Interstitial deletion in Xp22.3 is associated with X linked ichthyosis, mental retardation, and epilepsy

B C Gohlke, K Haug, M Fukami, W Friedl, M Noeker, G A Rappold, F Haverkamp

Abstract
We describe monozygotic male twins with an interstitial deletion of Xp22.3 including the steroid sulphatase gene (STS). The twins had X linked ichthyosis, X linked mental retardation, and epilepsy. A locus for X linked mental retardation has been assigned to a region between STS and DXS31 spanning approximately 3 Mb. Recently the locus was further refined to an approximately 1 Mb region between DXS1060 and GS1. By PCR analysis of flanking STS gene markers in our patients we succeeded in narrowing down the locus to between DXS6837 and GS1.

Keywords: Xp22.3 deletion; X linked mental retardation; X linked ichthyosis; epilepsy; Rudd syndrome

Methods
STS DELETION
DNA was prepared from fresh or frozen venous blood samples by the salting out procedure. Restriction enzyme digestion with TaqI and EcoRI and Southern blotting were performed by standard techniques. A full length CDNA of the steroid sulphatase gene (probe 5’3-STS, kindly provided by Dr von Figura, Göttingen) was used as hybridisation probe.

Case report
Patients 1 and 2 were male monozygotic twins who were born at term in 1987 after an uneventful pregnancy and caesarian section at term in 1987. Birth weights were 2525 g and 2870 g, lengths 48 and 50 cm, and head circumferences 32 and 33 cm. Apgar scores were 10/10/10 for both. Both had ichthyosis from birth and both had grand mal seizures from their first year of life onwards. Both had unilateral cryptorchidism and were operated on at the age of 2 years. At the age of 12 months psychomotor development was significantly retarded. At the age of 8 years, intelligence was tested (Kaufman-Assessment Battery for Children) and showed similar decreased intellectual abilities (IQs of 60 and 70, respectively). Height was normal (132 cm, 25th centile). MRI of the brain was normal in both patients.

There were two other male family members affected. One maternal uncle was reported to have epilepsy, ichthyosis, and mild mental retardation. He refused to be examined or tested. A three year old brother had ichthyosis, but no epilepsy. His psychomotor development was slightly retarded (developmental quotient 73, normal range >80). Three other sibs, two girls and one boy, were not affected and showed normal psychomotor development.
STS pseudogene were observed upon hybridization with the cDNA probe 5’3’ STS. The genomic interval between PABX and KAL was investigated with PCR analysis. PABX, DXS1060, DXS996, DXS6837, DXS278, and KAL were present, whereas DXS6834 and DXS1139 were deleted. Thus, the distal breakpoint maps between DXS6837 and DXS6834 and the proximal breakpoint between STS and DXS278 (fig 1).

By analysing the DNA samples of the family, we also found the same deletion in the partially affected brother and no deletion in the unaffected brother (data not shown). Results of the mother showed that she is a carrier, while two sisters are not carriers. The PCR results for DXS6837 and DXS6834 in the family are shown in fig 2.

Discussion
The monozygotic twins reported here have XLI, mental retardation, and epilepsy. Southern and PCR analysis in the patients showed an interstitial deletion with the telomeric breakpoint between DXS6837 and DXS6834 and centromeric breakpoint between STS and DXS278. The deletion was shared by the mother and by another affected brother. Since STS is deleted in our patients this would explain the X linked ichthyosis in this family. In addition, both of our patients and the affected brother are mentally retarded. This indicates that an X linked mental retardation (MRX) gene is deleted or disrupted in our patients. About 65 putative MRX loci have been mapped to the X chromosome so far. However, because of overlapping regions only 10 to 12 MRX genes can be considered. By deletion mapping, one locus has been located in the Xp22.3 region between DXS31 and STS, spanning approximately 3 Mb. Muroya et al analysed an interstitial deletion at Xp22.3 in a patient with mental retardation. The results of the deletion mapping in the patient were compared with the Xp22.3 deletion breakpoints of three patients with loss of STS, KAL1, and OA1 but without mental retardation described by Sunohara et al and Schaefer et al. Muroya et al further refined the MRX locus to an approximately 1.5 Mb region between DXS1060 and DXS1139. Recently, Weissörtel et al located the MRX gene between DXS1060 and GSI spanning a roughly 1 Mb region according to the X Chromosome Workshop consensus map. By deletion analysis in our patients, we succeeded in further narrowing down the locus of the putative MRX gene. The telomeric breakpoint of the interstitial deletion in our patients lies proximally to DXS6837. Therefore, we propose that the MRX gene is present in the less than 1.5 Mb region between DXS6837 and DXS1139. Epilepsy is an additional manifestation of our patients. However, another affected brother with the deletion in Xp22.3 does not have seizures. Spranger et al reported a men-
tally retarded patient with a terminal Xp22.3 deletion and myoclonic epilepsy. The break-point of the deletion was distal to GSI. DXS6837 and DXS6834 were not tested in this study. Since the patient described by Spranger et al15 had mental retardation, the putative MRX locus may be included in the deletion. Therefore, in this patient the distal part of the deletion present in our patients may also be deleted. Further studies are needed to determine if a gene predisposing to epilepsy is located between GSI and DXS6837.


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