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Analysis of 13q RFLP in Multiple Endocrine Neoplasia Type II Kindreds

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Multiple endocrine neoplasia type II (MEN-II or Sipple's syndrome) is an autosomal dominant disorder inherited with almost complete penetrance by the age of 40, characterized by medullary cancer of the thyroid, pheochromocytoma, and parathyroid adenoma [1–3]. Recently, Butler et al. [4] published results of chromosome and DNA studies in MEN-II. Apparent interstitial deletions of 20p12 were seen by blind, high-resolution chromosome analysis, similar to the findings reported by Babu et al. [5]. Interestingly, DNA sequences detected by the D20S5 probe localized to 20p12 did not detect DNA deletions in heterozygous MEN-II individuals, a finding consistent with the report of Goodfellow et al. [6].

Recently, Cavenee documented an acquired deletion of genomic sequences on 13q33 from a pheochromocytoma from one of 20 individuals with MEN-II. Using the recombinant plasmid p9A7 (13q33) as a probe, he found that DNA isolated from the patient's leukocytes and a pheochromocytoma contained two and one alleles, respectively [7; personal communication]. Because his result was analogous to previous findings of somatic deletions giving rise to retinoblastoma and Wilm's tumor [8, 9], we sought to determine if sequences detected by p9A7 comprise a portion of or are closely linked to the MEN-II locus. To do so we carried out linkage analysis of leukocyte DNA from unrelated MEN-II kindreds previously studied by Butler et al. [4] using restriction fragment length polymorphisms (RFLP) detected by multiple clones localized to 13q.

Five-microgram aliquots of leukocyte DNA from eight MEN-II individuals and their relatives of two unrelated kindreds were digested with *MspI*, *TaqI*, or *HindIII*. Southern blots were prepared and then hybridized, using standard procedures [10, 11], to radiolabeled anonymous genomic inserts from the recombinant plasmids p7F12, p 9D II, pLE8 and p9A7 (generous gifts of M. F. Hansen), which have been mapped to 13q12, 13q22, 13q22, and 13q33, respectively [7].

Of the four inserts studied, two (p 9D II and p9A7) were informative for RFLP. Assuming that the coupling phases of RFLP detected by p 9D II and p9A7 in both families are “– + MEN-II” for the affected individuals and that the eldest child (age 45 years) in family A (bottom left) is an “escapee”, then three and two recombinants are seen with p9D11 and p9A7, respectively (Fig. 1). Conversely, when it is assumed that the coupling phases are “+ + MEN-II” and “+ – MEN-II” for the affected individuals for p9D11 and p9A7, respectively, then three and one recombinants are seen.

Our results demonstrate that the MEN-II locus is not tightly linked to the p9D11 (in region 13q22) and p9A7 (in region 13q33) loci, and suggest that MEN-II tumors in families studied are not likely to be related to somatic deletions involving the 13q22 and 13q33 regions.

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Figure 1.

Autoradiograms of DNA from 11 members of two MEN-II kindreds (A and B) after digestion with *MspI*, *TaqI*, or *HindIII*, and hybridization with radiolabeled p9D11 and p9A7 inserts. Individuals having MEN-II are indicated by solid symbols. Fragment sizes (in kilobases) are shown on the right. Chromosomal haplotypes are separated by vertical lines. Recombinants are designated by solid dots on the vertical lines. See text for further details.