Pleural malignant mesotheliomas (MMs) are aggressive tumors that generally affect individuals older than 50 years of age and occur more frequently in men than in women (1). They are derived from mesothelial cells lining the pleural, pericardial, and peritoneal cavities. Approximately 3000 patients are diagnosed with MM in the United States each year. Its frequency is increasing worldwide, and this trend is expected to continue until the year 2020 (2). The increasing incidence of MM over the past 40 years is a reflection of exposure to asbestos fibers in industrialized countries, particularly in connection with the mining and shipyard industries (2). Epidemiologic studies have established that exposure to asbestos fibers is associated with about 80% of the cases (3); however, recent studies have implicated simian virus 40 (SV40) in the etiology of some MMs (reviewed in refs. 4–6).

Malignant mesothelioma is characterized by a long latency of 20 to 40 years between exposure to asbestos and tumor development, indicating that multiple somatic genetic alterations may be required for tumorigenic conversion of a normal mesothelial cell. Early evidence to support this idea was provided by karyotypic analyses, which revealed multiple cytogenetic alterations in most human MMs (reviewed in ref. 7). Specific chromosomal changes are not shared by all MMs; however, several prominent sites of chromosomal loss have been identified in this malignancy. Tumor suppressor genes (TSGs) located in these deleted chromosomal regions may be responsible for the tumorigenic conversion of mesothelial cells, and recent studies have begun to identify the specific TSGs that contribute to the development and progression of MM. This chapter presents an overview of recurrent chromosomal imbalances and molecular genetic alterations characteristic of this malignancy.
rearrangements of various chromosomes, particularly the short (p) arms of chromosomes 1, 3, and 9, and the long (q) arm of chromosome 6. Loss of one copy of chromosome 22 is the single most consistent numerical change seen in MMs. Losses or rearrangements of chromosomes 4, 14, and 17 and gain of chromosome 7 also have been commonly observed. Deletions and unbalanced rearrangements accounted for overlapping losses from the chromosome region 1p21-22 in 32 of 39 (82%) cases. Twenty-five of 39 (64%) MMs possessed interstitial deletions or other rearrangements resulting in losses from 3p21. Twenty cases (51%) showed losses from 6q, with the shortest region of overlap (SRO) being 6q15-21. Losses involving 9p were detected in 31 (79%) cases, with the SRO being 9p21-22. Loss or relative deficiency of chromosome 17 was observed in 11 of 39 (28%) cases. Loss of a copy of chromosome 22 was documented in 26 cases (67%). These recurrent losses of 1p, 3p, 6q, 9p, 17p, and 22 frequently occurred in combination in a given tumor. The complexity of the cytogenetic alterations observed suggest the emergence of tumor progression-associated changes. However, since cytogenetic data do not exist for early neoplastic/proneoplastic lesions of the mesothelium, it is not possible to discriminate between alterations associated with initiation and those associated with progression of the disease. However, the accumulated losses of DNA sequences from chromosomes 1p, 3p, 6q, 9p, 17p, and 22 appear to play a significant role in the pathogenesis of MM.

Comparative genomic hybridization (CGH) analysis has also revealed recurrent genomic imbalances in MM. Comparative genomic hybridization to metaphase chromosomes is a DNA-based, molecular cytogenetic technique that facilitates the identification of chromosome imbalances within the entire tumor genome in a single experiment. The CGH analyses were performed on 24 MM cell lines derived from patients from the United States (11); each of these cell lines exhibited numerous (6 to 25) genomic imbalances. Loss of 22q, documented in 14 of 24 (58%) cell lines, was the most prominent alteration. Also in agreement with earlier karyotypic findings, losses of 1p, 3p, 6q, 9p, and 9p were common, with each being detected in about 30% to 40% of cell lines. Moreover, the metaphase-CGH analysis uncovered other recurrent chromosome losses not highlighted by previous karyotypic studies. In particular, 13 of 24 MMs (54%) showed losses of part or all of 15q, with the SRO being 15q11.1-21. Additionally, losses of 14q24.2-qter and 13q12-14 were each observed in 42% of the cell lines. The most frequently overrepresented chromosomal arm was 5p (54% of cases), suggesting the involvement of a putative oncogene(s) in this region.

Many of the common genomic imbalances identified in MM cases from the United States were also detected in a series of MM specimens from Finland (12,13). Prominent among the recurrent alterations detected were losses of chromosome arms 4q, 6q, 9p, 13q, 14q, and 22q. However, three prominent imbalances in the series of MMs from the United States, i.e., losses of 15q11-21, 8p21-pter, and 3p21, were each observed in only one of 42 of the Finnish cases. Such variation between the data from Finland and from the United States may reflect dissimilarities in the type of asbestos exposure or genetic differences in the