

The genetic susceptibility in the development of malignant pleural mesothelioma

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Abstract: Malignant pleural mesothelioma (MPM) is a cancer of the pleural cavity whose main risk factor is exposure to asbestos. However, it has been shown that only a minority of exposed people develops MPM. In fact, the incidence among professionally exposed workers was shown to vary between 0.5% and 18.0%. Various hints suggested that other important cofactors could play a role, in particular the genetic susceptibility. Impressive is the case of Cappadocian families exposed to erionite and affected by an “epidemic” of MPM with about half of the inhabitants dying for the disease. However, no results for a “Cappadocia” gene of susceptibility to MPM have been obtained yet and more studies are needed. Among asbestos-exposed workers, several studies reported familial cases of MPM, suggesting that heredity could be important in the tumor development. However, large studies on familial clusters showed only weak increased risks that could be attributable also to indirect exposures in a contaminated household. Moreover, the risk of developing MPM is increased of a limited extent among people exposed to asbestos with a positive history of familial cancers. A particular is represented by carriers of germline mutations within *BAP1* gene. In families and in animal models, mutations within *BAP1* are strongly predisposing to develop MPM. However, also other types of cancer (such as uveal melanoma) are present, thus *BAP1* mutations are considered as responsible for a hereditary form of a multi-cancer syndrome. In any case, among sporadic MPM, the prevalence of germline *BAP1* mutations is negligible. Finally, genetic studies highlighted the presence of low-risk susceptibility alleles, such as those within *XRCC3*, *NAT2* or *GSTM1*. Two different genome-wide association studies could not find positive associations reaching the genome-wide statistical significance threshold, however, both were concordant in showing a weak signal within the *SDK1* gene region. Overall, it could be concluded that, as for other types of sporadic cancers, the susceptibility to develop MPM following asbestos exposure is modulated moderately by the individual genetic background. Further studies on larger series could help in a better characterization of more genes predisposing to MPM, being this tumor a rare disease.

Keywords: Mesothelioma; malignant pleural mesothelioma (MPM); asbestos; genetic susceptibility

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Introduction

Malignant pleural mesothelioma (MPM) is a cancer mainly caused by asbestos exposure and with a long latency between asbestos exposure and tumor diagnosis. However, according to the reports reviewed by Gibbs and Berry (1),

only a minority of exposed people develops MPM. In fact, the incidence among professionally exposed workers was shown to vary between 0.5% and 18.0%. Although this risk could be modulated by the type of asbestos handled by workers and by the protective measurements to lower

their individual exposure, various hints suggested that other important cofactors could play a role, in particular the genetic susceptibility. In fact, even a lifetime-risk of 18% following asbestos exposure does not explain, satisfactory, the observation of families with multiple cases. Furthermore, most of them show MPM among relatives without an ascertained exposure to asbestos. In this context, even more impressive is the case of Cappadocian families exposed to erionite. Moreover, genetic studies highlighted the presence of low-risk susceptibility alleles as well as other more penetrant inherited mutations. This review will explore the latest concepts of the genetic susceptibility to MPM.

Familial clustering of MPM

The hypothesis that genetics may be involved derives from the frequent reports (at least 20 so far) of MPM cases recurring in the same family. In 1980, Risberg *et al.* highlighted the heredity as a key element in determining MPM development. They described a familial clustering in which three brothers, one sister and their father died of MPM. All of them smoked, and 4 of the 5 cases have been probably occupationally exposed to asbestos (2).

The occurrence of MPM among relatives was reported also by Bianchi *et al.* (3). Forty MPM out of 610 analyzed were familial cases, all previously exposed to asbestos. The fact that genetic factors could be crucial for these patients had been suggested by the existence of blood relationships among their members in 15 different families.

In 2013, Kalogeraki *et al.* studied a single family in which MPM occurred in the father and daughter. Both of them developed this neoplasm characterized by similar clinic features. The father has been affected at the age of 42 years and the daughter at the age of 35 [14 years later (4)].

On the other hand, Ascoli *et al.* analyzed the features of MPM in blood relatives that could explain the disease clustering, recruiting 11 clusters (22 cases) identified among 1,954 Italian MPM cases, and 51 clusters (120 cases) extracted from 33 studies. The authors found MPM profiles similar in both consanguineous and unrelated patients and that the majority of clusters were linked to asbestos exposure, thus suggesting that a low proportion of familial cases is not influenced by a large genetic component (5). Moreover, de Klerk *et al.* suggested that the genetic component plays a role important but not weighty in mesothelioma, similar to what observed in other types of neoplasm. Indeed, they explored the history of 11,000

asbestos workers from the cancer and death registries of Wittenoom (Australia), and found 369 families with at least one case of mesothelioma and a further 25 cases of mesothelioma among relatives in the same families, with 12.9 predicted cases (6).

In summary, when a blood relationship exists between MPM cases, the presence of susceptibility factors interacting with asbestos exposure could be suggested. However, a strong confounder for a genetic study refer to indirect risk for relatives of asbestos workers, who can inhale fibers through daily behaviors such as washing contaminated working clothes, or even hugging the father with contaminated working clothes. Vianna and Polan recruited 52 women and matched controls and analyzed the risk to develop MPM when exposed to asbestos in indirect way (7). The authors observed that the risk was significantly increased when woman live with husbands or other persons working in asbestos-related industries. These evidences suggest that the shared asbestos exposure could be the main factor of MPM affecting different components (not genetically related) within the same family. This result has been reported also by Anderson *et al.* and other authors (8,9).

Is a cancer in a first-degree relative (FDR) a risk factor for MPM?

Heineman *et al.* performed telephone interviews to 196 MPM patients and controls and reported histories of cancer in FDRs (10). They highlighted a strong risk to develop mesothelioma for patients (exposed to asbestos) having cancer in two or more FDRs. Moreover, even if in a not statistically significant way, they noticed that the asbestos-related risk to develop MPM was higher among men with a reported family history of cancer compared to men without a positive familial history.

In 1998 Ascoli *et al.* identified a cluster of MPM in one cousin and three sisters (11). All of them were professionally exposed to asbestos. The authors hypothesized that inherited factors could play a role. Indeed, through a deep analysis of the pedigree, they noticed the presence of malignant-cancers in first-degree (pleura and lung, mother, and larynx, brother), second-degree (lung, aunt and uncle) and third-degree (lung, cousin) relatives.

Ohar *et al.* distinguished mesothelioma patients from others exposed to asbestos (12), and they found that subjects with mesothelioma were younger at first asbestos exposure, had a higher prevalence of a previous cancer diagnosis, and had a greater risk of cancer among FDRs (point estimate for

risk, 2.93; 95% CI, 2.50–3.50), considering other asbestos-exposed groups as reference.

These evidences are intriguing, but not strong enough, to confirm that a positive familial history of cancer could be a risk factor for mesothelioma, or could indicate an increased susceptibility to mesothelioma in association with asbestos exposure.

MPM cases in Cappadocia villages: an epidemic?

In three villages of Cappadocia (Tuzkoy, Karain, and “Old” Sarihidir), a study on “epidemic” of MPM was conducted given that about half of the occupant died for this malignancy. The erionite, a mineral of the zeolite family employed as building material, was considered as the unique etiologic factor. It has been supposed that inhalation of even low levels of erionite was sufficient to cause mesothelioma. Indeed, a study on rats showed that inhalation of erionite or its intraperitoneal inoculation caused mesothelioma in 27 out of 28 rats, and 40 out of 40, respectively, whereas other types of asbestos induced mesotheliomas at a lesser extent (19 out of 40, and 1 out of 28, respectively) (13). In 2001, Roushdy-Hammady and collaborators analyzed the pedigree of some families until the sixth generation (for a total of 526 individuals) to understand whether MPM could be genetically transmitted (14): in six families MPM showed obvious familial clustering in which 87 children were identified with at least one affected parent. Of these 87 children, 41 developed MPM as adults (on average 50% of offspring develops MPM when at least one parent is affected). Interestingly, they reported that MPM occurred mostly in certain families than in others. From these observations, they postulated that in Cappadocia villages, genetic predisposition and environmental erionite exposure would increase the risk of MPM with a synergistic effect. This finding was further corroborated by Dogan *et al.* (15), and Carbone and collaborators (16) who initially hypothesized that a unique and more carcinogenic erionite was present in certain houses and caused MPM just there. After the X-ray diffraction pattern analysis, they found the same type of erionite in all three Cappadocian villages, with or without a malignant mesothelioma epidemic, in households with high or no incidence of MPM. When high-risk malignant mesothelioma family members married into families at low risk, mesothelioma appeared in the progeny. On the other hand, genetically predisposed family members born and raised outside the malignant mesothelioma villages did not seem to develop this neoplasm. These results led

the authors to postulate that epidemic of mesothelioma is caused by erionite exposure in a population carrying a putative predisposing gene.

Metintas *et al.* studied a group of 162 immigrants coming from the village Karain and living in Sweden for many years (17). They recorded several data, as asbestos exposure, time residing in the Turkey village, and clinical features as pathological diagnosis. During the time of observation, 18 of the immigrants died, and 14 of them for MPM. Moreover, other five patients, still alive, were diagnosed with mesothelioma.

Thus, incidence rates remained similar to that of the two Turkish villages and very high with respect with Swedish rates. The risk increased with duration of residence: no cases were observed in subjects living in Karain less than 10 years.

All these findings suggest that malignant mesothelioma is not directly related to duration of erionite exposure, but (perhaps) a short exposure to erionite is needed for triggering the disease in susceptible people. Unfortunately, no results for a “Cappadocia” gene of susceptibility to MPM under erionite exposure have been obtained, yet.

Germline mutations and MPM

Testa *et al.* searched for specific genetic predisposing factors (18), and discovered two families with a high incidence of mesothelioma and characterized by germline mutations in BRCA1-associated protein 1 (*BAP1*), causing the biallelic inactivation of the gene. Six members of the first analyzed family, all affected by MPM presented the same mutation, whereas unaffected family members did not. In the second analyzed family, three individuals with MPM were characterized by a C>T change within exon 16, encoding for a stop codon. Moreover, the authors have identified that in addition to MPM, some *BAP1* mutation carriers developed uveal melanoma.

Two of 26 sporadic mesotheliomas patients were found to present germline *BAP1* mutations, and interestingly, both of them were previously diagnosed with uveal melanoma. It has been shown that aberrant *BAP1* expression and truncating mutations could be present also in sporadic mesotheliomas without germline mutations. From these findings, a *BAP1*-related cancer syndrome characterized by mesothelioma and uveal melanoma has emerged. Up to now, *BAP1* is the only gene known to confer an increased susceptibility to MPM. *BAP1* has several cell-intrinsic tumor suppressive functions, such as regulation of cell cycle and replication, gene transcription, DNA damage response,

as well as a modulation in the inflammatory response to crocidolite. For this reason, subsequent studies succeeded in the years to ascertain the role of this gene in MPM.

Xu *et al.* investigated the reason for which mesothelioma appears in some *BAP1* families and not in others, and whether asbestos exposure is a requirement for mesothelioma development in *BAP1* mutation carriers (19). For this reason, they generated a *BAP1* knockout mouse model, verified its susceptibility to mesothelioma following chronic exposure to asbestos and showed that these mice presented a significantly higher incidence of asbestos-induced mesothelioma than wild-type (WT) littermates (73% vs. 32%, respectively).

In a further *in vivo* study, Napolitano *et al.* demonstrated that mice heterozygotes for mutation within *BAP1* and exposed to asbestos fibers at minimal doses showed changes in the inflammation circuitry such as increased levels of inflammatory macrophages, and reduced levels of specific chemokines and cytokines, compared to their wild type littermates (20). Moreover, heterozygotes mice showed high rates of mesothelioma induced with minimal amount of asbestos fibers that could not induce mesothelioma in wild type mice. These results suggest that low doses of fibers increase the risk to develop the disease in genetically predisposed subjects carrying inherited mutations within *BAP1* and this could occur following to changes of the peritoneal inflammatory circuitry.

Thus, it has agreed that germline *BAP1* mutations are associated with a novel cancer syndrome characterized by uveal melanoma, cutaneous melanoma, melanocytic tumors, and other cancers like breast/ovary (21).

Several studies have investigated *BAP1* mutation in relation to sporadic MPM. Betti *et al.* described the mutational status of *BAP1* in five families with multiple MPM patients and in 103 sporadic cases (22). A familial proband carried an inherited mutation causing a truncated *BAP1* protein. The authors noticed that MPM developed in three subjects previously exposed to asbestos who carried the same mutation of the proband within that family, whereas a different type of tumor was observed in another carrier never exposed to asbestos (a muco-epidermoid carcinoma). All the other analyzed families and subjects did not show any mutation within *BAP1*. In summary, inherited mutations within *BAP1* are rare among sporadic MPM patients. Similar results have been found also by Rusch *et al.* [78 sporadic MPM analyzed and 1 germline Ser342Ser within *BAP1* identified, minor allele frequency (MAF) =0.2%] (23), and by Sneddon *et al.* (115 sporadic MPM analyzed and 0 germline variants within *BAP1* found) (24).

In addition to *BAP1*, mutations in neurofibromin 2 (*NF2*) have also been associated with the development of MPM. *NF2* maps to 22q12.2, a region frequently rearranged in MPM (25-27). This is a tumor suppressor gene, mutated in the type 2 neurofibromatosis (an autosomal dominant hereditary disease characterized by tumors of the nervous system). It has been shown that half of MPM cases present mutations within *NF2* gene (28,29). Although *NF2* disease is not usually associated with MPM (30), *NF2* patients show increased risk to develop MPM when exposed to asbestos (31), likely because of a potential link between asbestos exposure and the *NF2* inactivation (32). The loss of *NF2* function has been proposed to be an early event in the MPM (33).

Genetic polymorphisms and MPM

Several studies suggested that common polymorphisms within genes involved in the metabolism of xenobiotics or within the DNA repair systems could constitute a risk factor for the disease. Actually, there are studies reporting an association between MPM and polymorphisms within *GSTM1*, *NAT2*, or manganese superoxide dismutase (*MnSOD*). *GSTM1* belongs to the “glutathione S-transferase” gene family and allows the conjugation of glutathione with electrophilic substances, such as reactive oxygen species (ROS). It has been reported that the lack of the locus is associated with the risk of MPM (34,35). Increased risks were also reported for subjects with the null genotype for *GSTM1* gene, and slow acetylators for *NAT2* (36). The *NAT2* gene encodes the N-acetyltransferase, and other studies report that polymorphisms within this gene possibly are involved in the etiology of the MPM (37). The oxidative stress induced by asbestos fibers could be scavenged also by *MnSOD* (38). Although no activity of this enzyme is measurable in normal mesothelial cells, it is dramatically increased in MPM cells (39). The polymorphism Alanine-to-Valine at codon 16 within *MnSOD* is predicted to affect the protein secondary structure and it could cause an impairment in the transport of the enzyme to the mitochondria (40). Ninety cases of MPM and 395 controls were analyzed and the Ala/Ala genotype was associated with the risk of MPM (35). Among the genes of the DNA repair systems, associations with MPM were described for *XRCC3*, a protein involved in repairing DNA breaks through the homologous recombination. In a case-control study carried out in the Casale Monferrato area, variants of this gene were actually associated with increased risks (41). Moreover, associations between MPM and *XRCC3-241T* or *XRCC1-399Q* variants were found in a

different study focused on a larger area of the Piedmont (42). In a recent study by Betti *et al.*, ten germline and pathogenic truncating variants (PTVs) were identified within *PALB2*, *BRCA1*, *FANCI*, *ATM*, *SLX4*, *BRCA2*, *FANCC*, *FANCF*, *PMS1* and *XPC*. Interestingly, all these genes are involved in DNA repair pathways and are identified in almost 10% of the analyzed MPM patients, suggesting that they did not efficiently repair the DNA damages induced by asbestos (43).

Genome-wide association studies (GWAS) have provided significant progress in the field of cancer genetics. Two GWAS on MPM were performed so far. In both of them, no single nucleotide polymorphisms (SNPs) achieved formal genome-wide statistical significance, likely because of the limited number of patients enrolled. One study was performed by Cadby *et al.*, on 428 MPM cases and 1,269 controls from Western Australia (44). The other on 407 MPM cases and 389 controls from Italy, was performed by Matullo and collaborators (45). From the Australian study, suggestive results for MPM risk were identified within *SDK1*, *CRTAM* and *RASGRF2* genes, and within the 2p12 chromosomal region. These genes are important in cell adhesion and/or cell migration and they could have a role in the cellular response to asbestos fibers. Matullo's study revealed associations within risk of MPM and SNPs within specific loci often somatically rearranged in MPM. This is the case of SNPs within *SLC7A14*, *THRB*, *CEBP350*, *ADAMTS2*, *ETV1*, *PVT1*, *MMP14* and chromosomal regions 3q26.2, 4q32.1, 14q11.2, 15q14 and 7p22.2 associated with a 2–3-fold increased risk. The region 7p22.2 includes the *SDK1* gene region, detected also in the Australian study (44). *SDK1* encodes for an adhesion molecule. Cellular stress, e.g., by ROS, could cause an up-regulation of *SDK1*, such as it occurs in the secretome of starved cancer cells. Interestingly, the administration of this secretome to cell cultures stimulates the clonogenic capacities of various cell lines, and the proliferation and migration of human umbilical vein endothelial cells.

In summary, these studies do not shed a definitive light on the mechanisms of susceptibility to MPM. This is coming from the fact that the neoplasm is rare and it is difficult to carry out large case-control studies with an adequate sample size allowing the optimal statistical power.

Conclusions

From these findings, it seems that, following asbestos exposure, genetic susceptibility could play a mild role in affecting the risk to develop sporadic MPM, similarly as

it occurs for other human cancers. On the contrary, the risk of MPM can be affected greatly by inherited germline mutations within *BAP1* in a context of a multi-cancer syndrome. More studies are needed in order to evaluate the role of genetics among Cappadocians.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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