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Original Article

Germline mutations in DNA repair genes predispose asbestos-exposed patients to malignant pleural mesothelioma

Marta Betti [a, 1], Elisabetta Casalone [b, c, 1], Daniela Ferrante [d], Anna Aspesi [a], Giulia Morleo [a], Alessandra Biasi [a], Marika Sculco [a], Giuseppe Mancuso [e], Simonetta Guarrera [b, c], Luisella Righi [f], Federica Grosso [g], Roberta Libener [h], Mansueto Pavesi [i], Narciso Mariani [j], Caterina Casadio [k], Renzo Boldorini [e], Dario Mirabelli [l, m], Barbara Pasini [b, n], Corrado Magnani [d, m, *], Giuseppe Matullo [b, n, 2], Irma Dianzani [a, m, 2]

[a] Department of Health Sciences, University of Piemonte Orientale, Novara, Italy
[b] Department of Medical Sciences, University of Turin, Turin, Italy
[c] Human Genetics Foundation, HuGeF, Turin, Italy
[d] CPO-Piemonte and Unit of Medical Statistics and Epidemiology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy
[e] Department of Health Sciences, Section of Pathological Anatomy, University of Piemonte Orientale, Novara, Italy
[f] Department of Oncology, University of Turin at San Luigi Hospital, Orbassano, Turin, Italy
[g] Division of Medical Oncology, SS. Antonio e Biagio General Hospital, Alessandria, Italy
[h] Pathology Unit, SS. Antonio e Biagio General Hospital, Alessandria, Italy
[i] Pathological Anatomy Unit, Santo Spirito Hospital, Casale Monferrato, Italy
[j] Pathological Anatomy Unit, SS. Antonio e Biagio General Hospital, Alessandria, Italy
[k] Thoracic Surgery Unit, AOU Maggiore Della Carità, Novara, Italy
[l] Unit of Cancer Epidemiology, CPO-Piemonte and University of Turin, Turin, Italy
[m] Interdepartmental Center for Studies on Asbestos and Other Toxic Particulates "G. Scansetti", University of Turin, Turin, Italy
[n] Medical Genetics Unit, AOU Città Della Salute e Della Scienza, Turin, Italy

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a rare, aggressive cancer caused by asbestos exposure. An inherited predisposition has been suggested to explain multiple cases in the same family and the observation that not all individuals highly exposed to asbestos develop the tumor. Germline mutations in *BAP1* are responsible for a rare cancer predisposition syndrome that includes predisposition to mesothelioma. We hypothesized that other genes involved in hereditary cancer syndromes could be responsible for the inherited mesothelioma predisposition. We investigated the prevalence of germline variants in 94 cancer-predisposing genes in 93 MPM patients with a quantified asbestos exposure. Ten pathogenic truncating variants (PTVs) were identified in *PALB2, BRCA1, FANCI, ATM, SLX4, BRCA2, FANCC, FANCF, PMS1* and *XPC*. All these genes are involved in DNA repair pathways, mostly in homologous recombination repair. Patients carrying PTVs represented 9.7% of the panel and showed lower asbestos exposure than did all the other patients ($p = 0.0015$). This suggests that they did not efficiently repair the DNA damage induced by asbestos and leading to carcinogenesis.

This study shows that germline variants in several genes may increase MPM susceptibility in the presence of asbestos exposure and may be important for specific treatment.

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer caused by exposure to a single carcinogen, asbestos [1]. The frequency of MPM is dramatically higher in asbestos-polluted areas, as exemplified by the MPM epidemic in the northern Italy town of Casale Monferrato caused by the presence of an asbestos

* Corresponding author. Dipartimento di Medicina Traslazionale, Università del Piemonte Orientale SSD Epidemiologia dei Tumori, AOU Maggiore della Carità e CPO-Piemonte, Via Solaroli 17, 28100 Novara, Italy.
E-mail address: corrado.magnani@med.uniupo.it (C. Magnani).
[1] These authors participated equally in the work for this paper.
[2] These authors participated equally in the coordination and supervision of this research.

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cement factory (1907–1986). In this area, the average annual incidence in 2009–2013 was 51.2 among men and 20.2 among women (per 100,000, per year), approximately 10 times higher than the corresponding Italian incidence rates (http://cpo.it/workspace/files/pleural-mesothelioma-incidence-574400b9b1625.pdf).

Asbestos induces carcinogenesis by directly interfering with mitotic spindle formation and by inducing chronic inflammation [2–4] with the production of cytokines and reactive oxygen species (ROS) by activated macrophages. ROS are also generated by the iron contained in asbestos fibers [5].

As in cases of exposure to other carcinogens, not all individuals exposed to high level of asbestos develop cancer [6]. This observation and the reports of families with multiple cases suggest that an inherited predisposition may play a role, even though common asbestos exposure must be considered [7–10]. As for other tumors [11,12], low-risk susceptibility factors have been identified by Genome Wide Association studies (GWAs) on the germline genome of MPM patients [13,14].

The occurrence of a dominant inherited predisposition, termed a 'high-risk predisposition', is a well known concept in cancer and has been clearly demonstrated for several cancer types [15–18]. The most studied high-risk factor for MPM is inherited mutations in *BAP1*, a tumor suppressor gene that encodes a deubiquitinase involved in the modulation of transcription and DNA repair [19]. To date, 79 families in which individuals carry one of 65 germline loss-of-function (LOF) mutations in *BAP1* have been identified worldwide [20–24]. The carriers are at high risk of a number of tumors, including mesothelioma, cutaneous and uveal melanoma, clear cell renal carcinoma, and basal cell carcinoma. Patients are also prone to develop peculiar cutaneous tumors, called melanocytic BAP1-mutated atypical intradermal tumors (MBAITs), which are considered to be a marker of BAP1 syndrome [25].

Investigations on mesothelioma cases with germline *BAP1* mutations suggest that these patients require asbestos exposure to develop mesothelioma and that these tumors most often have an epithelioid histotype and may be associated with a long survival [21,26].

The identification of the BAP1 syndrome prompted us to analyze *BAP1* in 18 families with familial MPM or mesothelioma and melanoma. We found germline *BAP1* mutations in only two families [21,22], suggesting that other genes may play a role in the mesothelioma predisposition.

We decided to investigate the overall genetic predisposition conferred by 94 genes associated with cancer in 93 patients with MPM who lived in areas subjected in the past to high asbestos exposure. Asbestos exposure was quantitatively evaluated in all study participants.

Materials and methods

Patients and controls

The study included 93 Italian patients with MPM. Diagnosis was made as described in Betti et al. [22]. Seventy-seven patients were randomly selected from the previously reported case-control studies [27,28] and were classified as sporadic, whereas sixteen patients had a family history of mesothelioma. Six familial and five sporadic patients were studied for mutations in *BAP1* and other genes involved in familial melanoma, and they were found to be mutation-negative [22].

All patients lived in Piedmont (northern Italy) and signed an informed consent form. The study was approved by the local ethics committee.

Clinical details on gender, age at diagnosis, survival, histotype, asbestos exposure and family history for mesothelioma for all patients were collected from their oncologist and/or from the Malignant Mesothelioma Registry of the Piedmont Region (RMM) (Table 1). Information on family history was limited to first- and second-degree relatives. Information on asbestos exposure at work, at home and in the general environment was collected by the RMM using a standardized questionnaire [29], which was administered by trained interviewers. Asbestos exposure was classified in the following categories: occupational, para-occupational, environmental and household, as previously described [21]. Moreover, exposure was assessed quantitatively by considering the entire exposure history of every study subject [30]. In brief, an exposure index was computed for each exposure circumstance by multiplying frequency, intensity and duration of exposure. The sum of the indices provided an estimate of life-long cumulative asbestos exposure.

Table 1
Clinical features of 93 MPM patients.

Clinical features	MPM Patients (N = 93) N (%)	Patients with PTVs (N = 9) N (%)	Patients without PTVs (N = 84) N (%)	OR* (95% CI)
Gender				
Male	65 (69.9%)	6 (66.7%)	59 (70.2%)	0.8 (0.2–3.6)
Female	28 (30.1%)	3 (33.3%)	25 (29.8%)	1 (reference)
Histotype				
Epithelioid	62 (66.7%)	8 (88.9%)	54 (64.3%)	4 (0.5–33.6)
Biphasic	16 (17.2%)	1 (11.1%)	15 (17.9%)	1 (ref: biphasic and sarcomatoid)
Sarcomatoid	12 (12.9%)	–	12 (14.3%)	
Unknown	2 (2.1%)	–	2 (2.4%)	
Not available	1 (1.1%)	–	1 (1.1%)	
Asbestos exposure				
Occupational	53 (57%)	5 (44.4%)	48 (42.9%)	0.8 (0.2–3.4)
Para-occupational	17 (18.3%)	3 (33.3%)	14 (16.7%)	1 (ref: para-occupational,
Environmental	19 (20.4%)	1 (11.1%)	18 (21.4%)	environmental and household)
Household	1 (1.1%)	–	1 (1.2%)	
Not available	3 (3.2%)	–	3 (3.6%)	
History of cancer				
At least one first-/second-degree relative with mesothelioma	16 (17.2%)	2 (22.2%)	14 (16.7%)	
Not reported	75 (80.6%)	7 (77.8%)	68 (80.9%)	
Not available	2 (2.2%)	–	2 (2.4%)	
Age at diagnosis, years				**p (Mann-Whitney test)**
Mean ± SD	68 ± 12.3^	73.9 ± 7.2	67.4 ± 12.6^	0.13
Survival				**p (Log rank test)**
1-year (95% CI)	57% (46–67)	25% (4–56)	59% (47–70)	0.25
2-year (95% CI)	30% (20–40)	12% (1–42)	30% (20–41)	
Quantitative asbestos exposure				**p (Student's t-test)**
Mean ± SD	22.8 ± 137.9^^	3.8 ± 9.5	24.9±145.3^^	
Mean ± SD (after logarithmic transformation)	0.9 ± 1.8	−0.8 ± 2.3	1.1 ± 1.6	**0.0015**

Abbreviations: PTVs, pathogenic truncating variants; OR, odds ratio; CI, confidence interval; SD, standard deviation.
*Patients with PTVs *versus* Patients without PTVs; ^Not available for 3 patients; ^^Not available for 3 patients.