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Further Delineation of the Critical Region for Noonan Syndrome on the Long Arm of Chromosome 12

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Key Words

Noonan syndrome · Chromosome 12q · Mapping studies

Noonan syndrome (NS) is an autosomal dominant disorder characterised by typical facies, short stature and congenital heart disease [1], with an estimated incidence between 1 in 1,000 and 1 in 2,500 [2]. We have recently localised a gene for NS to 12q22-qter in a large 3-generation Dutch family [3, 4]. Recombination events placed the gene in a 14-cM interval between the markers D12S84 and D12S366.

In the present study, we analysed the 3-generation family with newly isolated CA-repeat markers derived from the interval between D12S84 and D12S366 (fig. 1a) [5]. Genotyping was performed as previously described [3]. At the proximal border of the critical region, a recombination was detected between D12S105 and D12S1637 (fig. 1b, III.3). D12S1605 was not informative. In the distal part of the critical region, a recombination was found between D12S79 and NOS1 (fig. 1b, III.4). Thus, the interval which contains the gene mutated in this family to produce NS is now defined by markers D12S105 and NOS1. As NOS1 has not been positioned genetically, it is impossible to determine precisely by what amount the physical and genetic intervals have been reduced by these new recombinations. Existing physical maps indicate that

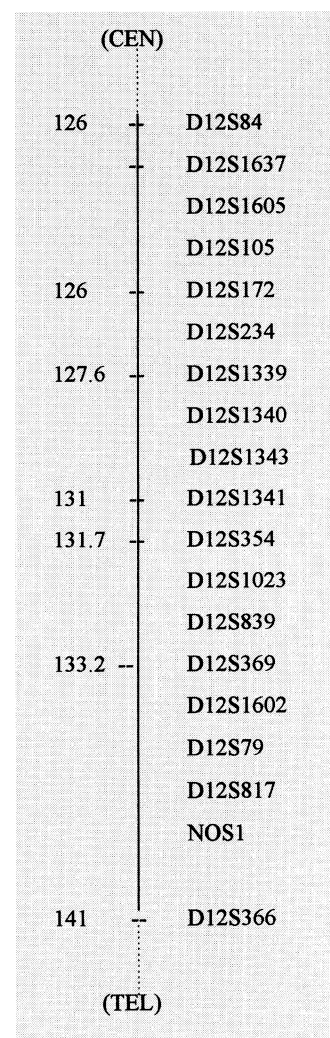


Fig. 1. a Genetic map of the relevant region of chromosome 12q. Distances are given in centimorgans [5, 6]. CEN = Centromere; TEL = telomere. **b** Pedigree and haplotypes of the Dutch family. The markers used for haplotype construction are shown. The cross-hatched bars represent haplotypes, which co-segregate with the disorder, the black bars represent areas of uninformative regions and the white bars represent the unaffected haplotype.

NOS1 is positioned less than 1.7 Mb distally of D12S79, the most distal marker in the NS interval to be assigned a genetic distance [5]. D12S79 is 6 cM distal to D12S105, so the NS interval can be summarized by: D12S105-(6 cM)-D12S79-(1.7 Mb)-NOS1, which is likely to represent a substantial reduction in the interval.

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