

Rapid short communication
Deletion of the DXS165 locus
in patients with classical Choroideremia

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Using various probes from the Xq21 region which is known to carry the choroideremia (tapeto-choroideale dystrophy, TCD) locus, we have screened the DNAs from eight unrelated male choroideremia patients for microdeletions. In two of these patients, but not in any of 45 males tested as controls, lack of hybridization signals with probe plbD5 suggested a deletion encompassing the DXS165 locus and (part of) the TCD gene. Absence of additional clinical features in these patients and the fact that two closely linked, and probably flanking, TCD markers (DXYS1 and DXS72) are not deleted may indicate that the physical distance between the DXS165 locus and the TCD gene is small.

Key words: Choroideremia; deletions; DXS165; X-chromosome.

The molecular defect underlying TCD is not known but recent studies have indicated close linkage with the polymorphic loci DXYS1, DXYS12, PGK1 and DXS72 (Sankila et al. 1987; Lesko et al. 1987) all of which are located in the Xq13-q21 region. Moreover, several patients with small deletions of band Xq21 have been described where TCD was associated with mental retardation (MR) (Hodgson et al. 1987), MR, cleft lip & palate and agenesis of the corpus callosum (Rosenberg et al. 1986) or with MR and deafness (Lesko et al. 1987). These observations indicate that the TCD gene is located in the Xq21.1-q21.33 region.

As part of an ongoing study aiming at the detection of submicroscopic deletions in clinically complex X-linked syndromes we have regionally assigned 15 random probes to this chromosome segment (Cremers et al. 1987; Cremers et al. in press; and unpublished results). Because of the conspicuous clustering of male-viable deletions in this

region we speculated that sizable deletions might also be found in patients where TCD is the only clinical feature. Therefore, we have screened DNA from unrelated TCD patients with several probes mapping in the relevant region of band Xq21. With one of these, deletions were found in two out of eight patients with typical TCD.

Material and Methods

In the 8 patients with TCD, blood was collected, DNA prepared and banked by the RP Center Münster for Medical Care and Research, a collaborative institution of the University of Münster and the German Retinitis Pigmentosa Association (Pawlowitzki & Brunsmann 1987). The diagnosis had been established by detailed ophthalmological examination. For patients 3.5 and 7.6, clinical findings have been reported (Hammerstein & Böhm 1985; Diekstall & Demeler 1986). DNA was isolated according to

standard protocols and digested with restriction endonucleases EcoRI or TaqI. Methods for electrophoresis, Southern blotting, probe labeling and autoradiography have been described previously (Cremers et al. 1987). The following probes were employed: pDP34 (DXYS1), pK65H7 (DXS72), pX2OR42 (DXS73), pX104f, p722 (DXS110), p784 (DXS121), pPA20 (DXS214), pXG7c (DXS95), pXG8b, and plbD5 (DXS165). Probes pX104f and pXG8b were obtained from Drs. B.N. White and P. Szabo, respectively. All other probes have been described elsewhere (Cremers et al. 1987; Goodfellow et al. 1985).

Results and Discussion

With 9 out of 10 probes that had been assigned previously to the relevant segment of band Xq21, and with probe pL2.98 (DXS56) which maps outside this region (Xq12-q13; unpublished results), normal hybridization patterns were observed in all individuals tested. In contrast, probe plbD5 (DXS165) reproducibly failed to detect homologous sequences in the DNA of two out of eight TCD patients studied (patients 3.5 and 7.6; see figure 1). To rule out the possibility that

probe plbD5 detects a deletion polymorphism, this probe was employed to screen genomic DNA from 45 unrelated male controls.

Consistently, normal hybridization patterns were observed. This renders a deletion polymorphism very unlikely and strongly argues for the deletions being the primary cause of TCD in these patients.

To our knowledge, this is the first time that interstitial deletions have been detected in patients where TCD was not associated with additional genetic defects. It is noteworthy that both deletions do not include the DXS72 and DXYS1 loci which show close linkage with TCD and probably flank the TCD locus (Lesko et al. 1987). This finding suggests that the physical distance between DXS165 and the TCD locus may be very small. If so, this should be a great asset for "reverse genetics" strategies aiming at the identification and isolation of the TCD gene.

For the molecular characterization of the two deletions found in this study, field inversion gel electrophoresis (FIGE; Carle et al. 1986) should be particularly helpful, and systematic FIGE screening of further TCD patients should soon clarify the role of deletions in the etiology of this disorder.

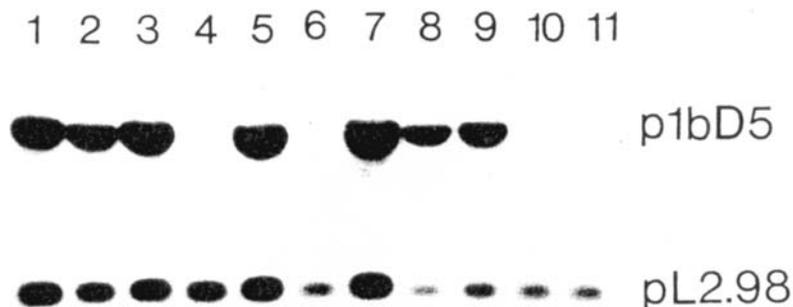


Fig. 1. plbD5 (DXS165) hybridization signals in 7 patients with typical TCD (individuals 2.1, 3.5, 5.1, 7.6, 9.2, 10.1, 13.2; lanes 3 to 9), 2 patients with visible deletions in the Xq21 band (lanes 10 and 11), and female and male controls (lanes 1 and 2). pL2.98 (DXS56) signals are shown as internal reference.

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