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A t(10;13)(q26;q31)*de novo* in a patient with mental retardation, epilepsy and ataxia

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Introduction

Approximately 2–3% of the human population present mental retardation (MR, IQ < 70). It is estimated that 5–10% of mild MR (IQ 50–70) and ~50% of severe MR (IQ < 35) have a genetic cause (1). Several genes for X-linked MR have been isolated, but elucidation of the molecular defects underlying autosomal MR remains a major challenge. Up to date, only one autosomal recessive gene involved in MR has been identified: PRSS12 (2). One approach to overcome this problem is to characterise MR-associated visible or submicroscopic translocations, inversions and deletions.

We report a, at the cytogenetic level, balanced translocation t(10;13)(q26;q31)*de novo* in a female patient with mental retardation, microcephaly, bilateral neurosensorial deafness, strabismus, epilepsy, ataxia, autistic behaviour, advanced bone age (3 years) and precocious puberty. Part of this phenotype is similar to infantile onset spinocerebellar ataxia (IOSCA) (OMIM 271245) described in 19 finish families by Nikali *et al.* (3) who found linkage between D10S192 and D10S1265, a narrow interval within 10q24 containing PAX2 and CYP17.

Linkage to 10q24 has also been reported for familial temporal lobe epilepsy with aphasic seizures (OMIM 600512) (4), where mutations have been demonstrated in affected members in LGI1. In addition, the CLN5 gene mutated in the Finnish variant of late infantile neuronal lipofuscinosis (LINCL) (OMIM 256731) with mental retardation, ataxia and myoclonic epilepsy, maps to the region of the other breakpoint, at 13q22.

Material and Methods

By G-banding of chromosomes from peripheral blood, a t(10;13)(q24;q22)*de novo* was identified. The translocation breakpoints were mapped by fluorescence in situ hybridisation (FISH) using bacterial artificial chromosomes (BACs) provided by the MCN Reference Center in Berlin (http://www.molgen.mpg.de/~cytogen/). FISH was carried out using 250ng BAC-DNA labelled indirectly with biotin-14-dATP by nick translation and hybridised to metaphase chromosomes from the patient. Signals were visualised using avidin-FITC on chromosomes counterstained with DAPI in a Leica DMRB epifluorescence microscope equipped with a Sensys 1400 CCD camera (Photometrics, USA) and an IPLab Spectrum imaging software (Vysis, USA).

Results

Since BACs RP11-771A16 and RP11-179B2 which cover most of the IOSCA region within 10q24, were found to be proximal to the breakpoint (Fig. 2a), we tested more distally located BACs. As a result, the breakpoint was mapped to 10q26.2-26.3 (Fig. 1), presently flanked by RP11-384P18 proximally and RP11-500B2 distally within a ~5Mb region (Fig. 2b and 2c).

The physical mapping of the second breakpoint in the 13q22 region showed that RP11-1131M20 is proximal to the breakpoint (Fig. 2d). Furthermore, RP11-447N10, located in 13q31 is also proximal to the breakpoint and a distal clone is yet to be identified.

Table 1. *Clinical features of the patient, IOSCA, and reported terminal 10q deletions.*

Clinical Features	IOSCA	Patient	1	2	3
Mental retardation		+	+	+	+
Epilepsy	+	+	+		
Ataxia	+	+			+
Deafness	+	+		+	
Strabismus	+	+		+	+
Athetosis	+				
Hypotonia	+				
Hearing deficit	+				
Ophtalmoplegia	+				
Sensory neuropathy	+				
Female hypogonadism	+				
Microcephaly		+			
Autistic behaviour		+			
Advanced bone age		+			
Precocious puberty		+			

+=clinical feature present
1- del(10)(q23→qter) mosaicism
2- del(10)(q26.1→qter)
3- del(10)(q26.1→qter) & dup(14)(q32.3→qter)

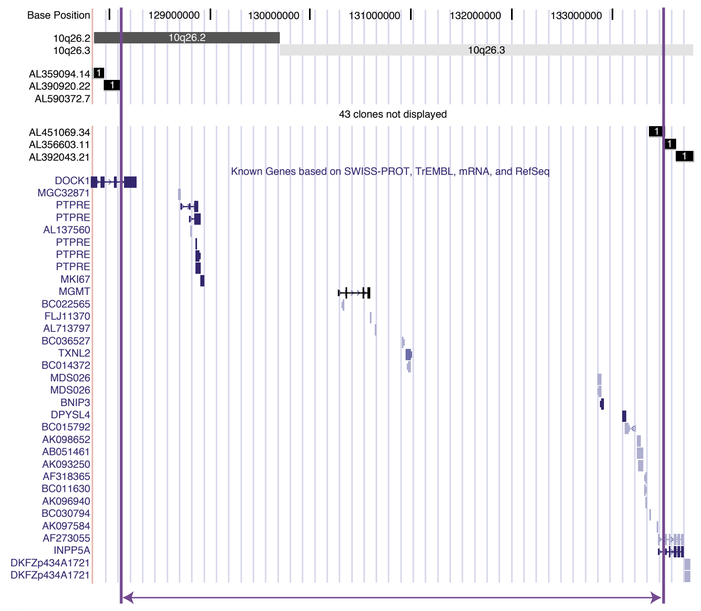

Fig.1. *Human genome browser image showing position of proximal and distal clones and known genes in the region. Vertical purple lines show, on the left, BAC RP11- 384P18, and on the right BAC RP11-500B2.*

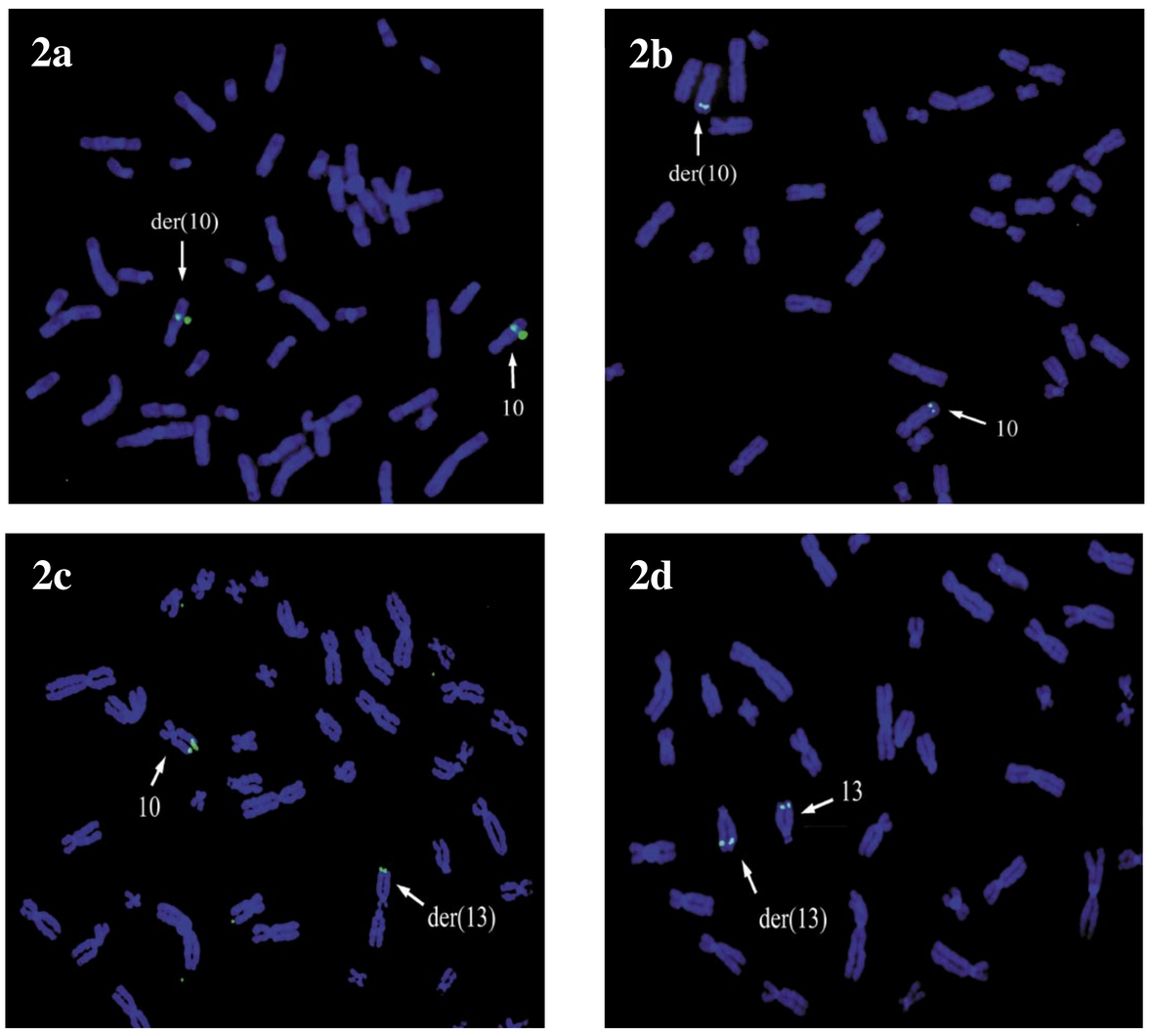

Fig.2. *FISH results for both chromosomes: (a) BAC RP11-179B2 or 771A16 showing signals on normal 10q (thin arrow) and der(10q) (bold arrow), (b) BAC RP11-384P18 showing signals on normal 10q (thin arrow) and der(10q) (bold arrow), (c) BAC RP11-500B2 showing signals on normal 10q (thin arrow) and der(13q) (bold arrow), (d) BAC RP11-447N10 probe, showing signals on normal 13q (thin arrow) and der(13q) (bold arrow).*

Discussion

Here we report a *de novo* translocation t(10;13)(q24;q22) identified by standard cytogenetic techniques (GTG banding), where we initially thought that the 10q24 breakpoint would be a good candidate for IOSCA. However, the FISH results indicated that the 10q breakpoint was located almost 30Mb distal to the IOSCA critical region, within 10q26. In addition, the 13q breakpoint was mapped to, so far, 13q31, also excluding the region of CLN5.

The patient reported here has partial clinical overlap with reported terminal deletions of 10q26, where MR, seizures, strabismus, deafness and ataxia are commonly reported as combined or individual traits (Table 1) (5). The present case may provide insight to the critical region for some of these features.

Acknowledgements

This study was supported by a Wilhelm Johannsen Scholarship to EE and by CIRIUS. The Wilhelm Johannsen Centre for Functional Genome Research is established by the Danish National Research Foundation.

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