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A Case of Angelman Syndrome Arising as a Result of a De Novo Robertsonian Translocation

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Abstract. A male child has been identified with Angelman syndrome. He has been shown to carry a de novo Robertsonian 15/15 translocation where both chromosome 15s have been derived from the father. Consequently the disease in this instance is due to paternal uniparental disomy.

Key words: Angelman syndrome, Uniparental disomy, Robertsonian translocation

INTRODUCTION

Angelman syndrome (AS) is a neurodevelopmental disorder originally described by Angelman [1] in 1965. The main clinical features are severe mental retardation, an ataxic, broad-based gait, jerky limb movements, seizures, an abnormal EEG and a happy disposition. There are often dysmorphic features including a wide smiling mouth, prominent chin, protruding tongue, and deep-set eyes. Microcephaly is a frequent finding and many patients are hypopigmented.

The locus for AS is on chromosome 15 at 15q11-13. Most AS patients (75-80%) have a deletion within this region, which is detectable by cytogenetic, [2, 3] or molecular genetic [4, 5] techniques. The remaining patients have apparently intact chromosomes 15 [6]. Some cases have uniparental disomy (UPD) for chromosome 15, both chromosomes being inherited from the father [7]. The syndrome develops because the AS locus is subject to genomic imprinting [8]. Patients with UPD account for only a very small proportion of AS cases, 1-2%. Maternal UPD of chromosome 15, on the other hand, gives rise to around 25-30% of Prader-Willi syndrome (PWS) cases. The PWS and As loci lie very close together, and this difference in incidence probably reflects the fact that maternal non-disjunction is more frequent than paternal meiotic errors. This is supported by the fact that maternal UPD is more frequent amongst offspring of older mothers. The chance of UPD occurring is also increased if a parent or child carries a

Robertsonian translocation [9]. Here we describe a child who presented with the clinical features of AS and who has been shown to have paternal UPD of chromosome 15 arising as a de novo event. To our knowledge, this is the first such report.

Case Report

GC was born following an uneventful pregnancy to a 32-year-old father and 29-year-old mother. Both parents were healthy. Birth weight was 3.2 kg. He was an irritable baby who slept poorly and his motor milestones were delayed. He walked at 19 months of age.

GC presented to the clinical geneticist at 4 years of age with developmental delay, ataxia, jerky movements and absent speech. He had a happy sociable affect but showed some autistic behaviour. He had minor dysmorphic features including a wide, smiling mouth, prominent chin and tendency to protrude the tongue (Fig. 1). He did not have seizures and was normally pigmented. A diagnosis of AS was suspected and cytogenetic and molecular cytogenetic investigations were carried out.

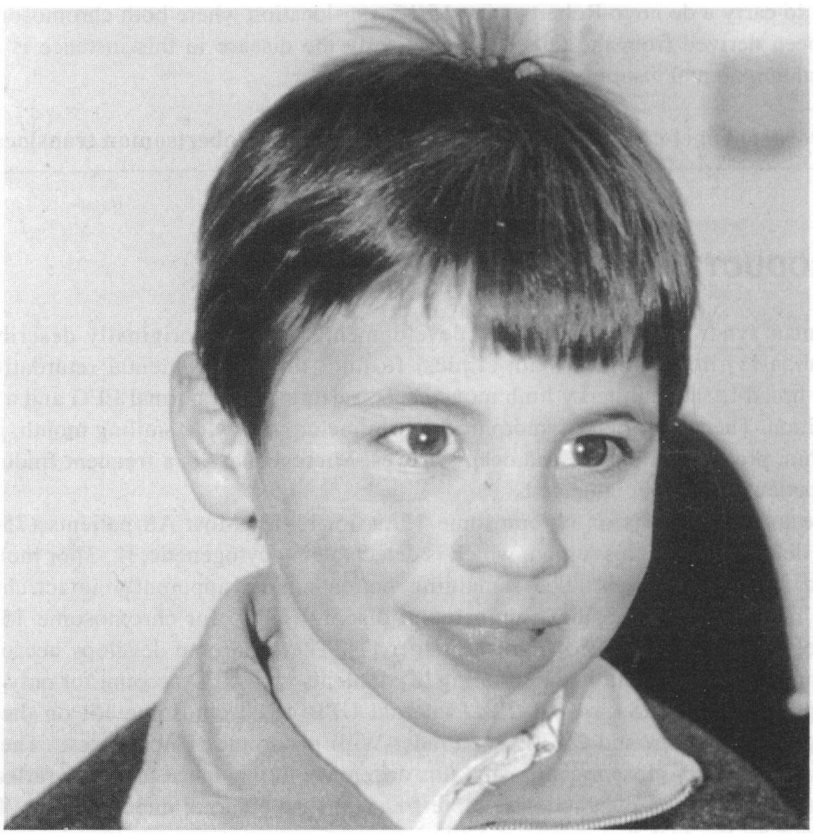

Fig. 1 - Patient GC.

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Cytogenetic and molecular investigation

Routine G-banding revealed a Robertsonian 15/15 translocation chromosome in GC and normal karyotypes in both parents (results not shown). Fluorescence in situ hybridisation (FISH) analysis was performed using standard protocols with Oncor probes 15A and 15B, which map to the D15S11 and GABRB3 loci, respectively, within 15q11-q13. This analysis showed that both chromosome 15 appeared intact, with no evidence of a 15q11-q13 deletion (Fig. 2).

A microsatellite at GABRA 5 was amplified according to Glatt et al. [10], resolved on 8% native polyacrylamide gels and visualised using silver staining. No maternal contribution was present in the patient at this locus which lies within the common deletion region for AS at 15q11-13 (Fig. 3).

For parent-of-origin methylation studies, genomic DNA was digested with *Hin*dIII and *Hpa*II and probed with PW71B [5]. This confirmed a methylation pattern in the patient consistent with no maternal contribution at 15q11-q13 (Fig. 4).

Thus, we were able to establish that both chromosomes involved in the Robertsonian translocation were of paternal origin, i.e. GC had paternal UPD for chromosome 15.

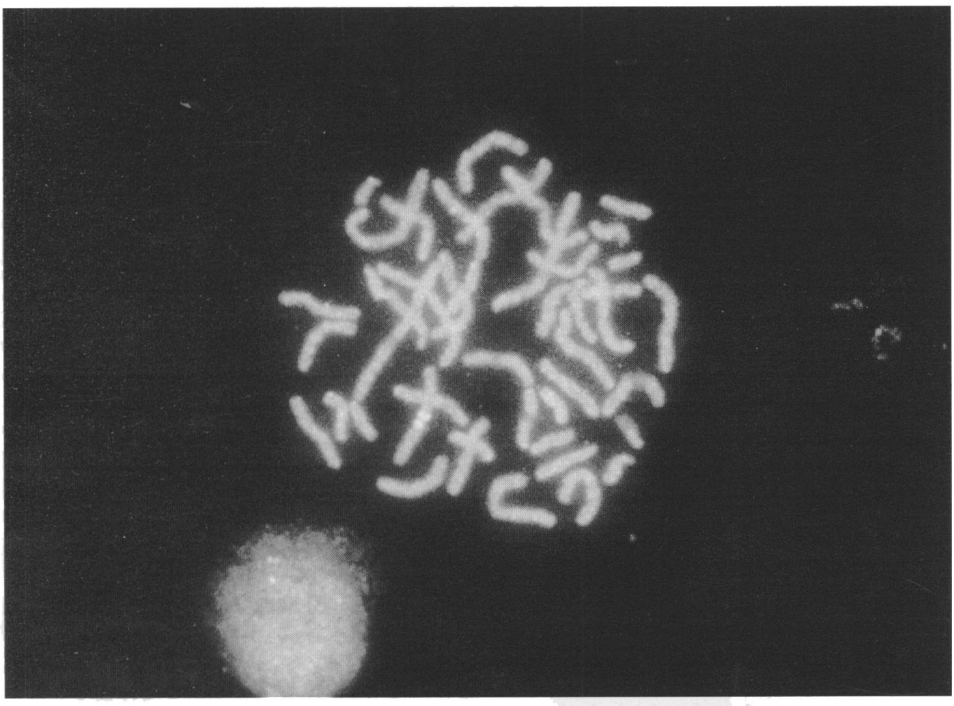

Fig. 2 - FISH analysis using Oncorprobe 15B. A signal on each arm of the translocated chromosome is clearly visible.

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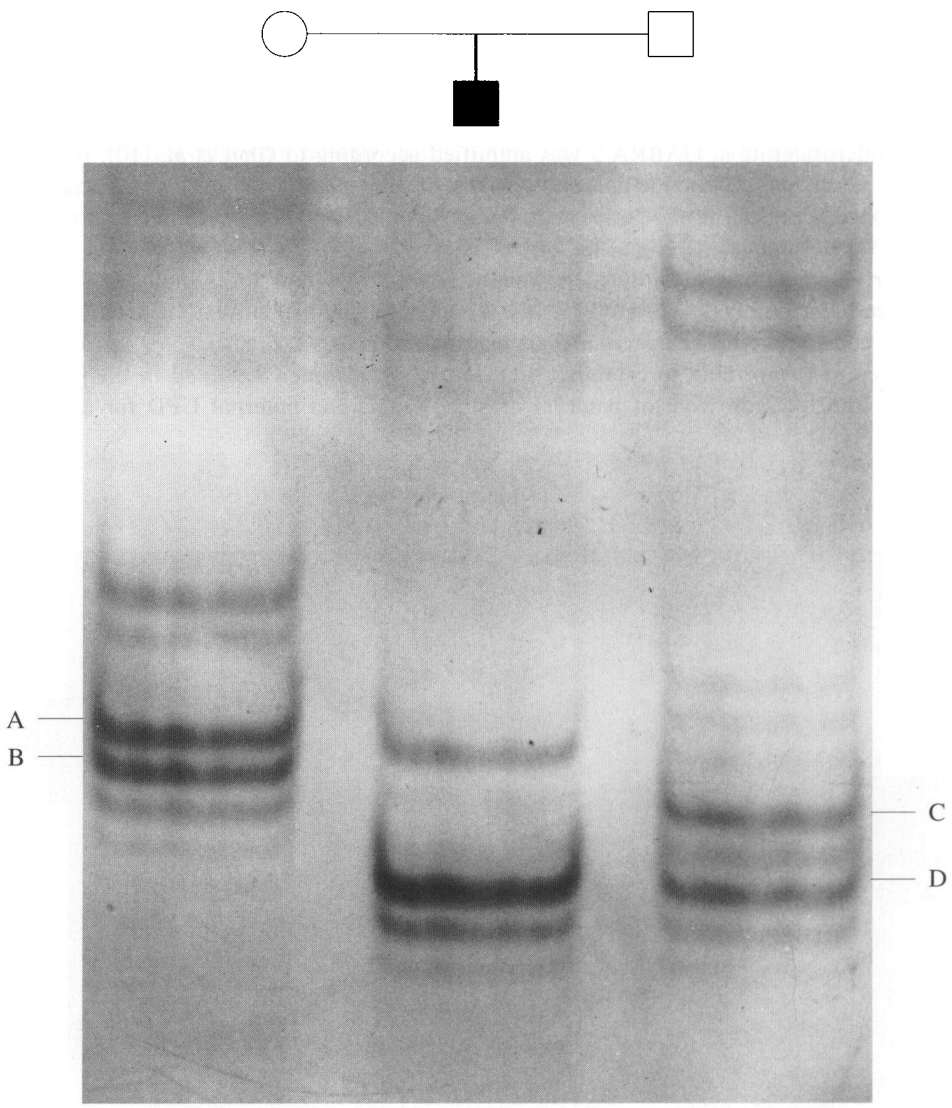

Fig. 3 - Microsatellite GABRA5 showing only a paternally derived allele (allele D) in the proband. This CA repeat has been run native on an 8% gel and visualised using silver staining.

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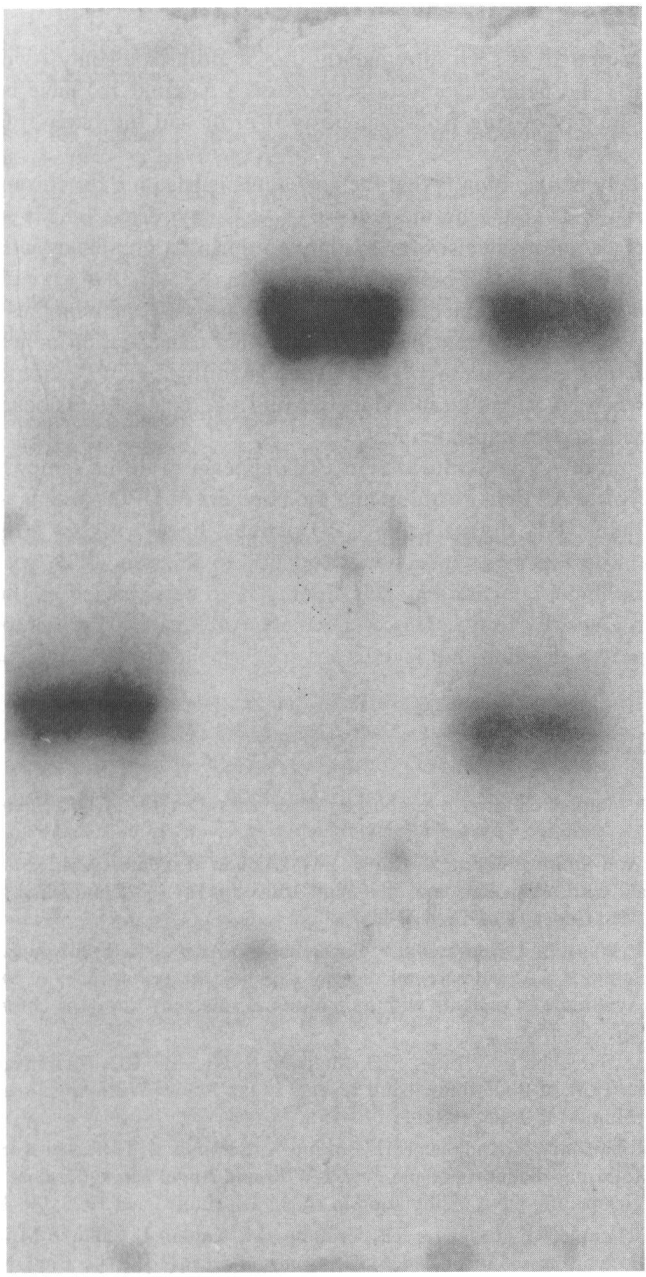

Fig. 4 - Probe PW71B hybridised against *Hind*III/*Hpa*II genomic double digests revealing a 6.6-kb maternally derived and a 4.7-kb paternally derived restriction fragment.
Lane 1 = G.C.; 2 = PWS control; 3 = normal control.

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CONCLUSIONS

UPD of chromosome 15 is seen infrequently in AS. Both isodisomy (two copies of the same paternal 15) and heterodisomy (a copy of each paternal 15) have been described, the former presumably arising from a meiosis II error and the latter from a meiosis I error.

The most likely explanation is that the conceptus is trisomic for chromosome 15 and then loses the maternal 15 during the process of "trisomy rescue". This is supported by the finding of placental mosaicism for trisomy 15 during a pregnancy which resulted in the birth of an individual with PWS due to UPD [11].

The incidence of UPD is increased in the offspring of older mother [2]. It is also increased in cases where a parent has a Robertsonian translocation or where a Robertsonian translocation arises *de novo* [13]. The possibility of UPD should therefore be borne in mind when investigating individuals with Robertsonian translocations involving chromosomes with known imprinted loci.

The phenotype of AS individuals with UPD appears to differ somewhat from those with the more typical AS deletion, although the numbers of UPD patients for comparison are small. Available data suggests that UPD patients have a higher birth weight, less delay in motor milestones and a reduced tendency to seizures (JCS, pers. obs.). They tend not to show hypopigmentation. This finding is to be expected as the locus within 15q11-13 which gives rise to type II oculocutaneous albinism [l4] is disrupted in patients with typical-sized AS deletions but is unlikely to be affected in UPD patients.

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