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Diabetes defect defined

McIlraith would be pleased — one hundred years after his documentation of nephrogenic diabetes insipidus, the pursuit of the molecular pathology behind this condition has finally succeeded.

THERE is a satisfying temporal neatness to be found in the centenary, this very month, of the first description[1] of nephrogenic diabetes insipidus (NDI). For, in the October issue of *Nature Genetics*, two groups[2,3] present a total of nine separate mutations associated with the disease. These papers reflect the quickening tempo of research.

For the past few months there has been little doubt that the defect underlying NDI, an X-linked recessive disorder, would be found within the gene for the vasopressin (antidiuretic hormone) V2 receptor[4,5]. In NDI patients, the renal tubule is insensitive to vasopressin, leading to an inability to concentrate urine despite elevated levels of the hormone. Untreated, the condition can cause severe dehydration, growth reduction and even mental retardation. The simple remedy is to ensure an adequate intake of fluids.

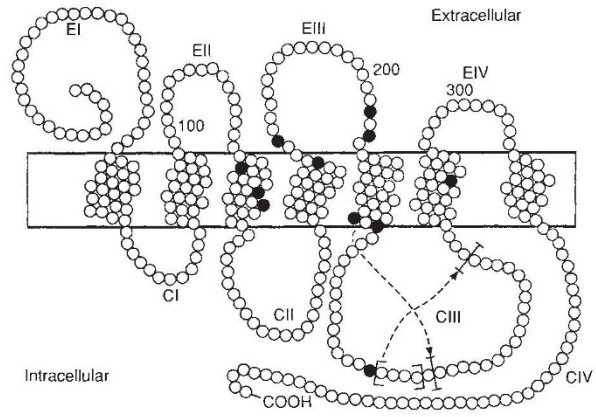
Barely four months ago, the cloning of the V2 receptor gene from human[6] and rat[7] was reported; furthermore, the human gene mapped to chromosome Xq28, making it a prime candidate for the NDI locus which had been previously assigned to the same region. Astute readers will recall that such suspicions were indeed confirmed two weeks ago with the description of mutations in the V2 receptor gene in two patients[8]. Now we have the association of nine separate mutations with the disease reported in *Nature Genetics*, and yet others have also been uncovered (see figure).

The V2 receptor is a member of the G-protein-coupled receptor family possessing the characteristic seven membrane-spanning regions[4] (see figure). Rosenthal *et al.*[8] amplified the V2 receptor gene from a severely affected Canadian patient and found a deletion of one of six consecutive guanosine nucleotides at codon 246, resulting in premature termination of the protein 23 residues downstream. A second patient had an alanine to aspartic acid substitution at codon 132 (Ala 132→Asp) in the third transmembrane domain.

As they now report, Bernard van Oost and colleagues[2] chose to concentrate on the region of the V2 receptor gene encoding the third extracellular domain (numbered according to ref. 4), thought to be important for the binding of the hormone. They found point mutations in three of eight NDI patients. Interestingly, all three extracellular mutations create new cysteine residues (from Gly 185, Arg 203 and Tyr 205) which might disrupt the tertiary structure of the receptor and interfere with vasopressin binding[2,4].

Meanwhile, Jane Gitschier's group[3] adopted single-strand conformational polymorphism analysis to search for deviations of the V2 receptor gene from the normal sequence. Five of the six patients analysed showed such abnormalities: sequencing revealed that three mutations occur within transmembrane domains (Gln 119→Stop, Tyr 128→Ser and Pro 286→ Arg); one lies at the start of the third extracellular domain and also generates a cysteine residue (Arg 181→Cys); and two changes occur in the third intracellular loop (a frameshift after Arg 230 and deletion of residues 247–250). One patient with a positive family history had two of these defects (Arg 181→Cys and the Arg 247–Gly 250 deletion). Finally, a fourth group has uncovered still more mutations — a cytosine insertion in codon 228 (Ile), also predicted to truncate the V2 receptor in the third cytoplasmic loop, and another creation of an extracellular cysteine residue (Arg 202→Cys) (A. Spiegel, personal communication).

Already, then, some notable trends are emerging. Mutations in the V2 receptor are clustered in three distinct parts of the molecule — the third transmembrane domain, the third extracellular domain (in all five cases creating cysteine residues that may interfere with disulphide bond formation) and the third cytoplasmic loop, where frameshift mutations lead to premature termination of the protein. These are predicted to produce a non-functional protein, genetically termed a *null* allele. In males, with only one copy of the X-linked gene, such (recessive) mutations confer the affected phenotype. These are not the first examples of recessive mutations in a G-protein-coupled receptor — Dryja and colleagues have described a mutation in the rhodopsin gene, which also produces a truncated protein and leads to autosomal recessive retinitis pigmentosa[9]. But the new studies do represent the first identified mutations in a G-protein-coupled hormone receptor.



Vasopressin V2 receptor mutations in NDI. Filled circles denote substitutions or frameshift mutations; arrows indicate truncated sites; brackets represent in-frame deletion. (Adapted from ref. 4.)

The new molecular data also allow examination of the so-called 'Hopewell hypothesis'. This holds that most NDI cases in the United States trace back to the Celtic settlers who landed in Nova Scotia in October 1761 aboard the ship *Hopewell* (see ref. 5), and therefore that only a small number of original mutations accounted for the disease. The hypothesis seems to have been sunk, however, with the discovery of at least 13 distinct mutations, many from families in North America[3,8]. **Kevin Davies**

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Also in this month's *Nature Genetics*: disruption of a *trithorax*-like gene in acute childhood leukaemia; potential defect in L1CAM, a neural cell-adhesion molecule, in X-linked hydrocephalus; typing DNA from dental remains; and disorders in skeletal muscle sodium channels in humans and race horses.

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5. Warren, S. T. *Dysmorph. clin. Genet.* (in the press).
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