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Chromosomes in Multiple Endocrine Neoplasia Type 2 Syndromes

Daniel L. Van Dyke, PhD,* V. Ramesh Babu, PhD,* and Charles E. Jackson, MD**

In 19 patients from nine MEN-2A families, high-resolution G-banded chromosome studies have revealed a visible deletion within sub-band 20p12.2, yet no abnormality was observed in a 10th family. A deletion indistinguishable from that in MEN-2A was observed in five patients from three MEN-2B families but not in two

In 1978 we began to use high-resolution cytogenetic techniques (1) to examine patients with a genetic predisposition to cancer, including patients with multiple endocrine neoplasia (MEN) syndromes. Initially, we studied three or four patients with MEN-2A and interpreted several high-resolution karyotypes as normal before we became suspicious of a deletion in the short arm of chromosome 20 in the fourth or fifth patient. With that information, we reevaluated the original slides on the first patients and became very suspicious of those as well. Next, we carried out one blind study (2,3), and after that, a second blind study (4). The second study was carried out after we experienced many of the pitfalls inherent in high-resolution cytogenetic studies (5).

The Figure illustrates a pair of chromosome 20s in prometaphase to show the MEN-2 deletion diagrammatically. The abnormality probably involves only the light-staining sub-band 20p12.2, and it appears to be a deletion within this sub-band. In order to detect the deletion in MEN-2, we selected chromosomes of sufficient resolution that sub-band 20p12.2 was consistently observable in both homologs of the control subjects. In specimens from affected individuals, sub-band 20p12.2 was narrower in one homolog than in the other, and in some cells the sub-band could be seen in only one of the two homologs. In the photographs published by Emmertsen, et al (6), sub-band 20p12.2 does not appear to be resolved in either homolog; thus, we consider the published resolution inadequate to interpret the presence or absence of the deletion in question.

In the second study (4) and the blind study that preceded it, all blood samples delivered to the laboratory were identified only by a code number. Slides were prepared, and the locations of a large number of prometaphase cells were identified. One cytogeneticist

other MEN-2B families. We found no abnormality in the entire karyotype of the four MEN-1 patients studied. These findings suggest that the mutation in most MEN-2 patients is a visible deletion in the short arm of chromosome 20.

scored all prometaphase cells to identify the chromosome 20s as either scorable or not scorable. Most cells in prometaphase are not scorable. If the chromosome 20p region was underneath another chromosome, that cell was not scorable. If chromosome 20p was bent or folded, which happens frequently in prometaphase, that cell was not scorable. Condensation of the chromosomes varies even within a single cell. Commonly, a chromosome 20 on the edge of a metaphase will be measurably longer than its homolog in the middle of the metaphase spread because of differential condensation, so that one must examine the whole chromosome 20 pair in minute detail to decide whether the homologs have a similar level of condensation. Actual measurements of chromosome 20 band length have not been any more helpful than subjective observations. Finally, two or three cytogeneticists independently scored all adequate cells for the presence or absence of the deletion.

The blind study included 30 independently scored blood samples from 25 subjects (4). Nine samples were taken from eight patients from four MEN-2A families, and all nine of those samples were scored as having the 20p deletion. Eight samples were from six patients from five MEN-2B families (two were scored twice). Five of the MEN-2B patients were scored for a 20p deletion, and three were scored for a normal chromosome 20. Two of the MEN-2B patients who were scored for a normal chromosome 20 were suspected to be new mutants, but

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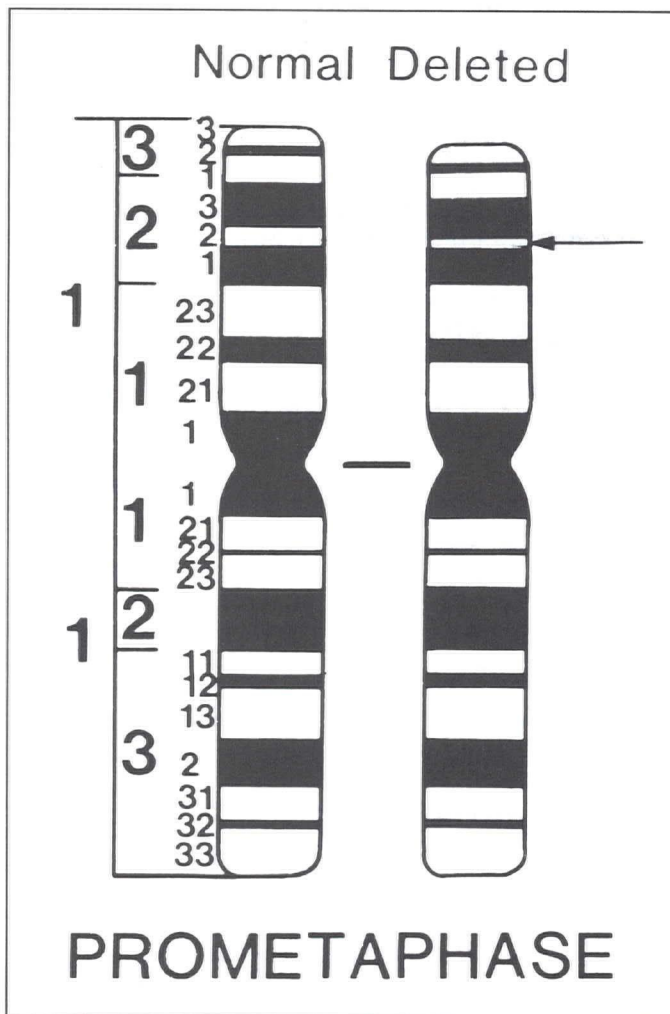
we have yet to obtain subsequent samples to confirm that no deletion was present. For one of the MEN-2B patients scored as negative for a chromosome 20 deletion, the mother and brother were studied. In a nonblind preliminary study, the mother showed the deletion. The brother was in the same blind study, and his karyotype was scored as having the deletion. Another specimen was sent on the two siblings in the blind study, and both were scored for the deletion. We interpret these observations as an error in scoring this one MEN-2B patient as normal on the initial examination.

Of the 13 control specimens, two were from MEN-2 family members at risk, but they were judged to be old enough and sufficiently well tested to establish that they did not have the gene (7); in both, chromosome 20 was normal. Nine of the remaining 11 control specimens were scored for normal chromosome 20s, and two were

scored as 20p-, clearly in error. Subsequent samples from both of these controls were scored as normal in the blind study.

In all, three errors were made in the blind study: one MEN-2B patient who was scored initially as having normal chromosome 20s and the two controls who were scored initially as having a 20p deletion. In retrospect, it is possible that we relaxed our stringent criteria in relation to the length of the chromosomes and the condensation problem we faced throughout the study. However, by 2x2 chi square analysis, the likelihood of having arrived at these scores by chance alone was less than 0.001.

Our interpretation of the findings is that most MEN-2 patients have a visible interstitial chromosome 20p deletion. When these findings are combined with our other blind studies and preliminary data (Table), we have studied a total of 19 patients from 10 MEN-2A families. All patients from nine of the 10 MEN-2A families have the deletion; one patient from the 10th family was scored for a normal chromosome 20. Five MEN-2B patients from three MEN-2B families have shown the deletion, and two other unrelated MEN-2B patients did not have the deletion. In four unrelated MEN-1 syndrome patients, the entire prometaphase karyotype appeared normal.



Figure

Diagrammatic illustration of chromosome 20. Arrow indicates area of deletion involving sub-band p12.2 on the homolog on the right.

TABLE

High-Resolution Chromosome 20 Studies in the MEN Syndromes*

	Patients	20p Deletion		20p Normal		% Families with 20p Deletions
		Patients	Families	Patients	Families	
MEN-2A	20	19	9	1	1	90
MEN-2B	7	5	3	2	2	60
MEN-1	4	0	0	4	4	0

*Summary of published (2-4) and unpublished findings from our laboratory.

In a number of MEN-2A and -2B patients, we addressed the question of chromosome instability, raised by T.C. Hsu and colleagues (8). We failed to find increased levels of sister chromatid exchanges in any of our patients, and, except for one patient, we found no increased levels of chromosome instability or chromosome breakage (9). We are attempting to determine the causes for the discrepancy between our two laboratories.

We were surprised to find a visible deletion in this large proportion of the families studied (Table). However, the technique is unlikely to have widespread, direct clinical application because the high-resolution chromosome studies necessary are so demanding technically. The deletion finding may be useful not as a

diagnostic tool but as a lead to MEN-2 detection by recombinant DNA or other techniques. It may also offer further insight into the mechanisms of neoplasia, as was the case with the chromosome 13 deletion in retinoblastoma (10).

Addendum

Results of restriction fragment length polymorphism presented at the First International Workshop on MEN-2 and later presented at the 1984 American Society of Human Genetics meeting by Goodfellow and associates (11) have provided evidence in three kindreds against

close linkage of MEN-2A and a marker reportedly localized to the approximate site of the deletion we have reported here. Cooperative studies are in progress to explain these apparently contradictory findings.

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