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Charles E. Jackson

Robert A. Norum

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Charles E. Jackson,* and Robert A. Norum†

Multiple endocrine neoplasia type 2B (MEN 2B) is similar to MEN 2A in that both autosomal dominant syndromes include medullary thyroid cancers and pheochromocytomas. It is distinct in that MEN 2B patients have much earlier age of onset with more aggressive tumors and mucosal neuromas of the lips and tongue. The neuromas allow ascertainment generally before age 5. Studies of two and three generations of 14 MEN 2B families disclosed close linkage of the MEN 2B gene to DNA markers to which MEN2A had been linked. Multipoint analysis utilizing additional results in three generations of a 15th family have disclosed a peak total lod score of 8.89 at the midpoint between the centromere markers D10Z1 and RBP3 on the long arm (band q11). One recombinant was observed between D10Z1 and MEN2B, but this individual was not recombinant with D10S94. These studies suggest physical proximity of MEN2A and MEN2B but do not establish allelism for the gene(s). (Henry Ford Hosp Med J 1992;40:232-5)

Multiple endocrine neoplasia type 2B (MEN 2B) is a syndrome in which medullary thyroid cancer (MTC) is associated with adrenal medullary pheochromocytomas and mucosal neuromas. MEN 2B is distinguished from MEN 2A by the presence in MEN 2B of neuromas of mucous membranes such as shown in Fig 1 (1), intestinal ganglioneuromas, and generally by the lack of parathyroid involvement (2-7). In addition, the MEN 2B MTCs have an earlier onset and are generally (7-9), but not necessarily (10), more aggressive. Thickened corneal nerves (11) and skeletal abnormalities are also observed in MEN 2B frequently with a marfanoid habitus and arachnodactyly. Both MEN 2A and 2B have an autosomal dominant inheritance with a greater proportion of MEN 2B cases arising as new mutations.

The gene for MEN 2A (MEN2A) has been localized to chromosome 10 by Mathew et al (12) and by Simpson et al (13) with confirmation by many other studies in diverse populations (14-19). In these studies no suggestion has been reported yet of genetic heterogeneity even for variant families in whom the whole spectrum of tumor involvement is not seen or even in those families of MTC only (20,21).

Studies of Norum et al (22) in two and three generations of 14 MEN 2B families established that the gene for MEN 2B (MEN2B) is closely linked to the same DNA markers to which MEN2A has been linked. Additional results in three generations of a 15th family (Fig 2) add data to confirm this localization with a peak total lod score of 8.89 at the midpoint between the centromere and RBP3 on the proximal long arm of chromosome 10 [Fig 3, (23)]. Table 1 shows the two-point linkage data between MEN2B and chromosome 10 markers. Lairmore et al (21) reported confirmation of this localization in six MEN 2B families, two of which had been those utilized in the study of Norum et al (22). The combined two-point linkage data are shown in Table 2.

In one family (Fig 4) linkage data provided evidence that MEN2B is on the proximal long arm of chromosome 10 since a recombinant was observed between the centromere marker D10Z1 and MEN2B and D10S94 (24) on the telomeric side of the long arm. This one family also provided evidence that the new mutation in this family was paternal in origin. Studies of three other new mutation cases showed the mutation to be paternal in one other family and maternal in two. In MEN 2B the availability of new mutation cases in whom DNA has been obtainable from both unaffected parents will be important in identifying the gene when possible candidate genes are ascertained. New mutation cases have been important in identifying the gene for neurofibromatosis type 1 (25). The availability of many new mutation cases is one of the advantages of studying MEN 2B. Another advantage is that the diagnosis of MEN 2B is evident at an early age by experienced parents or physicians by its phenotypic expression of the first mutational event (Fig 5).

We have suggested a contiguous gene theory as an explanation for the observation that the tissues involved with MEN 2 tumors are generally consistent within families with a variety of tumor involvement between families (20,26,27). The linkage of MEN2B to the same DNA markers to which MEN2A has been linked is compatible with this theory and the initiation of the MEN 2 tumors by the possible deletion of tumor-suppressor genes as in the retinoblastoma model. However, no chromosome 10 deletions were observed in high-resolution cytogenetic studies of 16 MEN 2A and 7 MEN 2B families (28). Also, no consistent chromosome 10 losses of heterozygosity in MEN 2A tumors have been observed (20,29-32) as in the retinoblastoma model. Losses of heterozygosity of 1p have been reported in

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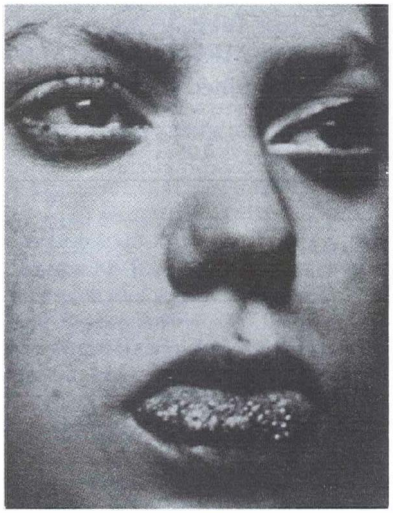
*Division of Clinical and Molecular Genetics, Henry Ford Hospital.
†Department of Dermatology, Henry Ford Hospital.
Address correspondence to Dr. Jackson, Division of Clinical and Molecular Genetics, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202.



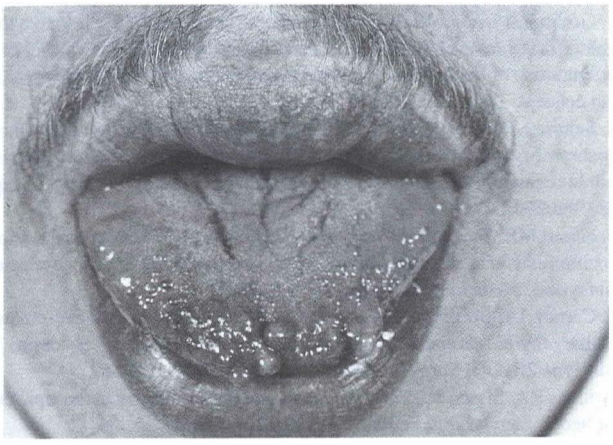


Fig 1—A) (top photo) Illustration of mucosal neuromas of tongue from 1923 publication by Froboese (1) (reprinted with permission, copyright © Springer-Verlag). B) (bottom photo) Bumpy lips and tongue of 20-year-old new mutation MEN 2B case.

MEN 2B tumors (33). The cause of the tissue specificity in MEN 2 and in other hereditary tumors such as the Beckwith-Weidemann syndrome (34) will remain an area of speculation until more knowledge is obtained on the nature of the genes involved (20).

The linkage data presented here indicate that MEN2B and MEN2A are closely linked to the same DNA markers but do not indicate that the gene(s) are allelic (22). Elucidation of the nature of the gene(s) may provide an understanding of the etiology of the mucosal neuromas, the ganglioneuromas, the marfanoid habitus, and the other unique phenotypic changes of MEN 2B as well as an explanation for the aggressiveness of the tumors of MEN 2B.

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Table 1
Pairwise Linkage MEN2B Versus Markers

	0	0.05	0.1	0.2
FNRB	3.43	3.69	3.44	2.62
D10Z1	6.41	6.35	5.75	4.22
RBP3	−1.51	1.50	1.44	0.69
D10S15	0.63	3.74	3.48	2.63

Multipoint peak LOD score 8.89 at the midpoint between D10Z1 and RBP3.

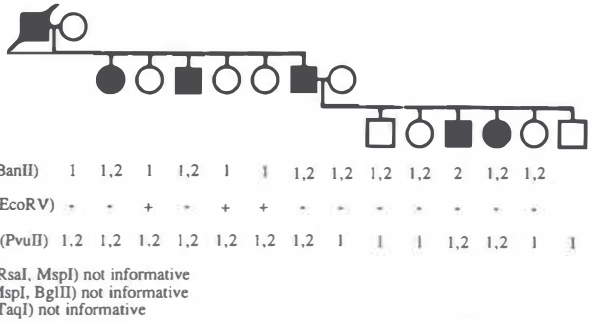


Fig 2—Pedigree of three generations of the 15th MEN 2B family studied with data on D10S94 (24), FNRB, and D10Z1. The D10S94 data were kindly provided by P. J. Goodfellow.

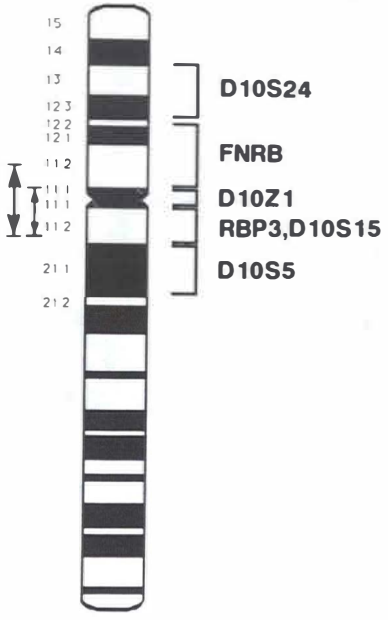
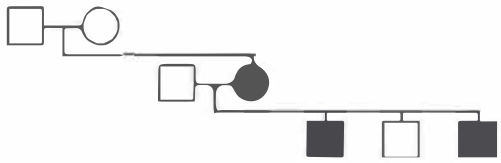


Fig 3—Illustration of the location of MEN2B in reference to pericentromeric DNA markers. The physical map of chromosome 10 has been modified from Smith & Simpson (23). The longer arrow indicates the likely location of MEN2A, and the shorter arrow indicates the location of MEN2B based on the crossover observed between MEN2B and the centromere marker D10Z1.



FNRB	F2	F1/F2	F2	F1/F2	F2	F2	F2	
D10Z1(BglII)					1600	580	580	580
				580	580	580	580	
D10Z1(ScaI)				570	570	570	570	
				420	570	570	570	
D10S94	A2	A1	A1	A1/A2	A1/A2	A1	A1/A2	

1. Crossover with FNRB and D10Z1 on one side, and D10S94 and MEN2B on the other side.
2. The new mutation was paternal.

Fig 4—Pedigree and linkage data on the family in which a recombinant is observed between the centromere marker D10Z1 and MEN2B and D10S94 telomeric to the centromere on the long arm. The D10S94 studies were kindly performed by P. J. Goodfellow.

Fig 5—Illustration of affected mother and infant son demonstrating the identification of MEN 2B individuals at young ages. In this family it was later possible to identify that a daughter was affected at birth.

2B families (22), to Dr. G. W. Sizemore of Chicago, IL, and Dr. S. Khosla of Rochester, MN, for providing access to the 15th family reported here (35), and to the cooperation of the many MEN 2B patients and their families.

Table 2
Pairwise Linkage MEN2B Versus Markers
Combined Data*

	0	0.05	0.1	0.2
FNRB	4.93	4.99	4.56	3.33
D10Z1	7.01	6.86	6.17	4.48
RBP3	−0.31	2.55	2.34	1.27
D10S15	1.53	4.53	4.04	3.07

*With Lairmore et al (21).

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