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A GENETIC LINKAGE STUDY OF DETRUSOR OVERACTIVITY

Hypothesis / aims of study

Studies of childhood nocturnal enuresis (NE) have hypothesised a genetic basis for the disease (linkage to chromosomes 4,8,12,13,22 has been observed). Amongst NE children who also daywet into adolescence, urodynamic tests reveal detrusor overactivity (DO) in most[1]. Adult patients with DO and a history of childhood daywetting have been shown to have a reduced response to treatment in the longterm[2].This suggests that there may be a genetic predisposition for DO in some patients. Our aim was to test whether one of the NE genetic loci implicated in the genesis of childhood nocturnal enuresis may be identified amongst a large family in whom detrusor overactivity / overactive bladder syndrome (OAB) / day-wetting was common.

Study design, materials and methods

Local ethics approval was obtained.

Determination of phenotype: . A standardised history of 'major' and 'minor' OAB symptoms was taken. All adult participants were offered urodynamic assessment to confirm the prescence of DO. If urodynamics were declined then phenotype was established from a combination of clinical symptoms. These combinations were 2 minor + 2 major, 3 minor + 1 major or 3 major symptoms The scheme is analogous to that used to diagnose systemic lupus erythematosis (SLE). Amongst children, the presence of daywetting past age 5 was taken as evidence of DO.

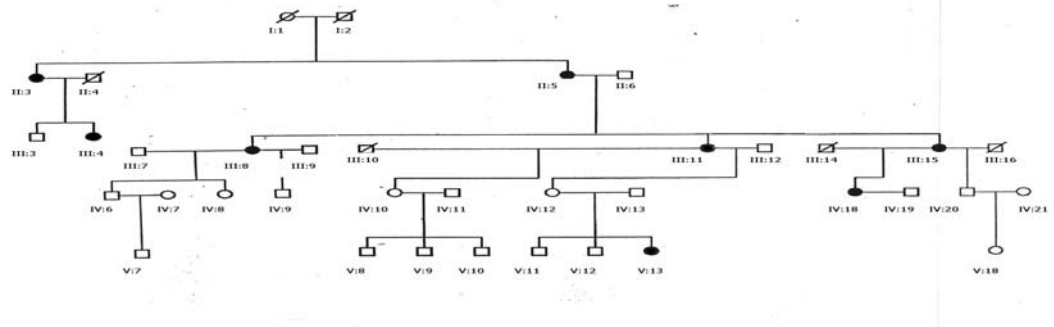
Table1 Symptoms used to define the DO phenotype in the absence of a cystometry test

Minor symptoms	Major symptoms
Frequency > 8 voids/day	Day wetting past age 5
Troublesome or regular urgency	Urge incontinence provoked by audiovisual stimuli eg running water
Urge incontinence	Bothersome leakage at orgasm
Nocturia	
Nocturnal enuresis	

Laboratory techniques:DNA was extracted from blood using standard methods. A partial genome was undertaken using markers at loci previously implicated in NE (D4S2960, D8S264, D12S80, D12S86, D13S263, D13S291, D22S343, D22S446). Preliminary logarithm of odds (LOD) score estimates were calculated manually assuming an autosomal dominant pattern of inheritance which is phase-known and with complete penetrance. A LOD score is a statistical measure of the likelihood that a locus contributes to the aetiology of the disease being studied. Following preliminary results, a higher resolution scan was undertaken on chromosome 13 (figure 2)

Results

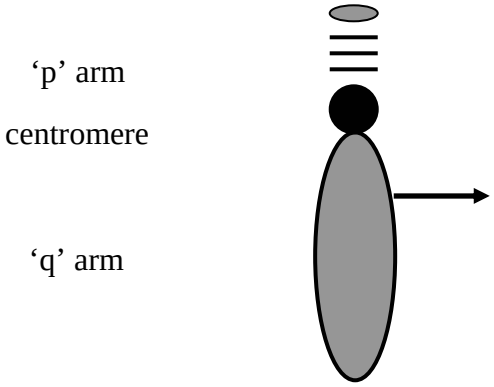
Figure 1. Pedigree of family (Affected members are in black, deceased are scored through)



A four generation family was identified. with members in Australia and the United Kingdom (Figure 1). Family members that were willing to be contacted by the investigators were invited to enrol in the study. Of these, 12 individuals agreed to participate comprising 10 (83%) adult females, 1 (8%) female child and 1 (8%) male adolescent. Urodynamics revealed DO in 2 of 12 (17%) (members II 5 & IV 18). A further 5 (42%) adult females declined testing but had the clinical phenotype of OAB, as did the child (persistent day-wetting). The remaining 4 (33%) were phenotypically normal.

Linkage analysis and LOD scores for loci previously associated with NE: The loci on chromosomes 4, 8, 12 and 22 did not segregate with the DO/OAB phenotype The locus D13S263 on chromosome 13 did segregate, with an approximate LOD score of 2.11 at a Recombination Fraction of 0.08. A high resolution scan was therefore undertaken (Figure 2)

Figure 2 Loci assessed in High Resolution Linkage analysis of proximal Chromosome 13



Locus	Genetic distance from centromere (cM)
D13S1236	6.17
D13S175	9
D13S1243	11.21
D13S1304	15.7
D13S217	22.17
D13S289	27.29
D13S171	31.07
D13S219	35.5
D13S218	39.34
D13S263	43.2

Two alleles at D13S171 and D13S219 segregated with the phenotype, being present in all affected females and absent in most unaffected females. An exception occurred in IV12 who was phenotypically normal and therefore an obligate carrier. However, D13S263 which was previously implicated in NE by other groups lies distal to, and does not overlap with, the region defined in this study. It was only possible to calculate a LOD score for D13S171, as the allele frequency of D13S219 within the Caucasian population is not known.

Table 2 Two point LOD scores for the microsatellite marker D13S171.

MARKER LOCUS	cM	**LOD SCORE AT =**						
		.0	.005	.01	.05	.1	.2	.4
D13S171		1.95	1.93	1.91	1.76	1.56	1.15	0.29

Interpretation of results

The pedigree suggests an Autosomal Dominant mode of inheritance with decreased penetrance. None of the NE loci showed linkage in this family. Despite the modest LOD score for D13S171, lack of recombination between loci D13S171 and D13S219 suggests linkage in this family amongst members with DO/OAB.

Concluding message

To our knowledge this is the first investigation of a possible genetic aetiology in DO/OAB. We have observed a locus (D13S171) which is present in all subjects with DO/OAB phenotype. It is unrelated to the loci previously seen in NE. Knowledge of such a locus may affect prognosis and open up new avenues of research, such as alteration in detrusor receptor proteins.

[1]Br Med J. 1(5954):364-7 [2]Neurourol Urodyn 2003;22(5):460-461