Nephrogenic diabetes insipidus: close linkage with markers from the distal long arm of the human X chromosome

N. Knoers¹, H. van der Heyden¹, B. A. van Oost¹, H. H. Ropers¹, L. Monnens², and J. Willems²

¹Department of Human Genetics and ²Department of Pediatrics, P. O. Box 9101, Catholic University Nijmegen, NL-6500 HB Nijmegen, The Netherlands

Summary. Ten families with nephrogenic diabetes insipidus (NDI) have been analysed for restriction fragment length polymorphisms (RFLPs). A search for linkage was performed using various chromosome-specific single-copy DNA probes of known regional assignment to the human X chromosome. Close linkage was found between the disease locus and the markers DXS52, DXS15, DXS134 and the F8 gene. This result assigns the NDI gene to the subtelomeric region of the long arm of the X chromosome. The regional localization of the gene by the identification of closely linked markers should have repercussions for genetic counselling and prevention in NDI families.

Introduction

Nephrogenic diabetes insipidus (NDI) is a rare inherited disorder, which was first described by Waring et al. (1945). Pedigree analyses indicate that the disease is transmitted by a single X-linked recessive gene (Williams and Henry 1947; Bode and Crawford 1969), although other modes of inheritance have been suggested (Robinson and Kaplan 1960).

NDI is characterized by renal resistance to the antidiuretic action of vasopressin. As a consequence, the kidney loses its ability to concentrate urine. The disorder becomes manifest early in infancy, with polyuria, periods of life-threatening dehydration, fever, anorexia, vomiting and failure to thrive. Without treatment, mental retardation may develop due to brain dehydration. The gene involved has not yet been identified and the molecular pathogenesis of NDI is unknown. However, it has been suggested that the defect underlying vasopressin resistance is located beyond the intracellular formation of cyclic AMP (Proesmans et al. 1975). Females are clinically asymptomatic, but in 60% of them a relative inability to concentrate urine can be demonstrated (Robinson and Kaplan 1960).

Subjects

Ten NDI families from the Netherlands were included in the study. Pedigrees are presented in Fig. 1. Nineteen patients and 95 family members were available for testing. All patients were males, four of them being sporadic cases, whereas in six families, transmission was compatible with X-linkage. Diagnosis of NDI was based on clinical symptoms and the lack of increase of urine osmolality after administration of the synthetic vasopressin analogue DDAVP (1-desamino-8-D-arginine vasopressin). Maximal urine osmolalities that could be achieved after DDAVP infusion were 51–198 mosmol/kg (normal > 805 mosmol/kg).

DNA analysis

Venous blood samples (40 ml) from affected and unaffected family members were collected in EDTA and stored at −20°C until use. DNA isolation was done as previously described (Knoers et al. 1987a): 20 ml of blood was added to 200 ml sucrose lysis buffer (0.32 M sucrose, 5 mM MgCl₂, 10 mM Tris • HCl, pH 7.5) and centrifuged for 10 min at 4°C and 2,800 g. The supernatant was aspirated and taken up in 50 ml lysis buffer. Then the centrifugation was repeated. The pellet of white cell nuclei was resuspended in 9 ml of 75 mM NaCl, 24 mM EDTA (pH 8.0), 0.5% SDS was added and the mixture was incubated at 50°C for 15–18 h. The supernatant was aspirated and taken up in 50 ml lysis buffer. Then the centrifugation was repeated. The pellet of white cell nuclei was resuspended in 5 ml of 75 mM NaCl, 24 mM EDTA (pH 8.0). To this suspension 250 µl 10% sodium dodecyl sulfate (SDS) and 500 µl 3 mg/ml proteinase K (Boehringer, Mannheim) in 0.2 M Tris • HCl (pH 8.0), 0.2 M EDTA, 0.5% SDS was added and the mixture was incubated at 50°C for 15–18 h. The digestion mixture was extracted with an equal volume of phenol, followed by extraction with chloroform:isoamylalcohol (1:1) and finally with pure chloroform.

DNA was precipitated with 0.75 volume of isopropanol and 0.01 volume of 5 M NaCl, washed twice with ethanol, dissolved in 10 mM Tris • HCl (pH 7.5). 1 mM EDTA and stored at 4°C. DNA samples were digested to completion using the

Offprint requests to: N. Knoers