Norrbottnian congenital insensitivity to pain.

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Abstract :

Congenital insensitivity to pain is a rare hereditary neuropathy. We present patients from a large family in Norrbotten, Sweden with a mutation in the nerve growth factor beta gene (NGFbeta). Using a model of recessive inheritance, we identified an 8.3-Mb region on chromosome 1p11.2-p13.2 shared by the affected individuals in the family. Analysis of candidate genes in the disease-critical region revealed a mutation in the coding region of the NGFbeta gene specific for the disease haplotype. All three severely affected individuals were homozygous for the mutation. The disease haplotype was also observed in both unaffected and mildly affected family members, but in heterozygote form. We have identified 43 patients, 3 homozygous and 40 heterozygous. The homozygous patients have a severe congenital form with onset of symptoms at an early age, most often affecting the lower extremities with insidious progressive joint swellings or painless fractures. Fracture healing was normal, but the arthropathy was progressive, resulting in disabling Charcot joints with gross deformity and instability. These patients lacked deep pain perception in bones and joints and had no protective reflexes, leading to gross bone and joint complications. They also had abnormal temperature perception but normal ability to sweat. There was no mental retardation. Clinically, they fit best into the group HSAN type V. Sural nerve biopsies showed a moderate loss of thin myelinated fibers (Adelta-fibers) and a severe reduction of unmyelinated fibers (C-fibers).