Varianti genetiche e interazione gene-asbesto nel mesotelioma pleurico

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INTRODUCTION 1

Malignant pleural mesothelioma (MPM)

rare, aggressive tumor, characterized by treatment resistance and poor prognosis.

Risk factors for MPM

- exposure to asbestos and other asbestiform minerals such as erionite and fluoro-edenite
- ionizing radiation for medical purposes

INTRODUCTION 2

Genetic component

might in part explain:

- relative rarity of MPM also in heavily exposed cohorts
- reports of familial clustering
- results of candidate-gene association studies

OBJECTIVES

The aims of this study were

1. identify genetic risk factors that might contribute to the development of MPM

2. investigates the interactions between candidate SNPs and asbestos exposure, and their effects in modulating MPM risk in Italian population

METHODS 1

Study sample

Cases (407):

Casale Monferrato (241):

Turin (91):

Genoa + La Spezia (75):

resident in the study area
at the time of diagnosis
pathological confirmation of
the diagnosis

individually matched by
age and gender

Controls (389):

Casale Monferrato (252):

Turin (56):

Genoa + La Spezia (81):

METHODS 2
Assessment of asbestos exposure

Questionnaire-based personal interviews

- absent/unlikely - no acknowledged occupational or environmental exposure -
- low - low exposure probability, or definite exposure at low level –
- high - definite and high exposure, corresponding in principle to asbestos-cement and asbestos-textile workers, insulators, shipyard workers and dockers and similar activities -

METHODS 3
Statistical analysis 1

After quality controls

759 subjects (392 cases and 367 controls)

330,879 genotyped SNPs

330,879 SNPs tested for their association with mesothelioma by 2-sided logistic regression analysis on a per-allele additive model after adjusting for age, gender, PCA cluster, centre of recruitment and exposure level

alpha = 1.51×10^{-7} (0.05/330879) threshold of significance.

METHODS 4
Statistical analysis 2

Binary classification

- asbestos exposure (exposed vs unexposed)
- genotypes (homozygous for major allele vs one or two copies of the minor allele)

	NO EXP	EXP
Hom.	1	$OR_{1,0}$
Minor allele	$OR_{0,1}$	$OR_{1,1}$

$OR_{i,j}$ MPM risk for a given SNP and asbestos exposure

- i asbestos exposure 0 : unexposed 1: exposed subjects
- j SNP genotype 0: homozygous for the major allele 1: one or two copies of the minor allele.

OR_{00}=1: unexposed and homozygous for the major allele

METHODS 5

Statistical analysis: interaction

Interaction was analyzed in respect to both additive and multiplicative models based on the ORs

Additive

Relative Excess Risk due to Interaction $RERI=OR_{11}-OR_{01}-OR_{10}+1$

Synergy Index $SI= [OR_{11}-1]/[(OR_{01}-1) + (OR_{10}-1)]$

Multiplicative

Logistic regression including interaction term (SNP × exposure)

$V=OR_{11}/(OR_{01} \times OR_{10})$ and likelihood ratio test

RESULTS 1

		CENTRE						Overall sample	
		Casale Monferrato		Genova		Torino			
		controls N (%)	cases N (%)	controls N (%)	cases N (%)	controls N (%)	cases N (%)	controls N (%)	cases N (%)
Gender	F	75 (31.65)	75 (32.61)	19 (25.33)	6 (8.22)	17 (30.91)	27 (30.34)	**111 (30.25)**	**108 (27.55)**
	M	162 (68.35)	155 (67.39)	56 (74.67)	67 (91.78)	38 69.09)	62 (69.66)	**256 (69.75)**	**284 (72.45)**
	Tot	237 (50.75)	230 (49.25)	75 (50.68)	73 (49.32)	55 (38.19)	89 (61.81)	**367 (48.35)**	**392 (51.65)**
Asbestos exposure	No	54 (22.78)	4 (1.74)	41 (54.67)	10 (13.70)	18 (32.73)	3 (3.37)	**113 (30.79)**	**17 (4.34)**
	Yes	183 (77.22)	190 (82.61)	34 (45.33)	63 (86.30)	37 (67.27)	86 (96.67)	**254 (69.21)**	**339 (86.48)**
	NA		36 (15.65)						**36 (9.18)**
	Age	63.36 11.06	67.61 11.14	58.59 15.03	69.64 9.64	68.31 8.80	68.74 8.84	**63.11 12.01**	**68.25 10.39**

759 subjects (392 cases and 367 controls)

RESULTS 2

	gene	OR (95% CI)
1	rs1508805	1.85 (1.41 – 0.71)
2	rs2501618 (CEP350)	2.23 (1.47 – 3.37)
3	rs4701085	2.05 (1.41 – 2.97)
4	rs10519201 (SHC4)	2.36 (1.57 – 3.56)
5	rs4290865	1.98 (1.44 – 2.71)
6	rs7632718 (SLC74A14)	1.85 (1.41 – 2.42)
7	rs73034881 (SDK1/FOXK1)	0.44 (0.29 – 0.67)
8	rs10815216	0.41 (0.27 – 0.60)
9	rs5756444	0.60 (0.47 – 0.76)

selected by logistic regression analysis on per allele additive model adjusting by age, gender, PCA cluster, center of recruitment and asbestos exposure level

	gene	OR (95% CI)
10	rs2236304 (MMP14)	1.72 (1.19 – 2.25)
11	rs742109	0.55 (0.43 – 0.71)
12	rs9536579	0.54 (0.40 -0.72)
13	rs3801094 (ETV1)	1.86 (1.39 – 2.48)
14	rs7841347 (PVT1)	0.51 (0.39 – 0.67)
15	rs9833191 (THRB)	0.55 (0.41 – 0.73)

RESULTS 3
interaction

		Deviation from additive model		Deviation from multiplicative model	
	gene	RERI (95% CI)	SI (95% CI)	V	P
1	rs1508805	5.92 (1.72 – 10.12)	2.74 (1.60 – 4.69)	10.6	<0.001
2	rs2501618 (CEP350)	10.69 (2.11 – 19.26)	2.87 (1.77 – 4.63)	4.56	0.016
3	rs4701085	6.52 (1.87 – 11.18)	3.21 (1.76 – 5.88)	7.28	<0.001
4	rs10519201 (SHC4)	12.56 (1.78 – 23.46)	2.89 (1.75 – 4.77)	4.06	0.043
5	rs4290865	9.38 (1.15 – 17.62)	2.37 (1.52 – 3.70)	2.51	0.106
6	rs7632718 (SLC74A14)	5.87 (0.38 – 11.17)	2.78 (1.35 – 5.71)	3.24	0.070
7	rs73034881 (SDK1/FOXK1)	-3.91 (-7.84 – 0.02)	0.51 (0.33 – 0.81)	1.56	0.537
8	rs10815216	-2.20 (-5.23 – 0.83)	0.57 (0.35 – 0.92)	3.32	0.048
9	rs5756444	-16.85 (-41.05 – 7.34)	0.54 (0.38 – 0.78)	0.18	0.005

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interaction

	Deviation from additive model		Deviation from multiplicative model	
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10 rs2236304 (MMP14)	10.53 (-2.30 – 23.36)	1.61 (1.11 – 2.33)	0.54	0.309
11 rs742109	-3.15 (-7.87 – 1.57)	0.64 (0.41 – 0.99)	1.24	0.780
12 rs9536579	-4.68 (-9.57 – 0.21)	0.51 (0.33 – 0.77)	0.96	0.951
13 rs3801094 (ETV1)	7.61 (-2.17 – 17.39)	1.46 (1.01 – 2.11)	0.55	0.333
14 rs7841347 (PVT1)	-3.80 (-9.73 – 2.13)	0.63 (0.40 – 0.99)	0.97	0.964
15 rs9833191 (THRB)	-10.73 (-22.41 – 0.96)	0.45 (0.29 – 0.65)	0.42	0.097

CONCLUSION 1

15 SNPs* (5 of them imputed and confirmed after genotyping) are associated to MPM in a GWAS on an Italian study sample of 407 MPM cases and 389 healthy controls, and concluded that

genetic risk factors may play an additional role in the development of MPM

*rs2236304, rs742109, rs1508805, rs2501618, rs4701085, rs4290865, rs9536579, rs7632718, rs9833191, rs10519201, rs5756444, rs10815216, rs73034881, rs3801094, rs7841347

CONCLUSION 2

positive deviation from additivity

rs1508805, rs2501618, rs4701085, rs4290865, rs10519201, rs763271:

deviated also from multiplicative models

rs1508805, rs2501618, rs4701085, rs10519201

CONCLUSION 3
SLC7A14

Rs7632718 is located in *SLC7A14* a chromosomal gain of this region has been described in MPM, suggesting a possible involvement of other neighboring genes

CONCLUSION 4
rs73034881

Rs73034881 (SDK1/FOXK1) - although not statistically significant - is suggestive of protective additive interaction between the variant allele and asbestos exposure

FOXK1 is an interactor of BAP1, whose deleterious mutations are responsible for a cancer prone syndrome that includes mesothelioma in its phenotype

CONCLUSION 5
limitation

- The sample size is critical in general for all gene–environment interaction studies, and in particular for MPM, a rare disease where only few cases are not exposed to asbestos.

CONCLUSION 6

- Genetic background of an individual may modulate asbestos-related carcinogenesis of the pleura.
- The interpretation of a specific interaction model is made difficulty by the limited a priori evidence of a functional role of the investigated genetic variants.
- Asbestos however remains the major risk factor for MPM

CONFLICT OF INTEREST

Dott. Dario Mirabelli and Prof. Corrado Magnani acted as expert witnesses for the public prosecutor in criminal trials on asbestos related cancers.

GRAZIE!