

Rubinstein-Taybi syndrome with deletions of FISH probe RT1 at 16p13.3: two UK patients

Julie M McGaughran, Lorraine Gaunt, Jonathan Dore, Fred Petrij, Hans G Dauwerse, Dian Donnai

Abstract

We report two patients with Rubinstein-Taybi syndrome out of a total of 16 tested who have a deletion of the region visualised by the cosmid probe RT1. These results further confirm this as a locus for Rubinstein-Taybi syndrome.

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Key words: Rubinstein-Taybi syndrome; probe RT1.

Rubinstein-Taybi syndrome (RTS) was first described in 1963¹ and is a well recognised dysmorphic syndrome causing mental handicap. It has been suggested that the condition probably occurred as an autosomal dominant mutation, either as a submicroscopic deletion or duplication or as a point mutation.² In 1990, a patient was described with the syndrome and a t(2;16)(p13.3;p13.3) translocation.³ Further patients have been described with breakpoints at 16p13.^{4,5} In 1993, Breuning *et al*⁶ used the cosmid probe RT1 in band 16p13.3 to look at 24 patients with RTS. It was found, using two colour fluorescence in situ hybridisation, that six of the patients had the RT1 signal missing from one chromosome 16. This indicated that RTS is caused by submicroscopic interstitial deletions within 16p13.3 in approximately 25% of the patients. The probe has subsequently been used in Japan and there only one patient out of 25 was found to have a deletion.⁷

Using the RT1 probe we investigated a group of British patients with Rubinstein-Taybi syndrome to ascertain how many of them had a similar microdeletion. All the patients had been examined by at least two clinical geneticists and confirmed as having Rubinstein-Taybi syndrome clinically. There were six female and 10 male patients; two of the female patients were twins.

FISH was performed using probe RT1 and following standard procedures.⁶ Briefly, probe DNA was labelled by nick translation using biotinylated 14-dATP. Slides were denatured in 70% formamide in 2 × SSC at 75°C for five minutes and subsequently dehydrated in an ethanol series; 15 µl of 10 µg/ml labelled probe with 100 µg/ml cot-1 DNA was hybridised to chromosomal DNA overnight. Stringency washes were performed at 42°C for 20 minutes in 50% formamide in 2 × SSC and followed by a 37°C incubation for eight minutes in 2 × SSC. Probes were detected with fluorescent avidin and slides counterstained with propidium iodine and DAPI. Ten cells were scored.

Two of the 16 patients tested were found to have a deletion of the signal from probe RT1 on one chromosome 16 homologue.

The first patient noted to have a deletion was a male with characteristic features of RTS, including downward slanting palpebral fissures, a beaked nose with the columella protruding below the nasal alae and broad, deviated thumbs and halluces. Because of a previous sib with Down's syndrome, his mother underwent an amniocentesis during her pregnancy with him. This had shown a deletion of most of the long arm of his Y chromosome. DNA was tested with four Y specific probes, three from Yp and one from the Y centromere. There was no evidence of these being deleted, giving the same result as the father and a male control. He was considered to be normal at birth with normal male genitalia. However, the RTS phenotype and developmental delay later became apparent. It was felt that his features were attributable to the diagnosis of RTS and not related to the Yq deletion, although it is interesting to note the presence of two de novo deletions in the same patient (in preparation). Both parents have also been checked with the RT1 probe and neither are deleted. Both have a normal karyotype and the father has a normal Y chromosome.

The second patient was also male with no cytogenetic abnormality and the typical phenotype, with features similar to the first patient. Both parents were checked using the RT1 probe and neither was found to be deleted. In each case therefore the deletion appears to be a de novo event.

Rubinstein-Taybi syndrome characteristically comprises broad thumbs and halluces, distinctive facial dysmorphism, growth retardation, and mental handicap. It has, until now, been a diagnosis based on clinical criteria only and the availability of a new test may help clarify the diagnosis where there is some uncertainty. However, when the RT1 probe has been used, only a maximum of 25% of clinically unequivocally diagnosed patients have been found to have a deletion. It may be that in some patients their deletion is too small to be detected by the probe or that the cause of the RTS phenotype in them is a point mutation. Another possibility is that RTS is heterogeneous. Uniparental disomy for chromosome 16 has been excluded previously in one group of patients.⁸ Clinically, there appears to be no obvious difference between those patients who are deleted and those who are not in our series.

Department of
Clinical Genetics,
St Mary's Hospital,
Manchester M13 0JH,
UK

J M McGaughran
D Donnai

Department of
Cytogenetics,
St Mary's Hospital,
Manchester, UK

L Gaunt
J Dore

Department of
Human Genetics,
Leiden University,
Sylvius Laboratories,
Leiden,
The Netherlands

F Petrij
H G Dauwerse

Correspondence to:
Dr McGaughran.

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As the region encompassed by the probe is better defined, the genes involved in the microdeletion will be elucidated and further understanding of the phenotype expression achieved. The RT1 probe will be a useful adjunct to clinical diagnosis and continued cytogenetic study of patients with RTS will be useful to look for evidence of heterogeneity.

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