Genetics and molecular epidemiology of multiple myeloma: The rationale for the IMMEnSE consortium (Review)

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Abstract. There is strong evidence suggesting the presence of a genetic component in the aetiology of multiple myeloma (MM). However no genetic risk factors have been unequivocally established so far. To further our understanding of the genetic determinants of MM risk, a promising strategy is to collect a large set of patients in a consortium, as successfully done for other cancers. In this article, we review the main findings in the genetic susceptibility and pharmacogenetics of MM and present the strategy of the IMMEnSE (International Multiple Myeloma rESEarch) consortium in contributing to determine the role of genetic variation in pharmacogenetics and in MM risk.

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1. Introduction: multiple myeloma

Multiple myeloma (MM) is a malignancy of plasma cells usually infiltrating the bone marrow, associated with the production of a monoclonal immunoglobulin (M protein) which can be detected in the blood and/or urine (1). The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, suppression of normal immunoglobulin production and renal insufficiency (2).

MM arises worldwide at an age-standardized (ASR) rate of 1.5 new cases every 100,000 people per year and is responsible of an ASR of mortality of 1 in 100,000 subjects per year. In Europe the ASR incidence is 2.9 new cases every 100,000 people, ranging from 4.2 in Luxembourg to 0.9 in Moldova, and is about 1.5-fold higher in males (ASR=2.9) than in females (ASR=2.0) (3-5). The highest annual incidence of MM has been found in African Americans followed either by Europeans or American Caucasians and Asians who present the lowest incidence even when they live in Western societies (6-11). The

overall incidence rates range from a high of 13.1/100,000 per year for black males to 2.9/100,000 per year for white females (8,11). MM is common in the elderly, with incidence rates increasing with age, it occurs rarely before 40 years (12) and presents an extremely low frequency in young people (9,13,14). It has been shown that MM could evolve from an asymptomatic premalignant condition termed monoclonal gammopathy of undetermined significance (MGUS) (15,16). The frequency of MGUS is over 3% in the population above the age of 50 years and over 5% in persons aged 70 years or older (17,18). This condition seems to be related to progression to MM or other plasma cell disorders at a steady rate of 1.5% per year, and after >25 years of observation about 15-17% of MGUS subjects develop MM (19). In some patients, an intermediate asymptomatic, but more advanced premalignant stage, defined as smouldering multiple myeloma (SMM) could be clinically recognized (20).

MM diagnosis requires 10% or more clonal plasma cells on bone marrow examination or a biopsy proven plasmacytoma and evidence of end-organ damage such as hypercalcemia, renal insufficiency, anaemia or bone lesions, defined as CRAB (calcium elevation, renal insufficiency, anaemia and bone lesions criteria) that can be related to the underlying plasma cell disorder (1,21).

Symptomatic (active) disease should be treated immediately, whereas asymptomatic myeloma requires only clinical observation, since early treatment with conventional chemotherapy has shown no benefit. The aim of the therapy is represented by the achievement of the best possible response: complete response (CR) or very good partial response (VGPR) (22-24). The level of response, and in particular achievement of CR, seems to be associated with an improved long-term outcome. Overall survival (OS) in myeloma has improved significantly in the last decade with the emergence of thalidomide (25), bortezomib (26) and lenalidomide (27). Bortezomib is a first-in-class proteasome inhibitor (28); the complete mechanism of action of thalidomide and lenalidomide is still unclear but both of them are immune-modulatory drugs (29). Treatment strategies include the use of therapy with thalidomide, lenalidomide or bortezomib plus hematopoietic autologous stem-cell transplantation (ASCT) for patients under the age of 65 years, who do not have substantial heart, lung, renal or liver dysfunction. Alternatively, the use of combination therapy including steroids and/or alkylating agents together with one or two of the new drugs (thalidomide, bortezomib and lenalidomide) is more appropriate for elderly patients or those with severe co-morbidities. The role of maintaining therapy is still a matter of debate (30).

2. Lifestyle, environmental and occupational-related risk factors in multiple myeloma

MM risk is clearly related to age (31), gender, ethnicity (11) and the presence of pre-malignant conditions such as MGUS (17). Additional factors have been suggested to have an effect on the risk of developing MM. There is epidemiological evidence supporting an increased risk of MM among obese people and for those who have a low intake either of fish or vegetables (32-36). A number of cohort and case-control studies have also described a positive relationship between MM and patients either with autoimmune diseases (37,38) or viral infections (39-41). Many other studies have investigated the relationship between exposure to toxins and increased risk of MM, with controversial results (42-46). While some studies have shown that exposures to pesticides (47-49), organic solvents (50), hairdresser's products (51), rubber (52) are associated with an increased risk of MM, other studies have not found a significant relationship (48,53-55). Researchers have also examined whether smoking (56), alcohol consumption (57) or ionizing radiation exposures (58) affected the risk of MM but, again, obtained data were largely inconsistent (59-61).

3. Genetic risk factors in multiple myeloma

Converging evidence of MM in monozygotic twins (62) and familial aggregation of MM (63-69) strongly suggest that MM aetiology has a robust genetic component. For many other types of tumors, association studies, including Genome-Wide Association Studies (GWAS), have shown that genetic risk is influenced by the effect of the co-inherited common genetic low-penetrance variants. Single Nucleotide Polymorphisms (SNPs) are the major source of genetic variation in humans and thought to be responsible, at least in part, for the individual differences in genetic susceptibility to complex diseases as tumors. This is likely to be the case for MM as well. Several genes belonging to different pathways have been associated with MM risk, although the results were controversial. Table I summarizes the positive associations reported in the literature between genetic variants and MM susceptibility in candidate gene studies. Up to date, a GWAS on MM risk is still lacking.

Polymorphisms in cytokine genes. The first study on SNPs in MM genetic susceptibility was reported in 2000 by Zheng *et al* and investigated the role of 3 SNPs, respectively, in *TNF-α* (-308G/A, rs1800629), *IL6* (-174G/C, rs1800795) and *IL1B* (+3954T/C, rs1143634) genes as well as a VNTR polymorphism in the *IL1RN* gene. In this study, no evidence of association between any of the studied genetic variants and MM risk was reported (70).

In general, cytokine-encoding genes have been extensively investigated (70-86), due to the high degree of polymorphisms characterized in these genes and to their important role in the bone marrow microenvironment and B-cell development.

One of the most investigated genetic loci in MM risk is the -308G/A SNP (rs1800629) which belongs to the *TNF-α* gene. While no association between MM risk and SNP -308G/A (rs1800629) of *TNF-α* gene was found in a previous study (70), Davies and colleagues showed a significantly higher percentage of heterozygous individuals for both *TNF-α* -308G/A SNP and *LT-α* +252A/G (rs909253) SNP among MM cases in respect to controls, suggesting that the higher *TNF-α* producers had a 2-fold higher risk to develop MM (78). In a subsequent study, Morgan *et al* failed to confirm the association between *TNF-α* -308G/A and *LT-α* +252A/G haplotype and MM risk, evidencing on the other hand an association between the *TNF-α* -308A allele and a decreased risk to develop MM (79). The association of the *TNF-α* -308A allele with a reduced risk to develop MM has been confirmed by two recent studies (73,83).

Investigations of SNPs in genes belonging to the *IL6* pathway are intriguing since IL6 and IL6-mediated signaling are thought

Table I. Associations of SNPs with MM risk.

Gene	SNP	Position/ Function	Cases	Controls	Description of association	Refs.
Polymorphisms in cytokine genes						
IL1A	rs1800587 (-889 C/T)	5'UTR	74	160	Heterozygotes for the *IL1A* -889 variant showed an increased risk to develop MM (OR, 5.66; 95% CI, 2.22-12.6; p<0.001)	(77)
IL1B	rs1143627 (-31 T/C)	5'Near gene	348	800	C/C homozygotes for the *IL1B* -31C/T SNP had a 1.37-fold increased risk of MM (OR, 1.37; 95% CI, 1.05-1.80; p=0.02)	(85)
	rs16944 (-511 C/T)	5'Near gene	74	160	Homozygotes for the *IL1B* -511C allele showed a decreased risk to develop MM (OR, 0.057; 95% CI, 0.018-0.186; p<0.001)	(77)
	rs1143634 (+3954 C/T)	Synonymous	74	160	C/C homozygotes for the *IL1B* +3954 SNP showed a decreased risk to develop MM (OR, 0.057; 95% CI, 0.019-0.167; p<0.001)	(77)
IL1RN	rs315952 (*Mspa1* 111100 C/T)	Synonymous	74	160	Homozygotes for the *IL1RN* Mspa1 +11100 C allele showed a decreased risk to develop MM (OR, 0.044; 95% CI, 0.011-0.171; p<0.001)	(77)
IL4R	rs2107356	5'Near gene	127[a]	545	Homozygotes T/T for the *IL4R* rs2107356 variant had a significantly increased risk to develop MM (OR, 1.91; 95% CI, 1.08-3.38)	(86)
IL6	rs1800796 (-572G/C)	5'Near gene	150	126	Carriers of the *IL6* -572 C allele showed an increased risk to develop MM (OR, 2.4; 95% CI, 1.2-4.7; p<0.05)	(75)
IL6R	rs6684439	Intronic	82	164	The T/T homozygotes for the *IL6R* rs6684439 SNP showed a significant 3-fold increased risk to develop MM and a border line global p-trend (OR, 2.9; 95% CI, 1.2-7.0; p=0.048)	(82)
	rs7529229	Intronic	82	164	The C/C homozygotes for the *IL6R* rs7529229 SNP showed a significant increased risk to develop MM and a near to significance global p-trend (OR, 2.5; 95% CI, 1.1-6.0; p=0.08)	(82)
	rs2228145 (D358A)	Missense	82	164	The C/C homozygotes for the rs2228145 showed a significant 2.5-fold higher risk to develop MM and a border line global p-trend (OR, 2.5; 95% CI, 1.1-6.0; p=0.038)	(82)
FCGR2A	rs1801274 (H167R)	Missense	127[a]	545	Homozygotes G/G for the missense variant rs1801274 showed a significantly increased risk of MM (OR, 1.95; 95% CI, 1.06-3.60)	(86)
TNF-α	rs1800629 (-308G/A)	5'Near gene	210	218	Carriers of the *TNF-α* -308 A allele showed a minor risk to develop MM in respect to G/G genotypes when compared among cases and controls (OR, 0.55; 95% CI, 0.33-0.91; p=0.02)	(73)
			181	233	Carriers of the A allele for the *TNF-α* -308 SNP showed a significantly decreased risk to develop MM (OR, 0.58; 95% CI, 0.36-0.81; p=0.01)	(79)
			94	141	Carriers of the *TNF-α* -308 A allele showed a decreased risk to develop MM in respect to G/G homozygotes when compared in cases and controls (OR, 0.40; 95% CI, 0.18-0.90; p=0.027)	(83)
TNF-α/LT-α	rs1800629 (-308G/A)/ rs909253 (+252 A/G)	5'Near gene	94	141	Carriers of the rare haplotype for the *TNF-α* -308/*LT-α* 252 AA/AA showed a decreased risk to develop MM (OR, 0.43; 95% CI, 0.19-0.97; p=0.041)	(83)
			198	250	Heterozygotes for *TNF-α* -308/*LT-α* 252 haplotype (GA/AG) showed a significantly increased risk to develop MM compared to the most frequent haplotype (OR, 2.05; 95% CI, 1.26-3.35; p=0.003)	(78)

Table I. Continued.

Gene	SNP	Position/ Function	Cases	Controls	Description of association	Refs.
Polymorphisms in cell signaling and growth factors genes						
CCR7	rs3136685	Intronic	103[a]	475	The *CCR7* rs3136685 G allele showed a significant protective effect on MM risk (OR, 0.38; 95% CI, 0.24-0.64; p=0.0004) and a significant p-trend (p=0.0001), not confirmed after permutation test (p=0.1611)	(94)
CD4	rs11064392	5'Near gene	108[a]	482	In the *CD4* gene region located on 12p13-q13, a total of 6 tag SNPs in 2 genes (*CD4* and *LAG3*) were significantly associated with MM risk (p-trend <0.05). The strongest association was observed for the G carriers of the *CD4* variant rs11064392 (OR, 2.53; 95% CI, 1.59-4.02)	(71)
IGF1	rs7965399	3'Near gene	82	2624	Heterozygotes C/T for the *IGF1* rs7965399 variant showed a significant trend for associations with an increased risk of MM (OR, 1.8; 95% CI, 0.9-3.6; p=0.0015)	(82)
	rs2195239	Intronic	82	2624	The G/G homozygotes for the *IGF1* rs2195239 variant showed a strongly significant p-global for associations with an increased risk of MM (OR, 2.6; 95% CI, 1.2-5.5; p=0.0001)	(82)
	rs2373722	Intronic	82	2624	Heterozygotes C/T for the *IGF1* variant rs2373722 showed a significant global p-trend for association with a decreased risk of MM (OR, 0.5; 95% CI, 0.2-1.1; p=0.0001)	(82)
IGFBP3	rs3110697	Intronic	82	2624	The A/A homozygotes for the *IGFBP3* rs3110697 SNP showed a significant 2-fold higher risk to develop MM and a border line global p-trend (OR, 2.0; 95% CI, 1.1-3.7; p=0.083)	(82)
IKB-α	rs2233406	5'Near gene	250	271	Carriers of the *IKB-α* rs2233406 T allele were underrepresented in MM patients, with a significant protective effect on MM risk (OR, 0.69; 95% CI, 0.50-0.96; p=0.024), although if not confirmed after permutation test	(93)
	rs3138054	Intronic	157	196	G/G homozygotes for the *IKB-α* rs3138054 variant showed a decreased risk to develop MM (OR, 0.61; 95% CI, 0.38-0.68; p=0.042)	(92)
	rs2233419	Intronic	157	196	C/C homozygotes for the *IKB-α* rs2233419 variant showed a decreased risk to develop MM (OR, 0.63; 95% CI, 0.39-1.00; p=0.048)	(92)
HGF	rs17501108	3'Near gene	103[a]	475	The *HGF* rs17501108 T allele was associated with a significantly increased risk of MM (OR, 2.75; 95% CI, 1.69-4.48; $p=4.6x10^{-5}$) and a significant p-trend ($p=5x10^{-5}$), almost confirmed after permutation test (p=0.074)	(94)
HPSE	rs4693602	Intronic	44	103	The A/A individuals for the *HPSE* rs4693602 were more frequent between MM cases in respect to controls (p=0.026)	(96)
IRS1	rs1801278 (G971A)	Missense	82	164	Heterozygotes for the *IRS1* rs1801278 SNP showed a significantly increased risk of MM respect to C/C homozygotes (OR, 4.3; 95% CI, 1.5-12.1)	(82)
	rs17208470	Intronic	82	164	Heterozygotes for the *IRS1* rs17208470 SNP showed a significantly increased risk of MM respect to most frequent homozygotes (OR, 2.2; 95% CI, 1.1-4.5)	(82)
RIPK1	rs9391981	Intronic	108[a]	482	Carriers of the *RIPK1* rs9391981 C allele showed a decreased risk to develop MM compared to G/G individuals (OR, 0.32; 95% CI, 0.12-0.81; p=0.017) and a significant p-trend for protective effect (p=0.016)	(95)
SERPINE1	rs2227667	Intronic	103	475	The rs2227667 G allele was significantly overrepresented in MM patients compared to controls, evidencing a protective effect on MM risk (OR, 0.39; 95% CI, 0.24-0.64; p=0.0002) and a significant p-trend ($p=2.1x10^{-5}$), confirmed after permutation test (p=0.0336)	(94)

Table I. Continued.

Gene	SNP	Position/ Function	Cases	Controls	Description of association	Refs.
TRAF3	rs12147254	Intronic	249	268	The *TRAF3* rs12147254 A allele showed a significantly decreased risk of MM (OR, 0.71; 95% CI, 0.62-0.82; p<0.001), confirmed after permutation test (p<0.001)	(93)
Polymorphisms in DNA repair, cell cycle and apoptosis genes						
BAX	rs1042265	3'UTR	108[a]	482	Carriers of the A allele for the *BAX* rs1042265 variant showed a lower risk to develop MM respect G/G homozygotes (OR, 0.40; 95% CI, 0.21-0.78; p=0.007)	(95)
CASP3	rs1049216	3'UTR	128[a]	516	Subjects with the C/C genotype for the *CASP3* Ex8+567 T>C SNP showed a border line association with a 5-fold decreased risk of MM (OR, 0.2; 95% CI, 0.0-1.0; p=0.05)	(101)
CASP9	rs1052576 (Q221R)	Missense	128[a]	516	A/A homozygotes for the *CASP9* Ex5+32 G>A SNP evidenced a decreased risk of MM (OR, 0.5; 95% CI, 0.3-0.9; p=0.02)	(101)
	rs7516435	Intronic	108[a]	482	G/G homozygotes for the *CASP9* rs7516435 variant showed a 2.6-fold higher risk to develop MM (p=0.007) and an overall significant p-trend (OR, 2.59; 95% CI, 1.30-5.15; p=0.005)	(95)
LIG4	rs1805389 (A3V)	Missense	270	220	Heterozygotes for the A3V variant of *LIG4* showed a decreased risk to develop MM (OR, 0.49; 95% CI, 0.27-0.89; p<0.05)	(99)
	rs1805388 (T9I)	Missense	270	220	T/T homozygotes for the I9T polymorphism of *LIG4* showed a decreased risk to develop MM (OR, 0.22; 95% CI, 0.07-0.70; p<0.05)	(99)
XRCC4	rs963248	Intronic	306	263	Carriers of the *XRCC4* rs963248 G allele showed an increased risk to develop MM (OR, 1.54; 95% CI, 1.07-2.20; p=0.024) and a statistically significant p-trend (p=0.026)	(98)
XRCC5	rs1051685	3'UTR	306	263	Homozygotes for the *XRCC5* rs1051685 G allele showed an increased risk to develop MM (OR, 8.3; 95% CI, 1.05-65.35; p=0.027) and a statistically significant p-trend (p=0.015)	(98)
Polymorphism in xenobiotic metabolism and transport genes						
CYP1A1	rs4646903 (*2A allele)	3'Near gene	116	176	Carrier of the *CYP1A1***2A* allele showed a minor risk to develop MM respect wild-type homozygotes (OR, 0.57; 95% CI, 0.33-0.99; p=0.048)	(120)
CYP1B1	rs1056836 (V432L)	Missense	279	742	Carriers of the *CYP1B1* rs1056836 G allele showed an increased risk to develop MM (OR, 1.42; 95% CI, 1.00-2.02)	(107)
mEH	rs2234922 (H139R)	Missense	102	205	The homozygotes G/G for the *mEH* SNP rs2234922 showed a significantly increased risk to develop MM (OR, 5.81; 95% CI, 1.26-35.71; p=0.01)	(106)
GSTT1	(pos/null)	Missense	90	205	Patients with null genotype for the *GSTT1* gene present a 2.5-fold increased risk to develop MM (OR, 2.47; 95% CI, 1.26-4.80; p=0.008)	(105)
MTHFR	C677T	Missense	798	3000	The results obtained from a meta-analysis evidenced an association between the *MTHFR* C677T gene polymorphism and risk of MM. T carriers had an increased risk to develop MM when analyzing all ethnic groups together (FE OR, 1.23; 95% CI, 1.04-1.47) and in Caucasian (FE OR, 1.54; 95% CI, 1.14-2.08), while not in East Asian (FE OR, 1.05; 95% CI, 0.82-1.34)	(118)
MTR	rs1805087 (2756A>G; D919G)	Missense	173	1700	Carriers of the G allele for the *MTR* A2756G variants showed a decreased risk to develop MM (OR, 0.61; 95% CI, 0.40-0.93; p=0.02)	(114)

Table I. Continued.

Gene	SNP	Position/ Function	Cases	Controls	Description of association	Refs.
			123	188	Carriers of the G allele for the *MTR* rs1805087 polymorphism showed an increased risk to develop MM (OR, 2.31; 95% CI, 1.38-3.87; p=0.001)	(112)
NAT2	(rapid/slow)	Phenotype	90	205	Slow metabolizers showed an increased risk to develop MM compared to the rapid one (OR, 1.89; 95% CI, 1.14-3.26; p=0.02)	(105)
PON-1	rs662 (Q192R)	Missense	90	205	Patients homozygotes for the *PON-1* 192R allele had an increased risk to develop MM (OR, 2.66; 95% CI, 1.20-5.88; p=0.02)	(105)

[a]This study has been conducted only in women.

to be relevant players in MM pathogenesis (87). Several reports investigated SNPs in *IL6*, *IL6R* and *IL6ST* genes (75,76,80-82) and up to date, several studies failed to evidence association with the well studied *IL6* promoter -174G/C SNP (rs1800795) (70,75,80-82). In one study the *IL6* -572G/C (rs1800796) was associated with an increased risk to develop MM for carriers of the -572C allele (75). However, this association was not confirmed in a following study (82), whereas an increased risk of MM was found for carriers of the minor allele of SNPs D398A (rs8192284), rs7529229 and rs6684439 in the *IL6R* gene. Nevertheless, association within *IL6R* SNP rs8192284 was investigated in a third study that did not confirm the previous findings (81). Several SNPs in other cytokines and immunity-related genes, such as *IL1B*, *IL1A*, *IL1RN* (77,85), *IL4R* and *FCGR2A* (86) have been found to be associated with MM risk, although there is a lack of replication studies limiting the applicability of these findings.

Polymorphisms in growth factors and cell signaling genes. The complex network of signaling pathways activated by several proteins present in the bone marrow microenvironment play a relevant role in malignant plasma cells proliferation, migration and survival (88). The activation of the nuclear transcription factor *NF-κB* is thought to be one of the most important factors to enhance cell proliferation in MM pathogenesis (89,90). The minor alleles of SNPs in genes related to the *NF-κB* pathway, such as the inhibitor *IκBα* (rs2233406, rs3138054, rs2233419) and the transcriptional activator *TRAF3* (rs12147254) have been associated with a protective effect on MM development (91-93).

Several polymorphisms in genes related to insulin metabolism resulted associated with MM risk. In particular, three SNPs in the *IGF1* gene (rs7965399, rs2195239, rs2373722), one in the *IGFBP3* (rs3110697) gene and two in the *IRS1* gene have been associated both with increased or decreased risk of MM (82).

Several SNPs in other immunity-related and adhesion/growth genes, such as *SERPINE I*, *CCR7*, *HGF*, *JAK3* (94), *CD4* (71), *RIPK1* (95) and *HPSE* (96) have been found to be associated with MM risk. Nevertheless, these results wait to be replicated in independent populations. Other reports did not evidence significant results (97).

Polymorphisms in DNA repair, cell cycle and apoptosis genes. SNPs in genes of the DNA repair system have been deeply investigated to uncover the genetic susceptibility of many cancer types, including MM (98-100). The observation of recurring translocation in MM patients involving the 14q32.3 cytogenetic band, which is considered the primary genetic event leading to the malignant transformation of the plasma cells, has supported the idea that alteration of the class switch recombination (CSR) process could play a fundamental role in MM pathogenesis. The *XRCC5* gene encodes for the Ku80 protein, that together with Ku70 (*XRCC6*) constitutes the Ku70/Ku80 complex that acts in the recognition of double strand breaks (DSBs). The DNA breakpoints recognized by Ku70/Ku80 are subsequently joined by the XRCC4/DNA ligase IV complex. Interestingly, some authors reported associations of *XRCC4* (rs963248), *XRCC5* (rs1051685) and *LIG4* A3V (rs1805389), T9I (rs1805388) SNPs with MM susceptibility (98,99). In particular, carriers of the *XRCC4* rs963248 G allele as well as carriers of the *XRCC5*

rs1051685 G allele showed an increased risk to develop MM (98), while heterozygotes for the *LIG4* A3V SNP as well as rare homozygotes for the *LIG4* T9I SNP have been shown to have a lower susceptibility to MM (99). SNPs in *BAX*, *CASP3* and *CASP9* genes were found to be associated with MM risk in women (95,101), while the *p53* codon 72 polymorphism (102) and SNPs in *XRCC3* and *ERCC2* genes (98,100) showed no associations with MM risk.

Polymorphisms in xenobiotic metabolism and transport genes. SNPs in genes codifying for enzymes acting in phase I, phase II metabolic reactions and phase 0/III transport have been also investigated for associations with genetic susceptibility to MM. Glutathione-S-transferases (GSTs) conjugate phase I activated metabolites to favour their excretion from the organism. Polymorphisms in the *GSTM1*, *GSTT1* and *GSTP1* loci have been investigated in several case-control studies with weak evidence of association (102-105). Although not confirmed in other studies, Lincz *et al* showed an association between the *GSTT1* null genotype and an increased MM risk. The authors also showed an association of both the rare homozygotes for the Q192R (rs662) SNP in the *PON-1* genes and *NAT2* rapid/slow phenotype with an increased risk of MM (105). In a following study on polymorphisms in genes involved in benzene metabolism Lincz *et al* evidenced an increased susceptibility to MM for carriers of 'high-risk genotypes/phenotypes' of *GSTT1* (null), *NQO1* (187PS/SS, rs1800566) and *mEH* (high activity) genes as well as for the G/G homozygotes for the *mEH* H139R (rs2234922) polymorphism (106). Nevertheless, in another study investigating *NQO1* P187S (rs1800566), *PON-1* Q192R (rs622) and *mEH* H139R (rs2234922) SNPs no associations were found (107).

Folate-metabolizing enzymes have been also intensely investigated in relation to MM risk. *MTHFR*, which has been found associated with cancer risk (108,109), is one of the most important enzymes involved in the regulation of folate homeostasis. Two *MTHFR* missense SNPs, C677T (rs1801133) and A1298C (rs1801131), were investigated in relation to MM susceptibility in various reports with evidence for association (110-112) as well as for no association (113-117). Recently, a meta-analysis confirmed a possible role for the *MTHFR* C677T (rs1801133) SNP in MM susceptibility, with an increased risk for carriers of the 677T allele (118). The minor allele (G) of the missense substitution A2756G (rs1805057) in the enzyme methionine syntase (*MS* or *MTR*) has been found associated with higher risk of MM in a mixed Caucasian and African-American population (112), but with decreased risk in an Asian population (114). However, this effect was not observed in a third study (117). SNPs in other genes such as *ABCB1*, *TYMS*, *CYP1A1* and *CYP1B1* have been also investigated and showed modest evidence of association with MM risk (107,112,114,119,120).

4. Pharmacogenetics of multiple myeloma

The study of pharmacogenetics in MM is relatively recent, the earliest studies dating back to early 2000. Several studies have explored factors influencing the individual response to chemotherapies and the resulting survival, while other studies have tried to further our understanding on adverse reaction to drugs.

Role of SNPs in therapy outcome and survival. Associations between several genetic variants and therapy outcome have been already reported. The *TNF-α* promoter SNP -238G/A (rs361525) has been associated with response to a thalidomide maintenance therapy in relapsed and refractory MM, showing a prolonged progression-free survival (PFS) and OS for carriers of the A allele (121). Interestingly, borderline association of *TNF-α* gene polymorphisms and PFS has been observed in previous studies (78,79) and a significant association of the *TNF-α* -238A allele with a better PFS and OS in patients treated with thalidomide and dexamethasone has been confirmed by recent findings (73).

Dasgupta *et al* showed association of the I105V (rs1695) SNP of the *GSTP1* gene with a better PFS in MM patients homozygous for the 105V allele after standard and high-dose chemotherapy (HDM) (122). A similar association between 105V homozygotes for the *GSTP1* SNP I105V (rs1695) and MM outcome after DAV (dexamethasone/adriamycin/vincristine) induction therapy has also been described by others (123,124).

Homozygotes for the T allele of *TYMS* +157C/T (rs699517) polymorphism have been shown to have a worse response to ASCT (124). An association with an improved outcome after HDM and ASCT in MM patients and a near-to-significance association with an improved OS for the T allele for the SNP rs1051296 in the folate transporters *SLC19A1* gene has also been reported (125).

Due to their importance in the determination of drug bioavailability, drug metabolizing enzymes and drug transporters coding genes are among the most investigated for a role in MM pharmacogenetics. Among these, *ABCB1* has been widely studied. In particular the well known *ABCB1* C3435T (rs1045642) and G2677A/T (rs2032582) polymorphisms were found associated with outcome of different treatments in MM patients (123,126-128). The T allele of the *ABCB1* C3435T has been associated with a better response to DAV treatment (123), a better response and a better PFS (T/T homozygotes) after bortezomib treatment of relapsed and/or refractory myeloma patients (128,129) and with better OS of MM patients (130). The rare T allele of the triallelic *ABCB1* SNP G2677T/A has been associated to a better response to DAV (123) and a better OS (127) in MM patients.

SNPs in genes encoding drug metabolizing enzymes belonging to the cytochrome P450 family have been investigated as well (i.e., *CYP2C19*, *CYP2D6*, *CYP3A4*) with controversial results (123,126,131,132). In a study investigating two polymorphisms of *CYP2C19* gene, poor metabolizer phenotype was associated with a poor response to thalidomide-based therapies (132). Vangsted *et al* showed the association of *ERCC2* K751Q (rs1052559), *XRCC3* T241M (rs861535), *CD3EAP* -21G/A (rs967591) (100) and *IL1B* -31T/C (rs1143627) (85) polymorphisms with outcome after ASCT in MM patients receiving HDM. In particular, carriers of the *ERCC2* K751Q C allele, the variant T allele of *XRCC3* T241M and the A allele of *CD3EAP* 21G/A SNP had a better time to treatment failure (TTF) in respect to homozygous wild-type carriers and the variant A allele of *CD3EAP* 21G/A resulted also associated with a better OS (100). Carriers of the variant C allele for the *IL1B* -31T/C SNP showed a significantly improved OS than T carriers (85). A role of the *NFKB1* -94 ins/delATTG polymorphism has been

Table II. The IMMEnSE consortium participating centres.

Centres	Country
Hospital and Clinical Centres	
Department of Oncology, Transplants and Advanced Technologies, Section of Haematology, Pisa University Hospital	Pisa, Italy
Department of Hematology, Medical University of Lodz	Lodz, Poland
Division of Hematology, University Hospital of Salamanca	Salamanca, Spain
Department of Hematology and Hemotherapy, University Hospital Virgen de las Nieves	Granada, Spain
Hospices Civils de Lyon	Lyon, France
Hospital de Braga	Braga, Portugal
IDIBELL-Catalan Institute of Oncology and University of Barcelona	Barcelona, Spain
Research institutions	
Genomic Epidemiology Group, DKFZ (German Cancer Research Center)	Heidelberg, Germany
Genomic Oncology Area, GENYO (Pfizer-University of Granada-Andalusian Government Centre for Genomics and Oncological Research)	Granada, Spain
Division of Genetics, Department of Biology, University of Pisa	Pisa, Italy
International Agency for Research on Cancer IARC, Genetic Cancer Susceptibility Group	Lyon, France
Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho	Braga, Portugal

shown in patients receiving Interferon-α (IFN-α) as maintenance therapy after HDM (133). Interestingly, in a recent study, Vangsted *et al* investigated additional genetic variants in the *IL1B* promoter region and their impact on TTF, OS and IFN-α maintenance therapy. Carriers of the T allele of the *IL1B* C-3737T (rs4848306) as well as carriers of the TGT haplotype resulting from the *IL1B* SNPs C-3737T, G-1464C (rs1143623) and T-31C (rs1143627) showed a reduced OS and TTF. In addition, carriers of the combination *IL1B*-3737T allele/ *NFKB1* -94 delATTG alleles showed a better TTF and OS in patients treated with a IFN-α maintenance therapy (134). An association between the carriers of the G allele for the -8C/G SNP in the 20S proteasome subunit coding gene *PSMA6* and a better 5-year OS has been also shown (135). Recently, Du *et al* evidenced the association of the carriers of the A allele of the *TRAF3* SNP rs11160707 with an improved PFS, while the variant alleles for two *NFKB2* SNPs (rs12769316 and rs1056890) were associated, respectively, with an increased and a decreased OS (93).

Role of SNPs in treatment-related side effects and toxicity. Treatment-related neuropathy is one of the most common side effects in MM and affects about 40-64% of the patients treated with bortezomib (136). Peripheral neuropathy has been registered also following thalidomide treatment in about 40% of the patients (137) and, at a minor grade, in patients treated with lenalidomide (138). Recently, Broyl *et al* showed several SNPs in different genes to be related with early- and late-onset bortezomib induced neuropathy. In particular, SNPs in *CASP9* (rs4646091), *RDM1* (rs2251660), *ALOX12* (rs1126667, rs434473), *LSM1* (rs7823144), *IGFR1* (rs1879612) and *NEK4* (rs1029871) genes associated with early-onset bortezomib induced neuropathy, while SNPs in *ERCC4* (rs1799800, rs1799801), *SRD5A2* (rs2300697), *IFNGR2* (rs1059293), *ERCC3* (rs2276583), *ATM* (rs189037, rs664677, rs664982), *MRE11A* (rs10501815), *SELP* (rs6131), *PTPRN2* (rs1130499), *STK31* (rs4722266) and *PPARD* (rs2267668) genes associated with late-onset bortezomib induced neuropathy (139). Several authors investigated the role of genetic variation in thalidomide-related adverse effects. Johnson *et al* analyzed a panel of over 3,400 SNPs in 964 genes in 1,495 patients from different clinical trials, showing overall associations of SNPs in *SERPINE1* (rs7242), *ADRB2* (rs2082382, rs1042714), *ID3* (rs1555026), *CYP2C9* (rs1934951), *CAMKK1* (rs7214723), *CYP2C8* (rs1058932), *SLC10A2* (rs2301157) and *NFATC2* (rs228832) genes with thalidomide-related neuropathy (140). The same SNP panel has been used to investigate the role of genetic variation in the occurrence of thalidomide-related venous thrombotic events (VTEs). The results showed a total of 18 SNPs, validated in 2 patient groups from different clinical trials, associated with the occurrence of VTEs in thalidomide treated patients (141). The use of bisphosphonates in MM could be associated with the development of osteonecrosis of the jaw (ONJ) (142) and Sarasquete *et al* showed a statistically significant association of the *CYP2C8* SNP rs1934951 with the occurrence of ONJ (143).

5. Limits and perspectives: the rationale for the IMMEnSE consortium

Despite several efforts towards the comprehension of the role of common genetic variability in modifying the individual risk to develop MM, to date no locus has been unequivocally established as risk factor for MM development. The fairly small sample sizes (ranging from 26 to 352 cases) of the published studies, due in part to the low incidence of the disease, could represent one fundamental limiting factor to detect genetic associations with MM risk. This is particularly important considering the fact that the genetic risk to develop MM is likely influenced by low-penetrance variants the

effect of which is difficult to detect in uncommon diseases. Moreover, this limit can explain, at least in part, the failure of the replication effort suffered by several studies so far reported. Even if meta-analyses can overcome the size limits that occur in single studies, limited data exist to date. One viable option to further our understanding in the genetic determinants of MM risk is to unify a large set of patients across different populations and cohorts in a consortium. This strategy has been shown to be successful for various cancer sites, as shown on one hand by several GWAS in which several new risk loci were discovered (144,145) and on the other hand by various candidate gene studies nested in large cohorts used to replicate or disproof known findings (146). This effort is of the uttermost importance for a low-prevalence disease such as MM. Moreover, a large collection of samples possibly joined by a meticulous collection of co-variates of clinical importance, not only provides a greater advantage in terms of power for risk study, but allows also a more exhaustive investigation of pharmacogenetics. Given the heterogeneity of the treatments in the patient populations, the possibility to unite several sets of patients allows the individuation of larger subgroups receiving similar therapies.

The IMMEnSE consortium. The International Multiple Myeloma rESEarch (IMMEnSE) consortium aims to improve the understanding of genetics and pharmacogenetics of MM. The driving idea of the IMMEnSE consortium is to join together the efforts of different research groups with the constitution of a large bio- and databank to allow more powerful and meaningful investigations able to uncover the role played by genetic variants in MM genetics, as successfully done for other diseases (147,148). To date, the IMMEnSE consortium brings together twelve basic and/or clinical research groups with a wide spectrum of expertise and spreads widely across six European countries (Table II). Recognizing the need for further expansion of this network, the recruiting of collaborators and partner institutions is continuously ongoing.

The cases included in the consortium population are defined by a confirmed diagnosis of MM, according to the International Myeloma Working Group (IMWG) criteria (1). For each patient, information about gender, age at diagnosis, β2-microglobulin, albumin, creatinin, haemoglobin, bone lesions and previous clinical history at diagnosis are collected. Detailed information concerning front line and relapsed/refractory patients therapies are collected, as well as the individual response to them. PFS from ASCT, OS and toxicity events are registered as well to investigate the role of genetic variants in the pharmacogenetics of MM. Moreover, with the aim to investigate genetic variables involved in the transition from MGUS to MM, positive history of MGUS is registered. So far, 743 MM cases diagnosed between 1992 and 2010 have been retrospectively recruited in each participating centre up to now and collected at the German Cancer Research Center, where the DNA bank and the central database have been set up. The collection of MM and MGUS cases is currently ongoing in every participating centre and the population is expected to reach 2000 cases within 3 years.

Different region-specific subpopulations of unmatched controls have been selected for a total of 950 healthy individuals

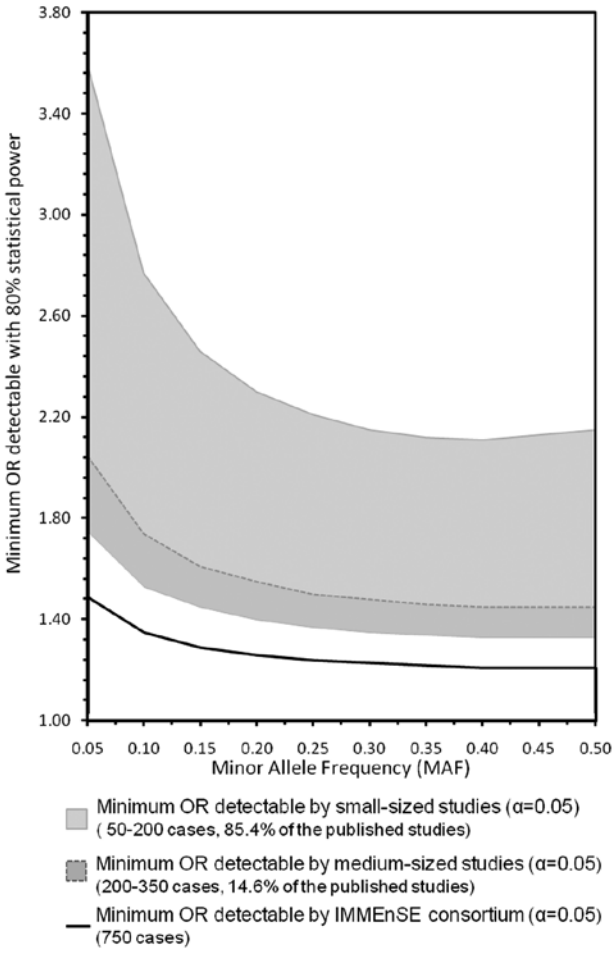

Figure 1. Statistical power of genetic association studies on MM (α=0.05). This figure describes the minimum OR detectable with a power of 80% and a MAF from 0.05 to 0.5 with a type I error α=0.05, depending on the sample size. The minimum OR detectable decreases considerably with larger sample sizes. The IMMEnSE population ensures the statistical power to detect possible associations between low-penetrance genetic variants and MM risk.

enrolled to date. Controls have been selected among the general population as well as among hospitalized subjects with different diagnosis excluding cancer. Gender and age at recruitment are collected for every subject enrolled. For each subject, informed consent to collect fresh blood and perform DNA extraction for research purpose has been requested and collected individually by each centre. Genetic analyses are being performed in the German Cancer Research Center (Heidelberg, Germany). Detailed information on the demographic and clinical characteristics of the IMMEnSE consortium population are described in Table III.

6. Future directions

Epidemiological studies have been shown to be of great value to the understanding of the biology of many other cancer types. The available results on genetic risk of MM clearly evidence the necessity of additional studies assessing also the interplay of genetic and clinical factors to fully understand the molecular mechanisms underlying the susceptibility to MM. At the same time, the consortium aims to contribute to the understanding

Table III-A. Demographic and clinical characteristics of MM cases.

	Cases						
Characteristics	1[a]	2[a]	3[a]	4[a]	5[a]	6[a]	All[a]
Age at diagnosis (years)							
Mean (±SD)	62.53 (±9.93)	61.85 (±10.41)	62.88 (±11.75)	64.25 (±9.90)	55.96 (±9.31)	66.78 (±10.49)	61.34 (±10.38)
Median (range)	63 (35-87)	62 (39-86)	62 (31-93)	64 (39-86)	58 (27-75)	68 (43-86)	62 (27-93)
Gender N (%)							
Male	122 (52.3)	71 (49.3)	67 (52.3)	39 (42.8)	52 (56.5)	26 (47.3)	377 (50.7)
Female	111 (47.7)	73 (50.7)	61 (47.7)	52 (57.2)	40 (43.5)	29 (52.7)	366 (49.3)
Total	233 (31.4)	144 (19.4)	128 (17.2)	91 (12.2)	92 (12.4)	55 (7.4)	743 (100)
Ascertainment period	1992-2009	1993-2009	1990-2009	1991-2006	1995-2005	2007-2010	1990-2010
Stage at diagnosis (%)							
Durie-Salmon I/II/III/ND	15.1/21.4/63.5/48.3						
ISS I/II/III/ND	52.9/23.0/24.1/76.6						
Prognostic markers							
β2-microglobulin (μg/l)	3.39 (1.99-5.90)[b]						
Creatinin (mg/dl)	1.0 (0.8-1.3)[b]						
Albumin (g/dl)	3.9 (3.5-14.6)[b]						
Haemoglobin (mg/dl)	10.8 (8.8-12.7)[b]						

B, Demographic characteristics of controls by population.

	Controls					
Characteristics	Italian	Polish	Spanish	French	Portuguese	All
Age at diagnosis (years)						
Mean (±SD)	58.81 (±10.95)	69.50 (±6.67)	65.21 (±13.45)	53.12 (±6.28)	60.68 (±7.72)	57.11 (16.09)
Median (range)	59 (35-89)	69 (55-98)	66 (24-92)	51.5 (41-68)	58 (51-85)	59 (18-98)
Gender N (%)						
Male	131 (52.3)	69 (49.3)	173 (52.3)	68 (52.5)	55 (56.5)	476 (52.1)
Female	106 (47.7)	81 (50.7)	158 (47.7)	64 (48.5)	45 (43.5)	437 (47.9)
Total	237 (25.0)	150 (15.8)	331 (34.8)	132 (13.9)	100 (10.5)	950
Control type	General population	Blood donors	Hospitalized	Blood donors	Blood donors	

[a]1, Department of Oncology, Transplants and Advanced Technologies, Section of Haematology, Pisa University Hospital, Pisa, Italy; 2, Department of Hematology, Medical University of Lodz, Lodz, Poland; 3, Division of Hematology, University Hospital of Salamanca, Salamanca, Spain; 4, Department of Hematology and Hemotherapy, University Hospital Virgen de las Nieves, Granada, Spain; 5, Hospices Civils de Lyon, Lyon, France; 6, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal. [b]Median (25th-75th). ND, no data.

of how the genotype may predict the clinical outcome and the degree of response to treatments, in order to offer new clues to optimize treatment and to improve patients' lives. Thus, the IMMEnSE consortium will also allow the optimization of the efforts towards the translational implementation of genetic findings.

Replication of best associated SNPs. In the proposed framework of the IMMEnSE consortium, the first objective is to conduct a comprehensive replication of the most important and significant genetic associations found with MM risk. As shown in Fig. 1, the current size of the IMMEnSE population is already enough to guarantee a statistical power over 80%

for the identification of an OR of 1.5 with a Minor Allele Frequency (MAF) of 0.05, up to an OR of 1.25 with a MAF of 0.25 or greater. Besides, taking into account the ongoing recruitment of MM cases, this power is destined to grow. Thus, these results should make a significant improvement to the interpretation of the controversial results published to date.

GWAS, validation of associated loci and rare SNP analysis. The contribution of GWAS in the identification of new loci associated with risk of several cancer types has been of extreme importance in the last few years. Up to date, no GWAS has been conducted on MM. As soon as GWAS data will be available also for MM risk, the IMMEnSE population will constitute a valuable tool for replication and confirmation of the most interesting results. Moreover, given that GWAS studies still lack the coverage of less common variants (i.e., MAF <5%), their investigation in candidate-gene approach studies will still be of primary importance in MM genetic risk assessment. In this context, the aim of the IMMEnSE consortium will be to investigate genetic variants in regions shown to be possible actors in the pathogenesis of MM.

Identification of tagged functional variants. Tagging SNPs are unlikely to be directly responsible for the effect seen on disease risk. The identification of functional genetic variants associated with tag SNPs is one of the most fascinating and important challenges in the near future. While tag SNPs can sufficiently cover linkage disequilibrium (LD) blocks within a region, direct sequencing or fine mapping of the associated loci are often needed to determine the effective genetic variants able to impact the MM risk. Availability of samples from MM cases will be paramount for these tasks, both to perform sequencing of targeted regions in order to discover potentially causal variants and/or to test whether such candidate variants show a stronger association than tag SNPs identified by GWAS.

Multifactorial risk scores. The impact of common low-penetrance variants taken individually is expected to be very small. Nevertheless, the interactions of many modest contributions could lead to a significant improvement of MM risk. The cumulative risk could be determined from interactions between genetic variants as well as from the interaction of genetic and environmental factors. The evaluation of gene-environment interactions according to a multiplicative or supra-multiplicative statistical model requires very large sample size to ensure an adequate power. However, the population collected in the context of the IMMEnSE consortium offers the possibility to build multifactorial risk scores based on additive models that take into account both genetic factors and clinical variables and evaluate their predictive power. This could lead to the identification of MM susceptibility models able to describe and better predict the risk of MM.

The identification of 'easy-to-use' prognostic markers. To establish clear and effective prognostic factors for staging, outcome and survival of MM patients remains one of the most important issues to be addressed. Genetic markers offer the great advantage to be easily determinable and invariant over time. Thus, they appear to be ideal candidates to be employed as fast markers in screening, prevention and diagnosis of diseases. Even if with the data currently available on MM we are still far from this goal, the translational potential of pharmacogenetics appears to be relevant. In the context of the IMMEnSE consortium, clinical parameters at diagnosis, response to treatments, PFS and OS will be evaluated in relation to genetic variants studied to individuate new genetic prognostic markers.

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