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Multiple myeloma gammopathies

Exome sequencing identifies germline variants in *DIS3* in familial multiple myeloma

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To the Editor:

Multiple myeloma (MM) is the third most common hematological malignancy, after Non-Hodgkin Lymphoma and Leukemia. MM is generally preceded by Monoclonal Gammopathy of Undetermined Significance (MGUS) [1], and epidemiological studies have identified older age, male gender, family history, and MGUS as risk factors for developing MM [2].

The somatic mutational landscape of sporadic MM has been increasingly investigated, aiming to identify recurrent

genetic events involved in myelomagenesis. Whole exome and whole genome sequencing studies have shown that MM is a genetically heterogeneous disease that evolves through accumulation of both clonal and subclonal driver mutations [3] and identified recurrently somatically mutated genes, including *KRAS*, *NRAS*, *FAM46C*, *TP53*, *DIS3*, *BRAF*, *TRAF3*, *CYLD*, *RBI* and *PRDMI* [3–5].

Despite the fact that family-based studies have provided data consistent with an inherited genetic susceptibility to MM compatible with Mendelian transmission [6], the molecular basis of inherited MM predisposition is only partly understood. Genome-Wide Association (GWAS) studies have identified and validated 23 loci significantly associated with an increased risk of developing MM that explain ~16% of heritability [7] and only a subset of familial cases are thought to have a polygenic background [8]. Recent studies have identified rare germline variants predisposing to MM in *KDM1A* [9], *ARID1A* and *USP45* [10], and the implementation of next-generation sequencing technology will allow the characterization of more such rare variants.

In this study, we sought to explore the involvement of rare germline genetic variants in susceptibility to MM.

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Within our discovery cohort of peripheral blood samples (see Supplementary Methods) from 66 individuals from 23 unrelated families analyzed by WES, *DIS3* (NM_014953) was the only gene in which putative loss-of-function variants were observed in at least two families. An additional cohort of 937 individuals (148 MM, 139 MGUS, 642 unaffected relatives and eight individuals with another hematological condition) from 154 unrelated families (including the individuals in the discovery cohort) were screened for germline variants in *DIS3* using targeted sequencing (Supplementary Table S1). In total, we detected *DIS3* germline putative loss-of-function variants in four unrelated families. The *DIS3* genotypes for the identified variants were concordant between WES and targeted sequencing (where available) and independently confirmed by Sanger sequencing on DNA extracted from uncultured whole blood. The variant allele frequencies (VAF) were close to 50%, as expected of a germline variant (Supplementary figure S1).

The *DIS3* gene, located in 13q22.1, encodes for the catalytic subunit of the human exosome complex, and is recurrently somatically mutated in MM patients [4, 5, 11, 12]. The somatic variants are predominantly missense variants localized in the RNB domain mainly abolishing the exoribonucleolytic activity [4, 13], and are often accompanied by LOH or biallelic inactivation due to 13q14 deletion, implying a tumor suppressor role for *DIS3* in MM [5, 12, 13].

The first *DIS3* variant, observed in 2 affected siblings (1 MGUS and 1 MM case) from family B (Fig. 1a), was located in the splice donor site of exon 13 (c.1755+1G>T; chr13: 73,345,041; GRCh37/hg19, rs769194741) (Supplementary Figure S1a). It is predicted to abolish the splice donor site and cause skipping of exon 13, introducing a premature termination codon (p.Arg557Argfs*3) and result in a truncated *DIS3* protein that lacks part of the exonucleolytic active RNB and S1 domains (Fig. 1b, c). The presence of this variant in two siblings, implying Mendelian segregation, is consistent with a germline, rather than somatic, origin. We investigated whether a *DIS3* transcript from the variant allele is generated but is subsequently eliminated by Nonsense Mediated Decay (NMD) by incubating Lymphoblastoid Cell Lines (LCLs) derived from the two c.1755+1G>T allele carriers with and without puromycin, which suppresses NMD. The mRNA transcript corresponding to the variant allele was clearly present in LCLs treated with puromycin in both carriers, whereas not detectable in untreated LCLs (Fig. 2a), consistent with the variant allele being transcribed but subsequently degraded via the NMD pathway. In line with this observation, analysis of *DIS3* mRNA expression by qRT-PCR showed an average 50% reduced expression in the c.1755+1G>T carriers (range 40.7–61.4%) as compared to non-carriers (Fig. 2b). A second splicing variant (c.1883+1G>C; chr13: 73,342,922; GRCh37/hg19) located in the

splice donor site of exon 14 within the RNB domain was identified in a MM case from family D (Fig. 1a, b, Supplementary figure S1c). However, the individual's mother (Q59), affected with amyloidosis, did not carry the variant, implying that MM in the allele carriers' maternal uncles is unlikely to be explained by this *DIS3* variant. Whether the mRNA transcript encoded by this germline variant undergoes NMD could not be explored due to lack of appropriate material (LCLs, RNA).

A third *DIS3* variant disrupting the wild-type termination codon (stop-loss) (c.2875T>C; p.*959Gln; chr13:73,333,935; GRCh37/hg19, rs141067458) (Fig. 1b, Supplementary Figure S1b) was identified in two unrelated families (A and C, Fig. 1a). This variant is expected to result in a putative read-through variant and a *DIS3* protein with an additional 13 amino acids in the C-terminus (p.*959Glnext*14). It was detected in 3 out of 4 affected siblings (2 MGUS (M63, O53) and 1 MM case (O29)), as well as 5 unaffected relatives (N14, N13, L41, M33 M50) from family A. The Mendelian segregation of this variant in this pedigree is also consistent with germline origin. An additional MM case from family C carried the variant, while we were unable to assess the other MM-afflicted family member (Fig. 1a). As expected of a stop-loss variant, NMD was not observed (data not shown), and gene expression analysis showed no effect on *DIS3* mRNA levels (Fig. 2b). However, western blot analysis demonstrated that *DIS3* protein levels were markedly lower (~50%) in the p.*959Glnext*14 carrier (O53, family A) compared to non-carriers (Fig. 2b, c).

Next, we sought to determine if rare, putative deleterious variants in *DIS3* were more frequent in an independent series of MM cases compared to unaffected individuals. We performed mutation burden tests between 781 MM cases and 3534 controls from the MMRF CoMMpass Study with WES data available. After testing for systemic bias in this dataset (see Supplementary Methods, Supplementary Figure S2), we undertook a burden test for association between functional *DIS3* variants and MM. *DIS3* putative functional variants (truncating and likely deleterious missense variants, see Supplementary Methods) were more frequent among MM patients (30/781) than controls (72/3534) (OR = 1.92 95% CI:1.25–2.96, $p = 0.001$). Although the p.*959Glnext*14 stop-loss variant was recurrently found in 10/781 MM cases and 15/3534 controls (OR = 3.07 95%CI:1.38 to 6.87, $p = 0.0007$), it did not entirely explain the excess of *DIS3* variants among cases as there is evidence for association with other putative functional variants (Supplementary Figure S3a). We additionally genotyped the p.*959Glnext*14 stop-loss variant in an independent series of sporadic MM cases and controls from the IMMEnSE Consortium. While this variant was very rare in this series (8/3020 MM cases relative to 3/1786 controls), there was a consistent but non-significant association between this variant and MM (OR = 3.15 95% CI: 0.74–13.43 $p = 0.122$).

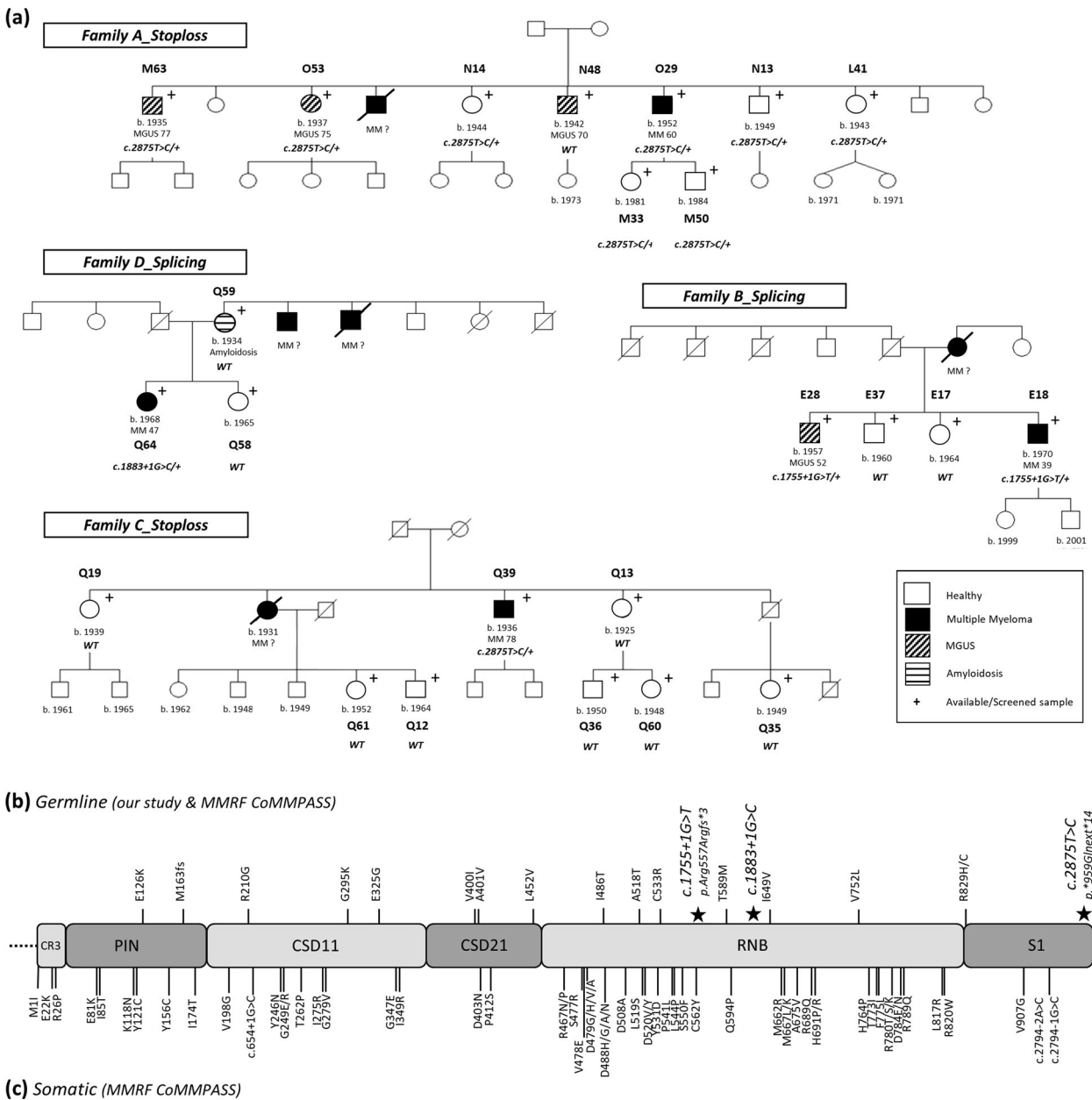


Fig. 1 *DIS3* variants in MM cases. **a** Pedigrees from families carrying a germline *DIS3* variant. Available samples for screening are marked with a “+” symbol. Families A and C carry the p.*959Glnext*14 (*c.2875T>C*) stop-loss variant. Family B carries the *c.1755+1G>T* splicing variant and family D carries the *c.1883+1G>C* splicing variant. The genotype of all screened individuals is shown on each pedigree. WT: wild type. **b, c** Schematic representation of identified germline and somatic variants in the distinct *DIS3* protein domains. **b** Germline variants were identified through WES and targeted

resequencing in families with reoccurrence of MM/MGUS as well as in a collection of sporadic MM cases (MMRF CoMMpass Study). The *DIS3* variants discussed in the present study are depicted with a star on the upper part of the figure. **c** Somatic *DIS3* variants were identified in sporadic MM cases from the MMRF CoMMpass Study. We observe that in contrast to the clustering of somatic *DIS3* missense variants in the RNB and PIN domains, germline variants are scattered throughout the gene and consist of splicing, stop-loss and missense variants

To explore the functional consequence of germline *DIS3* variants, we compared MM tumor transcriptomes from patients harboring germline ($n = 21$) and somatic ($n = 96$) *DIS3* putative functional variants to non-carriers ($n = 655$). Differential expression analyses showed an enrichment of pathways associated with global ncRNA processing and translational termination in germline *DIS3* carriers including

ncRNA processing, ncRNA metabolic process, translational termination, and RNA metabolism. Among somatic *DIS3* carriers, significantly enriched pathways include interferon alpha/beta signalling, mRNA splicing, mRNA processing and transcription (Supplementary Figure S3b, Supplementary tables S3 and S4a–d). These findings are consistent with the proposed *DIS3* role in regulating mRNA processing [14] and

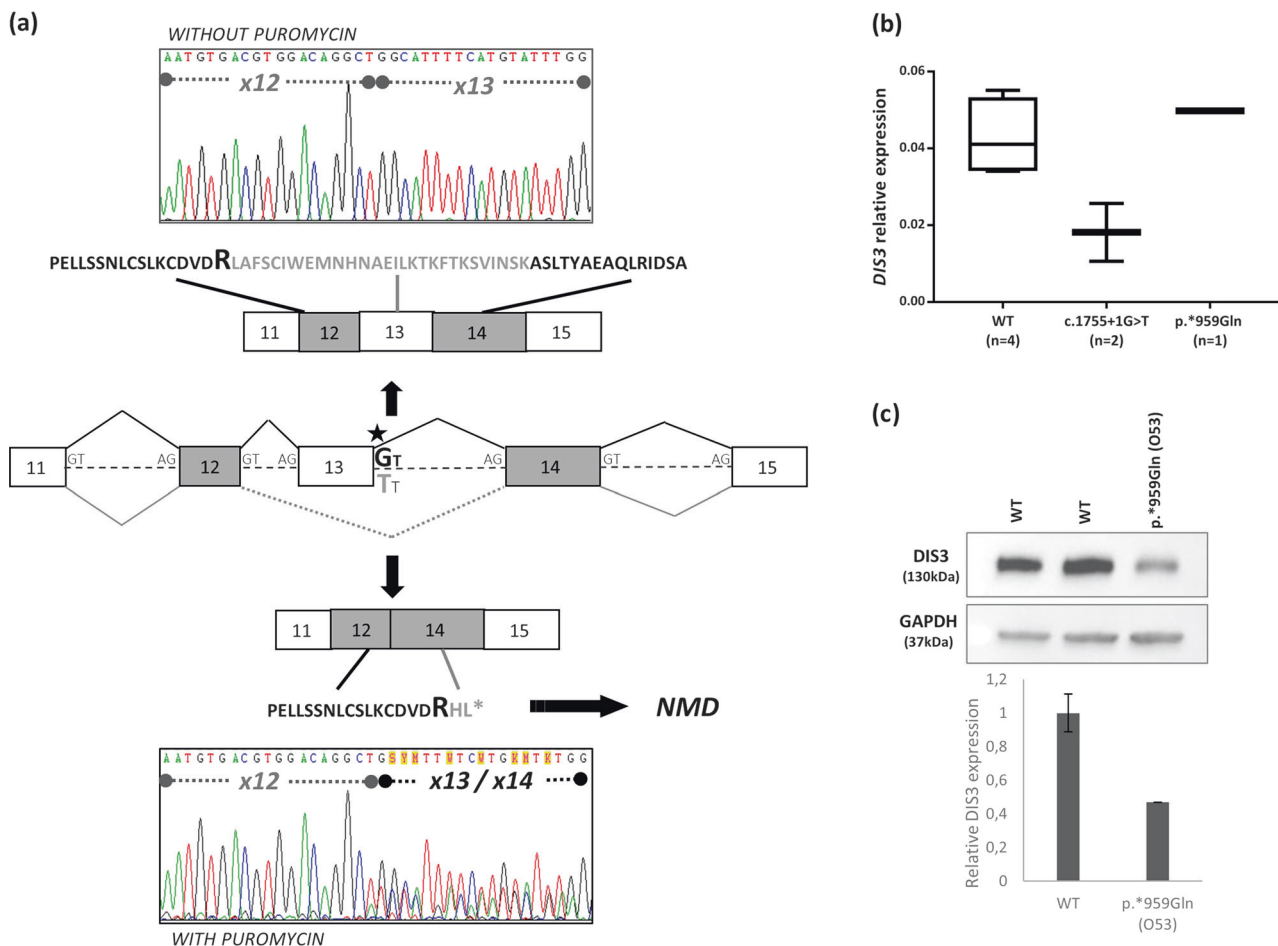


Fig. 2 *DIS3* c.1755+1G>T splicing variant results in nonsense-mediated mRNA decay (NMD) and affects mRNA expression, while the c.2875C>T (p.*959Gln_{next}*14) stop-loss variant affects protein levels. **a** LCLs from patients E18 and E28 (not shown) carrying the c.1755+1G>T splicing variant were cultured with and without puromycin. The chromatogram from treated cells (with puromycin) showed a mixture of the wild-type and mutant transcript lacking exon 13, which was not detected in the non-treated cells (without puromycin). Thus, the mutant transcript is degraded by NMD. **b** Box plot

more specifically mRNA decay, gene expression and small RNA processing [15]. We also observed that, several long-intergenic non-protein coding RNAs, non-coding and anti-sense RNAs were significantly enriched among *DIS3* carriers (Supplementary table S5a, b) supporting previous studies that demonstrate an accumulation of transcripts from non-protein coding regions, snoRNA precursors and certain lncRNAs in *DIS3* mutant cells, along a general deregulation of mRNA levels probably due to the sequestration of transcriptional factors from the accumulated nuclear RNAs [16].

To our knowledge, this is the first observation of germline *DIS3* likely deleterious variants in familial MM and our results suggest that the involvement of *DIS3* in MM etiology may extend beyond somatic alterations to germline susceptibility. We reported rare germline *DIS3* variants in ~2.6% of our cohort of families with multiple cases of MM and MGUS

representing the relative *DIS3* mRNA expression in c.1775+1G>A (n=2) and p.*959Gln_{next}*14 (n=1) carriers compared to non-carriers (n=4). All reactions were performed in triplicates. **c** Western blot with an anti-*DIS3* antibody was performed in LCLs from one p.*959Gln_{next}*14 carrier and two wild-type individuals (anti-GAPDH antibody as internal control). The relative *DIS3* expression in the p.*959Gln_{next}*14 carrier was reduced by 50% compared to non-carriers, suggesting that the mutant allele is translated but degraded shortly after

(4/154). The germline variants described here are predicted to have loss-of-function impact on *DIS3*. Consistent with this, the 1755+1G>T (rs769194741) splicing variant induces NMD and results in reduced *DIS3* mRNA expression, supporting the proposal that *DIS3* is acting as a tumor suppressor gene in MM [13]. Moreover, the c.2875T>C (rs141067458) stop-loss variant (p.*959Gln_{next}*14) results in reduced *DIS3* protein expression suggesting that the mutant allele is translated but degraded shortly after. Notably, in contrast to the clustering of somatic *DIS3* mutations in the PIN and RNB domains, germline variants identified both in familial and sporadic MM cases are scattered throughout the gene (Fig. 1b, c). Despite the fact that these variants do not segregate perfectly with MM in the identified families and the rarity of *DIS3* germline likely deleterious variants limits our statistical power, the subsequent mutation burden and transcriptome

analyses provided supportive data towards *DIS3* acting as an “intermediate-risk” MM susceptibility gene.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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