Congenital variant Rett syndrome in a girl with terminal deletion of chromosome 3p

Jan Wahlström, Anna Uller, Tonnie Johannesson, Deborah Holmqvist, Catarina Darnfors, Mihailo Vujic, Bernt Tonnby, Bengt Hagberg, Tommy Martinsson

Abstract
A girl fulfilling four/five of six inclusion criteria and eight/nine of 11 supportive criteria for atypical Rett syndrome had a cytogenetic deletion of chromosome 3p, del(3)(pter→3p25.1→25.2). The deletion was situated on the maternally derived chromosome and by molecular analysis the deletion breakpoint was shown to be between DNA markers D3S3589 and D3S1263. (J Med Genet 1999;36:343–345)

Keywords: chromosome 3; deletion; Rett syndrome

Rett syndrome (RS) is a neurodevelopmental disorder in girls with normal or near normal development during their first years of life, then with a sequence of characteristic disease stages and signs.1 It is a multi-impairment condition with variation in motor disability. All cases exhibit characteristic dyspraxia to complete apraxia with characteristic hand stereotypies. There is evidence to indicate that RS is a genetic disease, for example, monozygotic twins are concordant while dizygotic twins are never concordant, too many familial cases have been described to be explained by chance alone,2 and the only known pregnancy in a RS woman resulted in a girl who developed classical RS after completely normal early development.3 The mode of transmission, however, is still unclear.

In this paper we report on a girl with congenital variant Rett syndrome and a deletion of the distal part of the short arm of chromosome 3.

Materials and methods

CASE REPORT
This 8 year old girl is second of two children in a healthy family. The pregnancy was uneventful. The girl was born at 36 weeks of gestation and the delivery was uneventful. Apgar scores were 9 and 10, birth weight was 2390 g, length 44 cm, and head circumference 31.5 cm. Minor congenital anomalies including one extra toe were observed. The girl had poor sucking and had some single cleft neonatal fits. At 2-3 months, infantile spasms appeared but the EEG was normal. Both mental and motor development were very slow. She learned to sit at 1 year old, never acquired meaningful grasping, showed early hand stereotypies of an uncharacteristic type, and cannot speak. An early problem was inexplicable violent screaming attacks lasting for hours. Hypothyroidism was found and treated.

At 4 years, contact and communication had improved but only modestly. At 5 years, she was severely mentally retarded and had repeated hand stereotypes, often of the hand-wringing RS type. She was paroxic and showed abnormal distal lower limb neurology with dystonic plantar flexion deviations of her feet. These were small for her age and cold with intermittent profuse sweating. Over the years she has developed a number of the characteristic RS supportive manifestations, as described in the RS variant scheme of Hagberg and Skjeldal,4 including breath holding attacks, bloating, bruxism with creaking sounds, and long screaming and laughing attacks (also at night). In spite of this complex disability pattern, emotional contact has improved over the past few years. CT scan showed a small brain with otherwise normal morphology. Her EEG was initially normal, but when recorded at 4 years in a somnolent state showed more or less continuous spike activity in the occipital part of the left hemisphere. This activity was of Rolandic spike type and the sequential findings were compatible with RS. SPECT showed decreased perfusion patterns bitemporally, as well as a minor decrease in perfusion in the frontal lobes and around the third ventricle. This is a pattern usually not considered consistent with RS. A broad metabolic screen was negative.

CYTOGENETIC STUDY AND FLUORESCENT IN SITU HYBRIDISATION
The cytogenetic study was performed according to the method described by Johannesson et al.5 For the fluorescence in situ hybridisation analysis (FISH), the commercially available probe telomere 3p (digoxigenin labelled probe for locus D3S1444, Oncor) and a whole chromosome 3 probe (biotin labelled whole chromosome specific painting probe, Cambio) were used. FISH was performed according to the method described by Pinkel et al with a slight modification as described in Johannesson et al.7

DNA EXTRACTION AND PCR ANALYSIS
DNA was isolated from venous blood samples anticoagulated with EDTA and extracted using standard procedures. PCR reactions were performed as described previously. Simple sequence repeat polymorphisms (SSRPs) were determined by the length of amplified PCR products on a 6% polyacrylamide/7 mol/l urea sequencing gel. After drying, the gel was exposed to Fuji x-ray film overnight at room temperature. PCR based polymorphic markers and the primer sequences used in the study were derived from the Généthon6 and CHLC.
Results

CYTOGENETIC ANALYSIS

The karyotype showed a de novo deletion of the short arm of chromosome 3 (3pter→3p25.1~25.2, fig 2 (top)). The parents had normal karyotypes. Cytogenetic analysis in three other cases with congenital variants of Rett syndrome had normal 46,XX karyotypes.

FLUORESCENCE IN SITU HYBRIDISATION (FISH)

FISH showed loss of the probe telomer 3p in one of the chromosomes 3 from the proband (fig 2 (middle)). Using the whole chromosome 3 probe, no chromosome 3 material was found on any other chromosome (fig 2 (bottom)), thus confirming the terminal deletion of chromosome 3. In 14 girls with classical RS, no deletion of the short arm of chromosome 3 was found using telomer 3p as probe.

DELETION STUDY USING SSRP MARKERS

Molecular analysis confirmed the terminal deletion of chromosome 3p (fig 1). It also showed that the deletion was on the maternally derived chromosome 3 since the DNA from the girl lacked the maternal allele in all microsatellites tested distal to the breakpoint. The closest markers used that flanked the deletion breakpoint on the maternally derived chromosome were D3S3589 (lost on the maternal copy) on the distal side and D3S1263 (both alleles retained in the child) on the proximal side. Thus, the breakpoint must be between these two markers (fig 1).
Discussion
This girl fulfils five of the six basic inclusion A criteria for atypical RS according to the protocol of Hagberg and Skjeldal4 (table 1) and she already fulfils no less than eight or nine of the 11 supporting B criteria (table 2), which is a considerable amount even for classical RS girls of this age. However, she has eight of the 15 most frequent symptoms found in patients with del(3)(p25) (table 3).

As a similar deletion was not found in three other girls with congenital variants of Rett syndrome or in 14 girls with classical RS, it cannot be considered an essential cause of RS. However, in the search for a biological explanation for RS, the combination of a structural chromosome aberration in a girl and a phenotype of congenital RS is of particular interest. A potential gene for RS might be localised in the vicinity of the breakpoint or in the deleted part of the short arm of chromosome 3. Alternatively, the RS phenotype and the deletion may represent two independent conditions.

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