH studies.[15] Neither MR, facial dysmorphism, congenital developmental anomalies, nor prenatal or postnatal growth disturbance were observed. Subtelomeric rearrangements have been reported in approximately 5% of patients with moderate to severe MR and facial dysmorphism and in about 0.5% of patients with mild MR.[16–24] Secondly, contrary to the patients in this report, the large majority of patients heterozygous for a recombinant inverted chromosome 18 reported in the literature had severe MR/MCA with severe clinical morbidity and often with early lethal outcome.[1–10,25] In one instance holoprosencephaly (HPE11), in another congenital cystic adenomatoid malformation of the lungs was diagnosed prenatally.[13] In all these instances, either one or both breakpoints were closer to the centromere than the breakpoint locations observed in this family (Figure 3). Hence, the resulting structural aneuploidy was considerably larger and the pathological implications in the recombinants more prominent. In only one literature report,[12] one dup(18q)/del(18p) recombinant with a rather mild phenotype and two dup(18p)/del(18q) recombinants with severe phenotype were described in a single family (Figure 3). In the former minor dysmorphic features, small stature and obesity were observed. Learning difficulty was noticed only after the first year of primary school and a cognitive delay of 2 years recorded by psychometric testing at 8 years. Unfortunately, molecular breakpoint location was not available in the latter report. The large phenotypic difference between the two types of inversion chromosome 18 recombinants was most likely related to the large difference in the structural aneuploidy between them. The dup(18q)/del(18p) recombinant patient with the milder phenotype, the one with the smallest structural aneuploidy, shared partly the mild

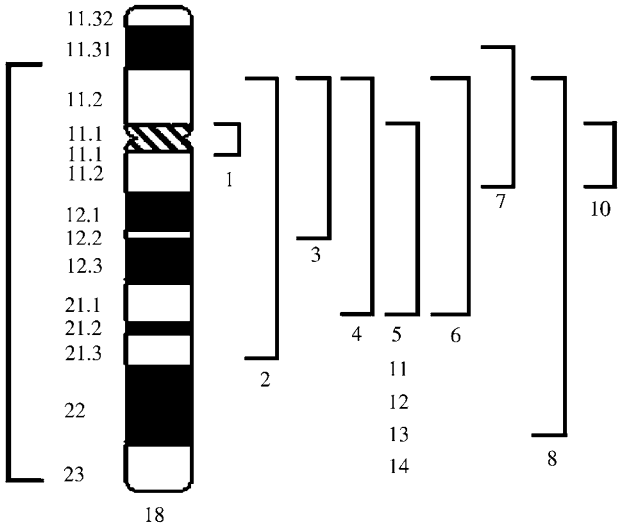

Figure 3 Ideogrammatic overview of reported familial occurrence of pericentric inversion 18 with segregating recombinants. Square bracket to the left of the chromosome indicates size and boundaries of the pericentric inversion in this report. Similar square brackets to the right of the figure represent size estimates in such inversion 18 reports in the literature; The roman numeral indicates the corresponding reference number: 1,[2] 2,[1] 3,[25] 4,[10] 5,[3] 6,[4] 7,[11] 8,[12] 10,[5] 11,[6] 12,[7] 13,[8] 14[9].

clinical phenotype in the patients presented here. The main phenotypic deficiencies in our patients were in the domain of social interaction. These adverse effects were not found in any of the nonrecombinant inversion chromosome 18 carriers. The learning difficulty experienced during the school years by the two dup(18p)/del(18q) individuals tested psychometrically (see electronic supplementary information, V.3 and VI.1) were probably related to their low average IQ. The learning difficulty in the subject with the dup(18q)/del(18p) recombinant chromosome (see electronic supplementary information; VI.2) with FSIQ scores equal to the population average, appeared to be related more to the variant personality characteristics. It is tempting to ascribe the phenotypic differences in either type of patient to the qualitatively different genetic imbalance. If such correlation is really observable it may be predicted that the dup(18q)/del(18p) karyotype encompassing the 8 Mb 18pter deletion involving the region with more sparsely distributed genes[26] and the 3 Mb duplication of 18qter, would consistently produce the more mild phenotype. Similarly, the dup(18p)/del(18q) karyotype comprising the alternate imbalance would be consistently associated with the more severe phenotype. However interesting, the differences actually observed may be fortuitous for several reasons: first, even when all three dup(18p)/del(18q) patients would have been available for psychometric and personality testing, the small numbers precluded statistical evaluation; second, in addition to similarities also differences were recorded among the dup(18p)/del(18q) subjects, some of which may or may not be related to differences in sex, age and/or experience in life; third, different generation and educational influences, early in life in particular, may blur personality and cognitive differences between the two types of recombinants; fourth, interference of genetic background, more specifically of the nonrecombinant inv 18 carrier parent as well as possible differences of imprinting cannot be ruled out. Three reports have documented patients with microscopically visible 18pter deletions and normal or borderline intelligence, similar to the patients presented. However, no personality testing was performed in any of the patients limiting the ability to compare specific phenotypic details.[27–29] Genetic counseling to the family is particularly challenging for more than one reason. Empirical or experimental data regarding recurrence risk in offspring are not available. In this family, genetic counseling is of relevance to the recombinant inversion 18 subjects. The probability of transmitting the unaltered recombinant chromosome may well be as high as 50% of viable offspring, since it is likely that either inclusion of the normal or the recombinant chromosome is equally probable. In any event, genetic counseling must include offering prenatal cytogenetic testing of future pregnancies.

The phenotypic abnormalities observed in the individuals with either one or the other of the recombinant chromosomes are attributable to imbalances of genes located in the 18pter and/or 18qter regions rather than to position effects, as all nonrecombinant inversion heterozygotes in the family were physically and mentally normal. Thus at present, it is impossible to identify which terminal region gene(s) in the recombinant chromosome 18 is (are) mainly responsible for the variant phenotype. Our observation and the ones reported by Mejia-Baltodano *et al*[12] are consistent with the consensus that the 18pter region contains a lower than average density of genes[26] or at least a low number of candidate genes affecting development, maintenance and/or function of the central nervous system (CNS). Myelin basic protein (MBP) gene[30] and a gene structurally related to a phospholipid-transporting ATPase (ATP9B)[31] reside in the 18pter region (see electronic supplementary information, eFigure 3). The products of either or both genes may be crucial for proper synthesis and/or maintenance of CNS myelin. The gene encoding the zinc-finger protein 236 (ZNF236) highly expressed in brain also resides in the 18qter region.[32] Further studies may show whether mutations in these genes individually or combined adversely affect human interactive behavior, as may have been the case in our partially aneuploid patients. This observation, the initial step towards molecular elucidation of the rather mild behavioral disorders in the affected, may be helpful as well

in defining the importance and role of structural aneuploidy in human so-called multifactorial disorders.

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Supplementary Information accompanies the paper on European Journal of Human Genetics website (http://www.nature.com/ejhg).