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# Genetic predisposition to multiple myeloma

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## ABSTRACT

Genetic myeloma risk research relied on genome-wide association studies to identify 24 common but low–impact germline predisposition alleles that account for an estimated one eighth of the heritable myeloma risk in Caucasians. Next-generation sequencing, particularly whole-exome sequencing, uncovered a handful of rare but high-impact myeloma risk loci that convey intriguing clues about etiology. The recent discovery of *NCOA1* as a myeloma susceptibility gene in Han Chinese has set the stage for the more complete elucidation of the genetic myeloma risk across ethnic barriers. Validating individual myeloma risk loci at the functional level and integrating predisposition genes in genetic networks and biological pathways are important research tasks going forward. Candidate pathways that are currently emerging include plasma cell development, autophagy, telomere maintenance, and cell cycle regulation. An outstanding knowledge gap in the area of gene-environment interaction concerns the possibility that tumor-promoting effects of myeloma susceptibility alleles depend on specific environmental or occupational exposures. An implicit promise of myeloma risk research is the detection of new molecular targets for myeloma treatments and preventions. A related outcome is new biomarkers for patient stratification, prognostication, and development of individualized treatment plans.

**Keywords:** plasma cell malignancy, germline risk, racial and ethnic factors, GWAS

**Abbreviations:** GWAS, genome-wide association study; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NGS, next-generation sequencing; OR, odds ratio; RAF, relative allele frequency; RR, relative risk; TWAS, transcriptome-wide association study; WES, whole exome sequencing

## DISCOVERY OF GENETIC MYELOMA RISK

The discovery of genetic predisposition to multiple myeloma (MM) goes back almost exactly a century ago to the 1920s, when for the first time families were described in which several members were affected by MM (familial myeloma) or its precursor condition, monoclonal gammopathy of undetermined significance (MGUS). Recent epidemiological case control studies have brought these early observational findings to date, including a large Swedish survey published in 2010, which analyzed nearly 14 thousand myeloma patients and more than fifty thousand healthy controls. The analysis revealed that first-degree relatives of myeloma patients had a 2.1-fold higher relative risk (RR) of developing both MM and MGUS[1]. RR of acute lymphoblastic leukemia was also increased by a factor of 2.1, suggesting that myeloma risk overlaps with that of less mature B-lineage neoplasms[1]. Hypothesis-driven genetic association

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studies that utilized a candidate gene or pathway approach to identify genetic variants that elevate myeloma risk complemented these investigations. This included polymorphisms in genetic networks one might intuitively implicate in the natural history of myeloma; e.g., cytokine-dependent immune responses, DNA repair, and apoptosis. However, less obvious connections, such as folate metabolism and insulin-like growth factor signaling, were also considered. A number of positive associations with myeloma risk were suspected, but none of these were independently replicated or free of (potentially fatal) flaws such as insufficient sample size or cryptic relatedness of probands[2]. The recent technological advance of GWAS, a method of unbiased genetic association testing, permitted the field to overcome these shortcomings and identify, for the first time, myeloma risk loci in a definitive fashion. ***Fig. 1*** depicts a brief timeline of myeloma risk studies, including ongoing research aimed at annotating genetic risk with biological functionality. The prospective epidemiologic PROMISE study, which attempts to predict myeloma progression in high-risk individuals, is also included. This review will summarize available findings on myeloma risk and identify knowledge gaps that should be addressed in future work. Included in the latter are racial and ethnic differences in myeloma risk between Han Chinese and people of Caucasian and African ancestry.

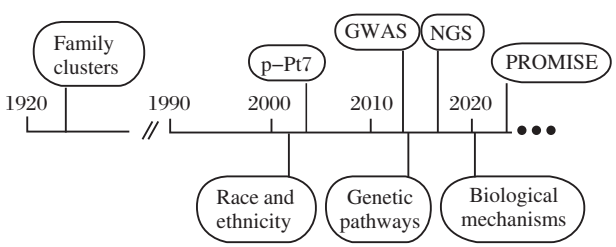


***Fig. 1*** **Milestones of inherited myeloma risk research.** Depicted is a timeline of discovery that began with the detection of familial myeloma a century ago and took a leap forward in the new century with the introduction of GWAS (genome-wide association study) and NGS (next generation sequencing). GWAS and NGS have uncovered common, low-impact and rare, high-impact risk alleles, respectively. PROMISE stands for Predicting Progression of Developing Myeloma in a High-Risk Screened Population.

## MYELOMA RISK ALLELES IDENTIFIED BY GWAS

GWAS, also known as whole genome association study or WGAS, is an observational method for assessing a genome-wide set of genetic variants (typically single-nucleotide polymorphisms or SNPs) in different individuals (e.g., patients *vs.* healthy controls) in order to determine whether any of these variants are associated with a particular trait such as susceptibility to MM. One strength of GWAS is the ability to achieve a stringent threshold of genome-wide significance ($5\times10^{-8}$ is usually required) and its flexibility in terms of considering independent study results for candidate locus confirmation. Beginning in 2012, GWAS identified myeloma susceptibility loci on chromosomes 3p22, 7p15.3, 8q24 and 2p23.3[3,4], with relative allele frequencies (RAFs) and per-allele odds ratios (ORs) invariably indicating common and low-risk variants (***Table 1***). By 2016 additional GWAS and case-control studies had uncovered association signals for 17 risk variants[5–7], a number that could be increased to 24 in the most recent reports[8, 9]. Some risk variants; e.g., located at 16p13, are also associated with survival of patients with myeloma[10]. Despite the leap forward made possible by GWAS, much of the heritable risk of myeloma remains unexplained as of today--a widely known and extensively discussed shortcoming of the method that perpetrates the entire cancer field. The 24 loci mentioned above explain but an estimated one eighth of the heritability for myeloma in Caucasians, with estimates that a sample size in excess of $5\times10^4$ is required to explain 80% of the heritability[8]. Some genetic risk variants exhibit myeloma subtype-specific preference; e.g., a variant at *CCND1* (cyclin D1, required for cell cycle G1/S transition) is associated with t(11;14)-harboring myeloma[5], whereas a variant at *CBX7* (chromobox 7, a transcriptional repressor) is linked to myeloma that does not carry the cyclin D1-deregulating chromosomal translocation[6]. Subtype associations of this sort are of interest for our working model on myelomagenesis because they point to independent pathways of tumor development distinguished by different cytogenetic and molecular features[11].

## MYELOMA RISK OVERLAPS WITH RISK TO MGUS AND AL AMYLOIDOSIS

In parallel to elucidating heritable myeloma risk, GWAS has been successfully employed to delineate the genetic risk of AL (immunoglobulin light-chain) amyloidosis, a closely related neoplasm, and the premalignant condition, MGUS[12]. Unsurprisingly, the underlying genetic risk loci exhibit major overlap[13]. The most recent meta-analysis of MM ($n$ = 4,403), AL amyloidosis ($n$ = 1,230) and MGUS ($n$ = 992), revealed 17 independent loci[14], nine of which are included in ***Table 1*** (indicated by asterisks in the first column) because they were

***Table 1*** **Myeloma risk variants discovered by GWAS and confirmed, in part, by TWAS**

| Genetic locus[1] | RAF[2] | OR[3] | GWAS candidate gene[4] | Ref.[5] | Meta-anal.[6] | TWAS candidate gene[7] |
|---|---|---|---|---|---|---|
| 2p23.3* | 0.81 | 1.24 | ***DNMT3A, DTNB*** | [3, 7] | √ | *CENPO, DNAJC27,* ***DNMT3A, DTNB****, EPT1, KIF3C, PTGES3P2* |
| 2q31.1 | 0.77 | 1.12 | *SP3* | [8] | – | – |
| 3p22.1* | 0.16 | 1.26 | ***ULK4*** | [3, 7] | √ | ***ULK4*** |
| 3q26.2* | 0.75 | 1.20 | ***ACTRT3,*** *GPR160,* ***MYNN,*** *PDCD10, LRRC31,* ***LRRC34,*** *PDCD10, PHC3, SAMD7, SEC62, SEC62–AS1, SERPINI1, SKIL, TERC* | [6–8] | √ | ***ACTRT3, MYNN, LRRC34,*** *LRRIQ4* |
| 5q15 | 0.75 | 1.17 | *ELL2, VPS13C* | [7, 58] | √ | – |
| 5q23.2 | 0.43 | 1.11 | *CEP120, SNX2, SNX24* | [8] | – | – |
| 6p21.3* | 0.29 | 1.20 | *CCHCR1, CDSN, POU5F1, PSORS1C1, TCF19* | [6–8] | √ | – |
| 6p22.3 | 0.02 | 1.37 | *JARID2* | [7] | √ | – |
| 6q21 | 0.21 | 1.18 | ***ATG5,*** *PRDM1, PREP* | [7, 8] | √ | ***ATG5*** |
| 7p15.3* | 0.65 | 1.38 | ***CDCA7L,*** *DNAH11* | [3, 37] | √ | ***CDCA7L*** |
| 7q22.3 | 0.74 | 1.12 | *CCDC71L* | [8] | – | – |
| 7q31.33 | 0.72 | 1.12 | *ASB15, IQUB, POT1, WASL* | [8] | – | – |
| 7q36.1* | 0.12 | 1.19 | *ABCF2, ASIC3, ATG98,* ***CHPF2,*** *SMARCD3* | [7] | √ | ***CHPF2*** |
| 8q24.21 | 0.32 | 1.13 | *CASC11, CCAT1, MYC* | [7, 8] | √ | – |
| 9p21.3* | 0.63 | 1.15 | *CDKN2A, CDKN2B–AS1, MTAP* | [7] | √ | – |
| 10p12.1 | 0.73 | 1.12 | *LYZL1, MASTL, WAC, YME1L1* | [7, 8] | √ | – |
| 11q13.3 | 0.51 | 1.82 | *CCND1* | [5] | – | – |
| 16p11.2 | 0.27 | 1.15 | *DCTPP1, DOC2A, FBRS, FBXL19, GDPD3, ITGAL, MYLPF, PPP4C,* ***PRR14, RNF40,*** *SEPHS2, SEPT1, SRCAP, TBC1D10B, ZNF48, ZNF771* | [8] | – | *C16orf93,* ***PRR14,*** *PRSS53, QPRT, RNF40, RP11–2C24.5* |
| 16q23.1 | 0.58 | 1.13 | *CFDP1, GABARAPL2, GLG1, HSPE1P, NPIPL2, PSMD7,* ***RFWD3*** | [7] | √ | ***RFWD3*** |
| 17p11.2* | 0.10 | 1.30 | *TNFRSF13B* | [6] | √ | *PEMT, TBC1D27, USP32P1* |
| 19p13.11 | 0.24 | 1.14 | *KLF2* | [8] | – | – |
| 20q13.13 | 0.08 | 1.26 | *ARFGEF2, PREX1* | [7, 8] | √ | – |
| 22q13 | 0.37 | 1.21 | *APOL3, CRYBB1, FBXO7, HMGXB4, HMOX1, LARGE, MB, RASD2, TOM1* | [8, 58] | √ | – |
| 22q13.1* | 0.44 | 1.23 | *APOBEC3B–AS1, CBX7, RPL3* | [6, 8] | √ | *APOBEC3C, APOBEC3D, APOBEC3H, APOBEC3F, APOBEC3G* |

[1] Chromosomal location of myeloma risk locus identified in genome-wide association study, or GWAS. Asterisk indicates locus is also associated with risk of MGUS and AL amyloidosis.

[2] Relative allele frequency reported by Went *et al*. 2018[8]. Mean value of RAFs: 0.445. Standard deviation: 0.255. Range: 0.02 –0.81.

[3] Odds ratio reported by Went *et al.* 2018[8]. Indicates that carrier status of risk allele increases the odds of developing myeloma from 11% (5q23.2) to 82% (11q13.3). Mean value of ORs: 1.22. Standard deviation: 0.146.

[4] Gene containing the risk SNP within or outside the gene body. In case of the latter, evidence indicates genetic interaction affects gene expression. Bold, confirmed by transcriptome-wide association study, or TWAS[59].

[5] References.

[6] Confirmed in recent meta-analysis carried out by Pertesi and associates[9].

[7] Myeloma risk locus identified by transcriptome–wide association study, or TWAS. Bold, confirmed by genome–wide association study, or GWAS.

previously identified in GWA studies on MM. Eight loci were newly identified (not included in the table) and pointed to candidate genes on chromosomes 2 (*ASXL2, KIF3C*), 4 (*RP11–818C3.1*), 5 (*ARHGAP26, GABRA1, GABRG2*), 6 (*HLA–DRA*), 8 (*TOX–CA8*), 11 (*B4GALNT4*) and 13 (*TPTE2*). Some of these genes are intriguing from a tumor development point-of-view; e.g., *ASXL2* (ASXL transcriptional regulator 2) at 2p23.3, because it is required for normal hematopoiesis and can function as a haplo-insufficient tumor suppressor, and *ARHGAP26* (Rho GTPase activating protein 26) because it is a fusion partner of *MLL* (mixed-lineage leukemia, officially designated *KMT2A* or lysine methyltransferase 2A), an important driver of leukemia. Genetic interaction--a newly developed approach to accomplish both annotating genetic risk patterns with biological functionality and integrating variant pair interaction with genetic network and pathway enrichment analysis-directed attention to B cell receptor (BCR) signaling regulated by PREX1 (phosphatidylinositol–3,4,5-trisphosphate dependent Rac exchange factor 1) and SETBP1 (SET binding protein 1) as putative drivers of neo–

plastic plasma cell transformation[15]. Of note, the overall estimated heritability of MGUS (25%) that can be explained by the sum of all genetic risk alleles identified to date is approximately twice as high as that of MM (13%) and AL amyloidosis (11%). This suggests that early, tumor-initiating stages of malignant plasma cell development that lead to MGUS are more strongly controlled by the genetic susceptibility network than later stages of tumor promotion that yield frank neoplasia (MM or amyloidosis).

## MYELOMA RISK ALLELES DETECTED BY DNA SEQUENCING AND PCR-BASED GENOTYPING

NGS and PCR-based genotyping provide additional approaches to myeloma risk allele discovery(***Table 2***). One example of the latter is the association of *NCOA1* with genetic susceptibility to myeloma in the Han Chinese population[16]. NCOA1, one of three members of the p160/ SRC family 33 of proteins, acts as transcriptional coactivator for steroid and nuclear hormone receptors, but how this translates to myeloma risk is unclear. Other variants, which were discovered by PCR analysis to be involved in myeloma risk and therapy response, were found in *CRBN* (cereblon) and *IRF4* (interferon regulatory factor 4)[17]. Variants of this sort can be added to a growing list of germline alleles that influence survival in myeloma; e.g., *BSG* (basigin) and *MCT1* (monocarboxylate transporter 1, officially designated *SLC16A1*)[18], *CDKN2A* (cyclin dependent kinase inhibitor 2A)[19], *FOPNL* (FGFR1OP N-terminal like)[10] and *AICDA* (activation induced cytidine deaminase)[20]. NGS, particularly WES (whole exome sequencing) and exome sequencing in SGS (shared genomic segment) regions, affords a powerful method for uncovering myeloma risk alleles. Examples include *ARID1A* (AT-rich interaction domain 1A) and *USP45* (ubiquitin specific peptidase 45), which were detected in a pedigree analysis implicating DNA repair and chromatin remodeling in multiple myeloma risk[21], and *EP300*[22], which encodes a histone acetyltransferase (HAT) known as p300 that regulates transcription via chromatin remodeling. Continuing with epigenetic regulators in the area of early-onset myeloma, WES recently identified germline N-terminal truncating mutations in the first autosomal-dominant MM predisposition gene: *LSD1* (lysine demethylase 1A, official gene symbol *KDM1A*)[23], which encodes a transcriptional repressor that primarily demethylates histone H3 on lysine 4. The finding that pharmacological inhibition of *LSD1* in antigen-challenged mice led to plasma cell expansion and the appearance of serum paraproteins supported the contention that the demethylase is involved in malignant plasma cell transformation[23]. WES followed by gene burden analysis additionally identi–

***Table 2*** **Candidate myeloma susceptibility genes identified in NGS studies**

| Symbol | Gene name | Principal finding | Ref. |
|---|---|---|---|
| *KDM1A* | Lysine demethylase 1A | WES analysis of 50 familial MM probands detected and validated first autosomal–dominant multiple myeloma predisposition gene associated with frank sporadic myeloma | [23] |
| *DIS3* | DIS3 homolog, exosome endoribonuclease and 3´–5´ exoribonuclease | WES analysis of 66 MM/MGUS patients from 23 families revealed 2 loss-of-function mutations. Follow-up studies produced strong evidence for association with frank sporadic myeloma | [60] |
| *ARID1A* | AT–rich interaction domain 1A | WES analysis uncovered 2 missense variants in *ARID1A* and additional variants in other DNA repair genes. However, an association of germline risk with frank sporadic myeloma was not demonstrated | [21] |
| *USP45* | Ubiquitin specific peptidase 45 | High-risk myeloma pedigree analysis identified two rare germline variants. However, an association of these variants with frank sporadic myeloma has not yet been demonstrated | [21] |
| *KIF18A* | Kinesin family member 18A | Comparison of WES data from patients with MM ($n$ = 513) and controls ($n$ = 1,569) suggested linkage. However, a significant association of germline risk and frank sporadic myeloma was not shown | [24] |
| *EP300* | E1A binding protein p300 | WES analysis of one family with multiple cases of MM / MGUS revealed a potentially deleterious missense variant, but an association with frank sporadic myeloma was not shown | [22] |
| *CDKN2A* | Cyclin dependent kinase inhibitor 2A | One 24-nucleotide duplication and one C-to-A point mutation detected in one sporadic case of myeloma, respectively. Association with other neoplasms in both cases | [19, 61] |
| *CTLA4* | Cytotoxic T-lymphocyte associated protein 4 | Analysis of 184 mutation carriers (of which 131 were affected) revealed 17 malignancies (12.9% cancer prevalence) that included ten lymphomas, five gastric cancers, and one myeloma | [62] |
| *NCOA1* | Nuclear receptor coactivator 1 | Myeloma in Han Chinese is linked with rs79480871 ($P \approx 10^{-4}$) at the *NCOA1* locus. Tentative additional associations with SNPs in HLA-Ⅰ and HLA-Ⅱ regions and at *CXCR5*, *ETS1* and LPP loci were also identified | [16] |

fied a candidate risk gene, *KIF18A* ($P = 3.6 \times 10^{-6}$), that encodes a member of the kinesin superfamily of microtubule–associated molecular motors. *KIF18A* displays a distinct pattern of expression across molecular subgroups of MM and is associated with patient survival[24]. Last but not least, WES analysis of 66 cases of MM or MGUS in 23 unrelated families uncovered 2 loss-of-function mutations in *DIS3*, which encodes the catalytic subunit of the exosome complex, and frequently undergoes (>10%) somatic mutagenesis in myeloma.

## MYELOMA RISK ALLELES UNCOVERED IN IMMUNOLOGICAL STUDIES

The risk alleles identified by GWAS (***Table 1***) are common but of low impact, whereas the risk genes/alleles included in ***Table 2*** are rare yet of relatively high impact. Nonetheless, the strongest risk factor for myeloma to date has not been identified in genetic but in immunological studies: the hyper-phosphorylated paratarg–7 (pP–7) carrier state. The RR for pP–7 carriers to develop MGUS/MM is 7.9[25]. Paratarg, which is short for paraprotein target, refers to the circumstance that paraproteins frequently bind to protein and other antigens. Patients with a paraprotein that binds to paratarg–7 (P–7, which was later identified as stomatin-like protein 2 or STOML2) carry a hyper-phosphorylated form of P–7 (pP–7) that is inherited in an autosomal dominant manner. pP–7 is found in over one third of MGUS/MM patients. Additional autoantigenic paraprotein targets were subsequently identified, all of which are hyper-phosphorylated in affected patients[26]. Hyper-phosphorylation may be the result of de-phosphorylation deficiency, based on the finding that de-phosphorylation of pP–7 is defective in pP–7 carriers due to low activity of protein-phosphatase 2A[27]. The work on paratargs described above and exciting new research by Dhodapkar´s group[28] are consistent with the hypothesis that immune responses to post-translationally modified proteins and lipids may play a role in myeloma development. The association of human leukocyte antigen (HLA) polymorphism with myeloma risk lends further support to this view[29] because HLA proteins are instrumental in initiating T cell-dependent immune responses by virtue of presenting immunogenic peptides to the T cell receptor (TCR). Predisposing or protective associations of HLA polymorphisms with myeloma were identified at the level of individual HLA alleles (A, B, C, DRB3/4/5, DRB1 and DQB1) and the level of haplotype combinations of these loci[29]. The predisposing HLA region, for example, that was identified by Chubb *et al*. at 6p21.3 (***Table 1***) [6] may represent *HLA-DRB5*01*[9].

## RACIAL AND ETHNIC DIFFERENCES IN MYELOMA

In the United States, the prevalence of MGUS and frank myeloma is significantly higher in African Americans (AA) than in Caucasian Americans (CA) of European ancestry[30]. For example, a study reporting that the overall myeloma incidence (cases per 100,000 persons) increased from 5.52 in the 5-year period from 1993 to 1997 to 6.08 in the 2008–2012 period ($P < 0.001$) found an increase of ~13% in CA men (6.39–7.22; $P < 0.001$) but an increase of ~17% in AA men (13.94–16.15; $P < 0.01$). Thus, in 2012 the myeloma incidence in AA men ($16.2 \times 10^{-5}$) was 2.24 times higher than in CA men ($7.22 \times 10^{-5}$) and the trend of disparity was increasing[31]. Another well-established racial difference is the mean age of diagnosing myeloma: it is 4 years younger in AA patients (65.8 years) compared to CA patients (69.8 years)[32]. Although confounding effects due to inequalities in health care and a host of environmental and lifestyle factors cannot be excluded, both the higher rate and earlier onset of MM in African Americans support the notion of a racial contribution to the etiology and natural history of MM. Realizing that myeloma disparity research may be hampered by uncertainty and bias introduced by self-reported race as opposed to objective genetic ancestry data, Rajkumar, Kumar and their associates took advantage of a genotyping tool dubbed Precision Medicine Research Array to determine biogeographical ancestry of myeloma patients in an unbiased, quantitative manner. Using this method, they were able to demonstrate that a major proportion of the racial AA *vs*. CA disparity in myeloma is driven by differences in the occurrence of myeloma-associated t(11;14), t(14;16) and t(14;20) translocations[33]. However, genetic myeloma risk is also involved, as discussed in greater depth in the following.

## RACIAL AND ETHNIC DIFFERENCES IN MYELOMA RISK

To determine myeloma susceptibility regions for AA and CA individuals in greater depth, Cozen *et al*. performed a GWAS meta-analysis that included a clever imputation-based fine mapping approach to identify functional variants that govern myeloma risk[34]. The study relied on several loci associated with myeloma risk (***Table 1***), including variants in

*ULK4* (unc−51 like kinase 4); a missense variant in *TNFRSF13B*, which encodes a B cell activating factor (BAFF) receptor from the TNF receptor family called TACI (transmembrane activator and calcium-modulating cyclophilin ligand interactor); SNPs around the promoter and enhancer regions of *CBX7* (chromobox 7); and, importantly, a SNP at *7p15.3* (rs4487645) that was independently confirmed in a GWAS that also implicated the *2q12.3* region in myeloma risk[35]. The *7p15.3* rs4487645 locus exhibits stronger association with MM in AA individuals compared to CA individuals[34]: 0.89 *vs.* 0.70 RAF and 1.37 *vs.* 1.23 OR (at 99% power in both cases and *P* values of $8.30\times10^{-5}$ for AA samples and $7.47\times10^{-4}$ for CA samples). To gain insight into the biological function of the *7p15.3* (rs4487645) risk locus in myeloma, Weinhold, Hemminki and colleagues carried out an expression quantitative trait locus (eQTL) analysis[36] which showed that the C risk allele results in elevated *CDCA7L* (cell division cycle associated 7 like) expression compared to the A "non-risk" allele. Following up on that, Li *et al*. demonstrated that the C risk allele-dependent increase in *CDCA7L* expression must be attributed to the generation of an IRF4 binding site in the 7p15.3 enhancer[37]. This connected the germline risk of myeloma to a genetic pathway of great significance for myeloma biology: IRF4–MYC. Li *et al*. also showed that *CDCA7L* mRNA levels may prognosticate survival of patients with myeloma. For example, in the GSE9782 trial, myeloma patients ($n$ = 265 total) in the top quartile of *CDCA7L* expression (measured in bone marrow plasma cells) exhibited significantly shorter overall survival than patients in the bottom quartile ($P = 3.1\times10^{-4}$; hazard ratio [HR] = 2.3). Wendy Cozen and her associates recently updated the meta-analysis mentioned above and demonstrated that African Americans in the top 10% of a newly constructed polygenic risk score exhibit an increase in the myeloma risk by 80%[38].

## RACIAL AND ETHNIC DIFFERENCES IN SOMATIC MUTATION PATTERNS

A recent NGS study on tumor-acquired somatic mutations in myeloma reported new insights into racial differences between AA and CA patients[39]. This included the discovery of significant differences in mutation frequency in 17 genes, with as many as 15 of them (88%) demonstrating a higher mutation frequency in AA than CA myeloma (***Table 3***). *IRF4* may be of special interest for two reasons: it is recurrently mutated in CA (3.2%) but not AA patients and it is linked to germline risk in the *CDCA7L* locus as described above. IRF4 is an important transcription factor in the hematopoietic system[40] that was identified as a myeloma driver in tumors that carry the *IRF4*-activating chromosomal t(6;14)(p25;q32) translocation[41]. *IRF4* expression is inversely correlated with myeloma clinical outcome[42] and *IRF4*-dependent modulation of Fas-induced apoptosis governs in part myeloma survival[43]. What is more, studies on *IRF4* target genes uncovered a positive auto-regulatory loop between *IRF4* and *MYC*[44]. *IRF4*$^{K123R}$ is the most

***Table 3*** **Genes exhibiting different somatic mutation rates in African American (AA) and Cau casian American (CA) patients with multiple myeloma**

| Gene symbo[1] | Gene name | Mutated in AA (%) | Mutated in CA (%) | AA *vs.* CA ratio | *P* value |
|---|---|---|---|---|---|
| *ABI3BP* | ABI family member 3 binding protein | 3.9 | 1.0 | 3.9 | 0.015 |
| *ANKRD26* | Ankyrin repeat domain 26 | 3.1 | 0.2 | 16 | $<10^{-3}$ |
| *AUTS2* | Activator of transcription and developmental regulator | 3.9 | 1.2 | 3.3 | 0.028 |
| *BCL7A* | BCL tumor suppressor 7A | 3.9 | 0.8 | 4.9 | 0.007 |
| *BRWD3* | Bromodomain and WD repeat domain containing 3 | 3.9 | 0.8 | 4.9 | 0.007 |
| *DDX17* | DAED-box helicase 17 | 3.1 | 0.7 | 4.4 | 0.016 |
| *GRM7* | Glutamate metabotropic receptor 7 | 3.9 | 1.0 | 3.9 | 0.015 |
| *IRF4* | Interferon regulatory factor 4 | ND | 3.2 | N/A | 0.041 |
| *MYH13* | Myosin heavy chain 13 | 3.9 | 0.8 | 4.9 | 0.007 |
| *PARP4* | Poly (ADP-ribose) polymerase family member 4 | 3.9 | 1.0 | 3.9 | 0.015 |
| *PLD1* | Phospholipase D1 | 3.1 | 0.3 | 10 | 0.002 |
| *PTCHD3* | Patched domain containing 3 | 4.7 | 1.0 | 4.7 | 0.003 |
| *RPL10* | Ribosomal protein 10 | 4.7 | 1.0 | 4.7 | 0.003 |
| *RYR1* | Ryanodine receptor 1 | 9.4 | 4.9 | 1.9 | 0.045 |
| *SPEF2* | Sperm flagellar 2 | 3.9 | 0.8 | 4.9 | 0.001 |
| *STXBP4* | Syntaxin binding protein 4 | 3.1 | ND | N/A | $<10^{-3}$ |
| *TP53* | Tumor protein p53 | 1.6 | 6.3 | 0.25 | 0.035 |

ND, not detected. N/A, not applicable.

common mutant allele in myeloma[39, 45], with the resulting lysine–to-arginine exchange in the IRF domain of the protein constituting a putative gain-of-function mutation. Somewhat paradoxically, however, Walker *et al*. recently reported that this mutation (and other exonic mutations in the gene body) results in improved survival in myeloma[45]. The reason for that is not clear but may be related to the possibility that tumor progression alleles such as *IRF4*$^{K123R}$ sometimes improve the treatment response. IRF4 is also of great interest from the therapeutic angle since it constitutes a "unifying Achilles heel" in myeloma, regardless of molecular subtypes[44]. For example, the backbone myeloma drug lenalidomide (Len) down regulates IRF4 indirectly by virtue of targeting cereblon (CRBN), the proximal regulator of the CRBN–IKFZ1/3–IRF4–MYC pathway[46–50].

## PROMISE

A big step towards enhanced understanding of racial disparity in myeloma is the PROMISE study (NCT03689595), which is funded as part of the United States National Cancer Institute Stand Up To Cancer Multiple Myeloma Dream Team. The acronym PROMISE stands for Predicting Progression of Developing Myeloma in a High-Risk Screened Population. The study will enroll an estimated 50,000 participants between 45 and 75 years of age, that are either AA individuals (self–identified) or individuals of any race who have a first-degree relative (parent, sibling or child) with frank myeloma or the precursor conditions MGUS and smoldering multiple myeloma (SMM). The $IgM^+$ plasma cell dyscrasia, Waldenström macroglobulinemia, will also be accepted as inclusion criterion. The completion of PROMISE, which is poised to close long-standing knowledge gaps on early stages of myeloma development, is envisioned for 2033. The primary outcome measure is time to progression (TTP) from MGUS/SMM to frank myeloma. The principal goal of the study is the definition of the clinical, (epi) genetic, genomic and/or immune environmental parameters that predict progression to overt cancer. PROMISE is co–led by Drs. Irene M. Ghobrial and Ivan M. Borrello from the Dana Farber Cancer Institute, Boston, Massachusetts and Johns Hopkins School of Medicine, Baltimore, Maryland, respectively. The study will not only address the high burden of myeloma in the African American population but will also catalyze fresh thinking about how to make myeloma a preventable disease.

## KEY POINTS AND FUTURE DIRECTIONS

GWAS has identified 24 common but low–impact myeloma risk loci (***Table 1***) that, taken together, explain approximately one eighth of the heritable myeloma risk in Caucasians. The risk of myeloma overlaps with that of MGUS and AL amyloidosis. WES analysis of MM / MGUS kindreds has additionally identified a handful of rare but high-impact myeloma risk loci (***Table 2***) that provide intriguing clues about myeloma etiology. The Chinese myeloma community is now challenged with complementing these results in Western populations with data on Han Chinese and the many smaller ethnic groups that live in the People´s Republic of China. A good starting point to that end may be the analysis of MM / MGUS kindreds in the PRC. A useful blueprint for the recruitment of kindreds for germline mutation studies on myeloma risk has been published just recently by an investigation team in Germany[51]. Equally important for progress is the continuation of the line investigation that led to the discovery of *NCOA1* as a myeloma susceptibility gene in Han Chinese[16]. The incidence of myeloma in the PRC is significantly lower than in Western countries, suggesting that major differences in GWAS-identifiable germline risk loci exist. Liu *et al*. recently reported an estimated 16,500 new myelomas in China in 2016[52], which translates to an age-standardized incidence rate of ~1 per 100,000 people. However, this number should be taken with a grain of salt because the burden of MM in the PRC exhibits stark contrasts at the provincial level and additional research must be carried out before the incidence of myeloma in China can be fully evaluated.

Going forward, the international myeloma community in close partnership with its Chinese colleagues is tasked with validating myeloma risk loci at the functional level. This process has already started, using *ELL2*[53, 54], *CDCA7L*[36, 37] and *CCND1*[5] as study objects, but much more needs to be done to complete the picture. In parallel to gene-centric studies, genetic network analyses should be performed to integrate myeloma risk alleles in functional pathways. Themes along this line that have recently emerged include B cell and plasma cell development (TNFRSF13B, ATG5, ELL2, CBX7, KLF2, and HLA region), autophagy (WAC, ULK4, TOM1), telomere maintenance (POT1,

TERC) and cell cycle regulation and DNA replication (CDCA7L, CDKN2A, CCND1, RFWD3)[9]. Another area of future work on genetic myeloma risk concerns the flip side of susceptibility: genetic resistance. The first myeloma resistance gene, *LIG4* (rs1555902), has been recently identified[20] but many more remain to be discovered. Elucidation of myeloma resistance may inspire new approaches to myeloma prevention. A third research area that warrants more attention is gene-environment interaction, exemplified by the possible link of occupational exposure to cholinergic agents (pesticides) with myeloma incidence and myeloma risk[55, 56]. An earlier example is the association of genetic variations in the benzene metabolism with myeloma risk[57]. The biological effect of many susceptibility/resistance genes may depend, at least in part, on specific environmental or occupational exposures. An implicit promise of all these efforts is the discovery of novel molecular targets for myeloma treatment and prevention. New biomarkers for improved patient management in the clinic, including individualized myeloma treatment plans, may also be brought to light.

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