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The exclusion of three candidate genes from the pathogenesis of Noonan Syndrome by fluorescence in situ hybridisation

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Noonan Syndrome (NS) is an autosomal dominant developmental disorder which occurs at a frequency of 1:1000 - 1:5000 live births. Linkage analysis in one large three generation NS family has permitted the assignment of a gene for NS to an 8cM interval on the long arm of chromosome 12 at 12q22-q24, whilst a similar analysis in smaller two generation families reveals genetic heterogeneity for this disorder. In the absence of any chromosome rearrangements associated with the disease, one approach currently being employed to identify the underlying gene responsible for this disorder is the examination of various candidate genes. In the current report, we present the exclusion of three interesting candidates from chromosome 12. Two of these genes (epidermal growth factor receptor pathway substrate-8 and decorin) are potentially interesting functional candidates and have been assigned to the proximity of the NS critical interval. Interestingly, mutations in the murine homologue of the third gene (high mobility group protein 1) produces a mouse which exhibits some of the NS characteristics. Using FISH analysis, we have determined the locations of the genes and positioned them outside the NS region, thereby excluding these genes from having a role in the pathogenesis of the disease.