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Cancer Epidemiology, Biomarkers & Prevention

Null Results in Brief

Genetic Variants and Multiple Myeloma Risk: IMMEnSE Validation of the Best Reported Associations—An Extensive Replication of the Associations from the Candidate Gene Era

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Abstract

Background: Genetic background plays a role in multiple myeloma susceptibility. Several single-nucleotide polymorphisms (SNP) associated with genetic susceptibility to multiple myeloma were identified in the last years, but only a few of them were validated in independent studies.

Methods: With the aim to conclusively validate the strongest associations so far reported, we selected the polymorphisms rs2227667 (*SERPINE1*), rs17501108 (*HGF*), rs3136685 (*CCR7*), rs16944 (*IL1B*), rs12147254 (*TRAF3*), rs1805087 (*MTR*), rs1800629 (*TNF-α*), rs7516435 (*CASP9*), rs1042265 (*BAX*), rs2234922 (*mEH*), and rs1801133 (*MTHFR*). We genotyped them in 1,498 multiple myeloma cases and 1,934 controls ascertained in the context of the International Multiple Myeloma rESEarch (IMMEnSE) consortium, and meta-analyzed our results with previously published ones.

Results: None of the selected SNPs were significantly associated with multiple myeloma risk (*P* value range, 0.055–0.981), possibly with the exception of the SNP rs2227667 (*SERPINE1*) in women.

Conclusions: We can exclude that the selected polymorphisms are major multiple myeloma risk factors.

Impact: Independent validation studies are crucial to identify true genetic risk factors. Our large-scale study clarifies the role of previously published polymorphisms in multiple myeloma risk. *Cancer Epidemiol Biomarkers Prev; 23(4); 670–4. ©2014 AACR.*

Genetic background plays a role in multiple myeloma susceptibility. Many studies on genetic variants and multiple myeloma risk were published from 2000–2010 (reviewed in refs. 1, 2). Candidate genes were selected for their functional relevance in multiple myeloma and in cancer biology. They belonged to four main categories: cell signaling and growth factors, cytokines, xenobiotic metabolism and transport, and DNA repair and apoptosis. The main limitation of these studies was often a small sample size and lack of statistical power.

Three loci were recently found associated with multiple myeloma in the first genome-wide association study (GWAS; ref. 3), and were subsequently replicated in the International Multiple Myeloma rESEarch (IMMEnSE)

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Table 1. Demographic characteristics of IMMEnSE cases and controls

	Cases			Controls			
Region[a]	Gender M/F (total)	Mean age (±SD)	Median age (range)	Gender M/F (total)	Mean age (±SD)	Median age (range)	Control type
IT	121/111 (232)	62.5 (±9.9)	63 (35–87)	131/106 (237)	58.8 (±10.8)	59 (35–89)	General population
PL	172/189 (361)	62.2 (±10.5)	63 (34–86)	126/234 (360)	50.6 (±19.5)	49.5 (18–98)	Blood donors
ES	133/137 (270)	63.1 (±11.4)	63 (27–75)	229/198 (427)	63.1 (±11.9)	62 (24–92)	Hospitalized subjects
FR	46/35 (81)	55.5 (±9.4)	57 (27–75)	101/90 (191)	43.7 (±15.5)	48 (18–68)	Blood donors
PT	32/36 (68)	66.0 (±11.2)	67.5 (41–86)	55/45 (100)	60.7 (±7.7)	58 (51–85)	Blood donors
HU	49/90 (139)	66.2 (±11.3)	68 (34–90)	50/54 (104)	73.4 (±10.1)	74.5 (51–95)	Hospitalized subjects
DK	203/144 (347)	55.2 (±7.1)	56 (29–69)	293/222 (515)	43.3 (±11.7)	44 (17–97)	Blood donors
Total	756/742 (1,498)	60.9 (±10.6)	61 (27–93)	985/949 (1,934)	62.0 (±13.3)	63 (18–98)	

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consortium (4). A more recent extension of the GWAS yielded four more loci (5).

We attempted to replicate the strongest associations reported for multiple myeloma. Among 43 studies on single-nucleotide polymorphisms (SNP) and multiple myeloma risk (excluding those performed in the context of IMMEnSE and the GWAS), 25 reported at least one significant association at the conventional threshold of $P < 0.05$. From these, we selected all SNPs reported with $P \leq 0.01$. The selected variants encompassed all the four groups of genes previously described and included: rs2227667 (*SERPINE1*), rs17501108 (*HGF*), rs2195239 (*IGF2*), rs2373722 (*IGF1*), rs3136685 (*CCR7*), rs1800587 (*IL1A*), rs16944 (*IL1B*), rs315952 (*IL1RN*), rs12147254 (*TRAF3*), rs1805087 (*MTR*), rs7965399 (*IGF1*), rs1800629 (*TNF-α*), rs7516435 (*CASP9*), rs1042265 (*BAX*), rs2234922 (*mEH*), and rs1801133 (*MTHFR*). We excluded rs2195239 (*IGF2*), rs2373722 (*IGF1*), and rs7965399 (*IGF1*) as in the original study they reached statistical significance only in a secondary analysis but not in the first case–control set (6). We excluded also rs1800587 (*IL1A*) and rs315952 (*IL1RN*), because they were strongly deviating from Hardy–Weinberg equilibrium (HWE) in the controls in the original study (7). We thus selected 11 SNPs for genotyping: rs2227667 (*SERPINE1*), rs17501108 (*HGF*), rs3136685 (*CCR7*), rs16944 (*IL1B*), rs12147254 (*TRAF3*), rs1805087 (*MTR*), rs1800629 (*TNF-α*), rs7516435 (*CASP9*), rs1042265 (*BAX*), rs2234922 (*mEH*), and rs1801133 (*MTHFR*).

Our study population consisted of 1,498 multiple myeloma cases and 1,934 controls recruited from 7 European countries in the context of IMMEnSE (Table 1; ref. 5). Cases were defined by a confirmed diagnosis of multiple myeloma according to the International Myeloma Working Group criteria. Region-specific controls were selected among the general population or among hospitalized subjects with diagnoses excluding cancer. For each subject, informed consent was obtained and the study was approved by the relevant ethical committees. Some of the samples had been already genotyped for some of the SNPs in previously published studies and were therefore excluded from genotyping.

We performed the genotyping with TaqMan (Applied Biosystems) and KASPar (KBioscence) technologies. Ten percent of the samples were duplicated for quality control; their genotypes showed greater than 99% concordance. Once subjects with call rate <75% were removed, all SNPs had a call rate over 96%, which was uniform between cases and controls and in all the subpopulations. All the SNPs were in HWE in controls, except rs1800629 (*TNF-α*) in the Polish subpopulation ($P < 0.001$), which was therefore excluded from further analyses.

Association between SNPs and multiple myeloma risk was assessed with unconditional logistic regression using codominant and dominant inheritance models, adjusting by age, gender, and region of origin. Additional models (log-additive and recessive) were tested depending on the

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Table 2. Associations between selected SNPs and multiple myeloma risk in the IMMEnSE consortium

		IMMEnSE					Original study		
Gene	SNP	Cases *N* (%)	Controls *N* (%)	OR (95% CI)	*P*	P_{trend}	Best OR (95% CI)	*P*	Inheritance model
SERPINE1	rs2227667						0.39[c] (0.24–0.64)	0.0002	Dominant
	A/A	762 (59.2)	1,080 (59.6)	1 (—)	—	0.930			
	A/G	457 (35.5)	623 (34.4)	1.00 (0.85–1.17)	0.981				
	G/G	68 (5.3)	109 (6.0)	0.83 (0.60–1.15)	0.257				
	A/A vs. A/G+G/G			0.97 (0.84–1.13)	0.717				
	A/A+A/G vs. G/G			0.91 (0.77–1.07)	0.251				
	A vs. G			0.95 (0.84–1.08)	0.460				
CCR7	rs3136685						0.38[c] (0.22–0.64)	0.0004	Dominant
	G/G	907 (70.2)	1,275 (70.2)	1 (—)	—	0.650			
	A/G	342 (26.5)	486 (26.8)	1.03 (0.87–1.22)	0.719				
	A/A	43 (3.3)	54 (3.0)	1.17 (0.77–1.80)	0.458				
	G/G vs. A/G+A/A			1.04 (0.89–1.23)	0.588				
	G/G+A/G vs. A/A			1.08 (0.87–1.33)	0.479				
	G vs. A			1.05 (0.91–1.21)	0.486				
HGF	rs17501108						2.75[c] (1.69–4.48)	4.6×10^{-5}	Dominant
	G/G	984 (77.2)	1,366 (76.6)	1 (—)	—	*0.017*			
	G/T	274 (21.5)	386 (21.7)	1.03 (0.86–1.24)	0.718				
	T/T	16 (1.3)	30 (1.7)	0.74 (0.40–1.39)	0.352				
	G/G vs. G/T+T/T			1.01 (0.85–1.21)	0.894				
	G/G+G/T vs. T/T			0.86 (0.63–1.17)	0.340				
	G vs. T			0.99 (0.84–1.16)	0.865				
BAX	rs1042265						0.40[c] (0.21–0.78)	0.007	Dominant
	C/C	1,076 (83.4)	1,469 (81.5)	1 (—)	—	0.799			
	C/T	194 (15.0)	317 (17.6)	0.85 (0.70–1.04)	0.120				
	T/T	20 (1.6)	16 (0.9)	1.89 (0.96–3.74)	0.065				
	C/C vs. C/T+T/T			0.90 (0.74–1.09)	0.293				
	C/C+C/T vs. T/T			1.39 (0.99–1.96)	0.055				
	C vs. T			0.96 (0.80–1.45)	0.648				
CASP9	rs7516435						2.59[c] (1.30–5.15)	0.007	Recessive
	A/A	623 (49.2)	895 (49.7)	1 (—)	—	0.725			
	A/G	534 (42.1)	724 (40.3)	1.05 (0.90–1.23)	0.514				
	G/G	110 (8.7)	179 (10.0)	0.91 (0.70–1.19)	0.511				
	A/A vs. A/G+G/G			1.03 (0.88–1.19)	0.730				
	A/A+A/G vs. G/G			0.94 (0.83–1.07)	0.388				
	A vs. G			0.99 (0.89–1.11)	0.905				
MTHFR	rs1801133						1.27 (1.02–1.58)	—	Dominant (meta)
	G/G	554 (43.8)	767 (42.7)	1 (—)	—	0.721			
	A/G	525 (41.5)	787 (43.8)	0.91 (0.78–1.07)	0.267				
	A/A	185 (14.7)	243 (13.5)	0.96 (0.77–1.21)	0.757				
	G/G vs. A/G+A/A			0.92 (0.80–1.07)	0.312				
	G/G+A/G vs. A/A			1.00 (0.90–1.12)	0.929				
	G vs. A			0.96 (0.86–1.07)	0.500				
mEH	rs2234922						5.81 (1.27–35.7)	0.01	Recessive
	A/A	860 (67.0)	1,150 (63.4)	1 (—)	—	0.635			
	A/G	369 (28.7)	596 (32.8)	0.86 (0.74–1.02)	0.081				
	G/G	55 (4.3)	70 (3.8)	1.14 (0.78–1.66)	0.502				
	A/A vs. A/G+G/G			0.89 (0.76–1.04)	0.155				
	A/A+A/G vs. G/G			1.09 (0.91–1.31)	0.356				
	A vs. G			0.94 (0.83–1.07)	0.378				

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Table 2. Associations between selected SNPs and multiple myeloma risk in the IMMEnSE consortium (Cont'd)

		IMMEnSE					Original study		
Gene	SNP	Cases *N* (%)	Controls *N* (%)	OR (95% CI)	*P*	P_{trend}	Best OR (95% CI)	*P*	Inheritance model
MTR	rs1805087						2.31 (1.38–3.87)	0.001	Dominant
	A/A	858 (67.3)	1,201 (66.2)	1 (—)	—	0.974			
	A/G	372 (29.2)	549 (30.3)	0.97 (0.83–1.14)	0.734				
	G/G	45 (3.5)	63 (3.5)	1.18 (0.78–1.77)	0.430				
	A/A vs. A/G+G/G			0.99 (0.85–1.16)	0.916				
	A/A+A/G vs. G/G			1.09 (0.89–1.33)	0.402				
	A vs. G			1.01 (0.88–1.16)	0.852				
IL1β	rs16944[a]						0.057 (0.02–0.18)	0.0001	Log-additive
	G/G	471 (44.1)	686 (43.6)	1 (—)	—	0.522			
	A/G	461 (43.2)	718 (45.7)	0.90 (0.76–1.07)	0.240				
	A/A	136 (12.7)	169 (10.7)	1.11 (0.86–1.45)	0.427				
	G/G vs. A/G+A/A			0.94 (0.80–1.11)	0.476				
	G/G+A/G vs. A/A			1.08 (0.96–1.22)	0.212				
	G vs. A			1.00 (0.89–1.13)	0.944				
TNF-α	rs1800629[b]						0.58 (0.39–0.87)	0.01	Log-additive
	G/G	478 (75.9)	859 (72.7)	1 (—)	—	0.187			
	A/G	143 (22.7)	289 (24.5)	0.88 (0.70–1.12)	0.317				
	A/A	9 (1.4)	33 (2.8)	0.48 (0.22–1.05)	0.066				
	G/G vs. A/G+A/A			0.84 (0.67–1.06)	0.152				
	G/G+A/G vs. A/A			0.71 (0.48–1.04)	0.077				
	G vs. A			0.83 (0.67–1.02)	0.072				
TRAF3	rs12147254						0.709 (0.62–0.82)	<0.001	Dominant
	G/G	630 (49.1)	911 (50.5)	1 (—)	—	0.644			
	A/G	536 (41.7)	712 (39.5)	1.09 (0.93–1.28)	0.271				
	A/A	118 (9.2)	180 (10.0)	0.97 (0.75–1.27)	0.846				
	G/G vs. A/G+A/A			1.07 (0.92–1.24)	0.380				
	G/G+A/G vs. A/A			0.97 (0.85–1.10)	0.611				
	G vs. A			1.03 (0.92–1.15)	0.660				

NOTE: All analyses are adjusted for age (continuous), gender, and region. Differences in the overall number may be due to failure in genotyping. For each SNP, we present the result of analyses of heterozygotes vs. homozygotes for the common allele, homozygotes for the rare allele vs. homozygotes for the common allele, dominant model, recessive model, and per-allele model. The model corresponding to the association reported in the original publication for each SNP is underlined.

[a]For this SNP, samples collected in Italy were already published and therefore omitted from the analysis.

[b]For this SNP, samples collected in Italy and Hungary were already published and therefore omitted from the analysis. Samples from Poland were out of HWE and therefore omitted as well.

[c]The original studies were conducted only in women (8, 9).

original findings. Mantel–Haenszel and Breslow–Day statistics were used to test for heterogeneity among the IMMEnSE subpopulations. Because this is a replication study, the conventional threshold of $P < 0.05$ was considered statistically significant. We had greater than 92% statistical power to replicate all the selected findings at the same level of significance of the original study, and greater than 99% to replicate the results from the studies in which cases were only women, conducting gender-stratified analyses.

We performed meta-analyses of this replication with results of previous studies with a fixed-effects model. In case of significant heterogeneity among the original study and the replication set, we used a random-effects model. The significant inheritance model in the original study was used for each meta-analysis.

None of the SNPs showed statistically significant associations with multiple myeloma risk (Table 2). The trend test was significant for rs17501108 (*HGF*; $P = 0.017$). A stratified analysis by gender was performed for rs2227667 (*SERPINE1*), rs17501108 (*HGF*), rs3136685 (*CCR7*), rs7516435 (*CASP9*), rs1042265 (*BAX*), as the original studies were conducted only in women (8–9). The G/G homozygotes for rs2227667 (*SERPINE1*) showed a significantly

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decreased risk to develop multiple myeloma in women [OR = 0.56; 95% confidence interval (CI), 0.34–0.92; $P = 0.022$], consistent with the original results. Analyses performed in men did not show any significant result for any of the five SNPs tested (data not shown).

None of the meta-analyses showed any significant association with multiple myeloma risk (data not shown).

In a large study with high statistical power, we showed that none of the previously reported associations with multiple myeloma risk at 11 SNPs replicates convincingly, possibly with the exception of rs2227667 (*SERPINE1*) in women. Therefore, it is unlikely that any of the investigated SNPs plays a major role in multiple myeloma etiology.

Disclosure of Potential Conflicts of Interest

V. Andersen is a consultant/advisory board member of MSD/Merch. No potential conflicts of interest were disclosed by the other authors.

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Cancer Epidemiology, Biomarkers & Prevention

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Genetic Variants and Multiple Myeloma Risk: IMMEnSE Validation of the Best Reported Associations––An Extensive Replication of the Associations from the Candidate Gene Era

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