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RESEARCH

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FAM72D in plasma cell myeloma: a friend or enemy

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Abstract

Background Plasma cell neoplasm is characterized by complex genetic and prognostic heterogeneity. FAM72D, a gene located on chromosome 1, and the association between its expression and tumor progression and prognosis remain elusive.

Methods The present study aims to assess FAM72D mRNA expression in 60 PCM patients and correlate its expression level with clinical and laboratory markers involved in diagnosing and prognosis of PCM using real-time PCR.

Results Unpaired t-test revealed a significantly higher FAM72D expression level in the patients than in the control group with a median of 0.890 vs. /0.030, respectively, and *p* value = 0.000. The highest median level was denoted in newly diagnosed or relapsed patients (1.905, *p* value = 0.000). A significant positive correlation was found between FAM72D expression level and each of BMPCs count, M band, and β2 microglobulin ($p = 0.000$, $p = 0.002$, $p = 0.024$, respectively), and negative correlations with both serum albumin and hemoglobin level ($p = 0.000$, $p = 0.035$, respectively). The risk of relapse was 18.3-fold when the FAM72D level was greater than 1.547.

Conclusion The higher FAM72D expression level in newly diagnosed and relapsed myeloma patients and its positive correlation with BMPCs confirm the stimulating effect of FAM72D on myeloma cell proliferation and its poor prognosis.

Keywords Plasma cell, Myeloma, FAM72, 1q21

Introduction

Plasma cell myeloma (PCM) is characterized by clonal proliferation of monoclonal immunoglobulin-producing plasma cells with multifocal propagation of those neoplastic cells in the bone marrow. It usually originates from a preceding asymptomatic stage known as monoclonal gammopathy of undetermined significance (MGUS) [1]. It accounts for about 2% of all cancers with a worldwide incidence of about 160,000 cases and a global mortality of about 106,000 patients for the year 2018, according to the International Agency for Research on Cancer (IARC) [2, 3].

A complex array of genetic and epigenetic changes leads to the neoplastic transformation of plasma cells, resulting in their uncontrolled growth within the bone marrow (BM) and secretion of large amounts of non-functional monoclonal antibody (known as paraprotein or M protein) into the circulation [4]. Identification of these changes at diagnosis may be pivotal for better risk stratification of PCM patients.

Genetic aberrations include translocations mainly of the immunoglobulin heavy chain (IGH) locus on chromosome 14q32, methylation modifications, gene dysregulation, and copy number abnormalities [5]. Gain and amplifications of the long arm of chromosome 1 (+1q)

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are very common in newly diagnosed multiple myeloma patients (NDMM) and, recently, were proven to have an independent poor prognostic value in NDMM [6].

Family with sequence similarity 72 (FAM72) is a gene located on chromosome 1 with four paralogs (A-D) in humans [7]. In physiological states, FAM72 is expressed in the neural stem cells of the brain hippocampus. It is overexpressed in different cancers such as prostate cancer (FAM72B), and B cell lymphoma where FAM72B, C, and D were up regulated. Recently, FAM72D expression was implicated in the prognosis of PCM [8].

Our study aimed to assess FAM72D messenger ribonucleic acid (mRNA) expression in PCM patients and correlate its expression level with clinical and laboratory markers used in diagnosing and prognosis of PCM.

Subjects and methods

Subjects

This prospective randomized study was conducted on 60 PCM patients, attending the Haematology/Oncology unit of Ain Shams University Hospitals, during the period from January 2021 to December 2021. The selected patients were diagnosed according to the International Myeloma Working Group (IMWG) updated criteria for the diagnosis of multiple myeloma [9]. The patients were divided into two groups: Group I included thirty newly diagnosed or relapsed plasma cell myeloma patients and thirty follow-up cases of plasma cell myeloma in remission represented Group II.

In order to get a relative quantification of FAM72D mRNA expression, 20 age and sex-matched healthy subjects with no history of any cancers were further included as a control group.

Informed consents were obtained from all enrolled subjects. The study was approved by the Scientific and Ethical Committee, Ain-Shams University (FMASU MD 252/ 2020) and was in accordance with the Declaration of Helsinki.

Initial assessment

All the included subjects were subjected to comprehensive history taking and thorough clinical examination, laying stress on the presence of anemic symptoms, bone aches, and renal impairment.

Two milliliters of EDTA (ethylene diamine tetra acetic acid) anticoagulated venous blood were collected from each patient to perform a complete blood count (CBC) using LH 750 cell counter (Coulter Electronics, Hialeah, FL, USA), with a morphologic examination of Leishman-stained smears. Serum albumin, serum creatinine, serum protein electrophoresis, and ß2 microglobulin were analyzed using 3–4 ml of clotted venous blood.

Four-to-five milliliters of bone marrow aspirate were obtained, where the first 0.5 to 1 ml was used to prepare Leishman-stained smears. One ml was collected on lithium heparin for cytogenetic analysis. The rest were divided into 2 K2-EDTA tubes in order to perform immunophenotyping (IPT) and PCR. All tests were performed on the same day of collection except PCR samples were frozen at −80 °C till use.

IPT was performed on the Coulter Navios flow cytometer (Coulter Electronics, Hialeah, FL, USA), using the standard panel for multiple myeloma.

Further assessment

Bone marrow samples were analyzed for the detection of FAM72D mRNA expression levels by real-time PCR (RT-q PCR) following TaqMan® Gene Expression Assays User Guide—single-tube assays (Publication Number 4401212 & 4333458).

Total RNA was extracted from whole blood using GeneJET™ RNA Purification Kit supplied by ThermoFisher Scientific, USA. The samples were processed according to ThermoFisher Scientific reagents' manual steps. Then reverse transcription of FAM72D mRNA into complementary DNA (cDNA) was done using the Thermo Scientific™ RevertAid™ First Strand cDNA Synthesis Kit. The target cDNA was amplified using TaqManR Genotyping master mix and ready-made TaqMan™ SNP genotyping assay supplied by Applied Biosystems, ThermoFisher Scientific, USA.

Relative quantification of the results was done (target gene versus control gene) after determining the cycle threshold (CT) for each sample. The ΔCT value for each sample was calculated (ΔC_t = Ct target gene−Ct of housekeeping or control gene). The average (mean) ΔC_t was calculated for samples of the control group, and next, the ΔΔCT value for each sample was calculated by subtracting the average ΔCT value of the calibrator from the ΔCT value of the experimental sample: ΔΔCT = ΔCT (sample)−average ΔCT (calibrator). Finally, the normalized level of target gene expression was calculated using the following formula ($2^{-(\Delta\Delta CT)}$).

Statistical analysis

The sample size was calculated using STATA® version 11 programs, setting alpha error at 5% and power at 80%.

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23.

The quantitative data with parametric distribution were presented as mean, standard deviations, and ranges while skewed data were presented as median with inter-quartile range (IQR). Qualitative variables were presented as numbers and percentages. The chi-square test was used

to compare groups with qualitative data. The comparison between two groups with quantitative data and parametric distribution was done by using an independent t-test while the comparison between two groups with quantitative data and non-parametric distribution was done by using the Mann–Whitney test. The comparison between more than two groups with quantitative data and non-parametric distribution was done by using the Kruskal-Wallis test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group.

The receiver operating characteristic curve (ROC) was used in the quantitative form to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve (AUC), and best cutoff point for FAM72 to predict relapse of the studied patients. The probability level (p-value) was considered non-significant (NS) if the p-value was ≥ 0.05, significant (S) if the p-value was < 0.05, and highly significant (HS) if the p-value was < 0.01.

Results

Sixty PCM patients (30 newly diagnosed or relapsed represented group I and 30 in remission for group II) were enrolled in the study. Their age ranged from 33 to 70 years with a mean of 54.9 years and a male/female ratio of 1.5:1.

Demographic, clinical, and laboratory characteristics of the studied patients are illustrated in Table 1.

The comparison between group I and group II demonstrated a highly significant statistical difference as regards the anemic symptoms, bony aches, and international staging system (p value = 0.000). Moreover, a significant statistical difference was revealed upon comparing the two groups as regards all laboratory data except platelet count. Total leucocytic count (TLC), serum creatinine, β2 microglobulin, and bone marrow plasma cell counts (BMPCs) were higher in group I (p value = 0.043, 0.011, 0.000, and 0.000, respectively). On the other hand, both hemoglobin and serum albumin were lower in group I (p value = 0.000 for both) (Table 2).

Table 1 Descriptive demographic, clinical, and laboratory data of the studied patients

Parameter		All patients $n = 60$	Group I $n = 30$	Group II $n = 30$
Age (years)	Mean ± SD	54.93 ± 9.48	56.43 ± 8.60	53.43 ± 10.22
Gender n (%)	Male	36 (60.0)	15 (50)	21 (70)
	Female	24 (40.0)	15 (50)	9 (30)
Bone aches n (%)	Yes	38 (63.3)	28 (93.3)	10 (33.3)
	No	22 (36.7)	2 (6.7)	20 (66.7)
Anemic symptoms n (%)	Yes	39 (65)	28 (93.3)	11 (36.7)
	No	21(35.0)	2 (6.7)	19 (63.3)
Renal impairment n (%)	Yes	14 (23.3)	10 (33.3)	4 (13.3)
	No	46 (76.7)	20 (66.7)	26 (86.7)
International staging system n (%)	I	31 (51.7)	5 (16.7)	26 (86.7)
	II	12 (20.0)	8 (26.6)	4 (13.3)
	III	17 (28.3)	17 (56.7)	0
TLC ($X10^3/\mu l$)	Mean ± SD	6.31 ± 2.57	6.97 ± 3.03	5.64 ± 1.82
Hb (g/dl)	Mean ± SD	10.82 ± 2.12	9.47 ± 1.63	12.16 ± 1.67
PLT ($X10^3/\mu l$)	Mean ± SD	244.97 ± 108.16	228.03 ± 109.70	261.90 ± 105.71
Serum albumin (g/dl)	Mean ± SD	3.35 ± 0.59	2.91 ± 0.40	3.79 ± 0.39
M band (g/dl) n (%)	Absent	12 (20)	0 (0)	12 (40)
	Present	48 (80.0)	30 (100)	18 (60)
S.creatinine (mg/dl)	Median (IQR)	1 (0.8–1.5)	2.95 (0.95–6.3)	0.9 (0.8–1.1)
β2 microglobulin (mg/L)	Median (IQR)	3.2 (2.5–5.7)	5.7 (3.9–10.5)	2.5 (2.1–2.9)
BMPCs (%)	Median (IQR)	7.5 (3–55)	55 (30–80)	3 (1.5–4)
FAM72D	Median (IQR)	0.89 (0.43–2.014)	1.905 (0.671–4.563)	0.747 (0.260–1.101)

TLC, total leucocyte count; SD, Standard deviation; *n*, number; Hb, hemoglobin; PLT, platelet; M band, monoclonal band; IQR, Interquartile range; BMPCs, bone marrow plasma cells

Table 2 Comparison between group I (Newly diagnosed/Relapsed) and group II (In remission)

Parameter		Group I *n* = 30	Group II *n* = 30	*p*-value	Significance
Age (years)	Mean ± SD	56.43 ± 8.60	53.43 ± 10.22	0.224	NS#
Gender n (%)	Male	15 (50)	21 (70)	0.114	NS*
	Female	15 (50)	9 (30)		
Bone aches n (%)	Yes	28 (93.3)	10 (33.3)	**0.000**	**HS***
	No	2 (6.7)	20 (66.7)		
Anemic symptoms n (%)	Yes	28 (93.3)	11 (36.7)	**0.000**	**HS***
	No	2 (6.7)	19 (63.3)		
Renal impairment n (%)	Yes	10 (33.3)	4 (13.3)	0.067	NS*
	No	20 (66.7)	26 (86.7)		
International staging system n (%)	I	5 (16.7)	26 (86.7)	**0.000**	**HS***
	II	8 (26.6)	4 (13.3)		
	III	17 (56.7)	0		
TLC ($X10^3$/μl)	Mean ± SD	6.97 ± 3.03	5.64 ± 1.82	**0.043**	**S#**
Hb (g/dl)	Mean ± SD	9.47 ± 1.63	12.16 ± 1.67	**0.000**	**HS#**
PLT ($X10^3$/μl)	Mean ± SD	228.03 ± 109.70	261.90 ± 105.71	0.228	NS#
Serum albumin (g/dl)	Mean ± SD	2.91 ± 0.40	3.79 ± 0.39	**0.000**	**HS#**
M band (g/dl) n (%)	Absent	0 (0)	12 (40)	**0.000**	**HS***
	Present	30 (100)	18 (60)		
S.creatinine (mg/dl)	Median (IQR)	2.95 (0.95–6.3)	0.9 (0.8–1.1)	**0.011**	**S****
β2 microglobulin (mg/L)	Median (IQR)	5.7 (3.9–10.5)	2.5 (2.1–2.9)	**0.000**	**HS****
BMPCs (%)	Median (IQR)	55 (30–80)	3 (1.5–4)	**0.000**	**HS****

TLC, total leucocyte count; SD, Standard deviation, *n*, number, Hb, hemoglobin, PLT, platelet; M band, monoclonal band; IQR, Interquartile range; BMPCs, bone marrow plasma cells

* Chi-square test

Independent t-test

**Mann–Whitney test

FAM72D mRNA median expression level was 0.89 ranging from 0.43 to 2.014 with the highest median level in group I (1.905 and ranging from 0.671 to 4.563) with subsequent highly significant statistical differences between both groups (p value = 0.000) (Table 3). Furthermore, an unpaired t-test revealed a significantly higher FAM72D expression level in the patients than in the control group with a median of 0.890 vs 0.030, respectively, and p value = 0.000 (Fig. 1).

For further assessment of the role of FAM72D in PCM, patients were subdivided into FAM72D with a high expression level group (≥ 1) and FAM72D with a low expression level group (< 1) (46.7% & 53.3%). The study revealed that 78.6% of patients represented with bone aches and anemic symptoms had higher levels of FAM72D expression (p value = 0.022, p value = 0.039, respectively). Moreover, patients with elevated FAM72D expression levels had higher BMPCs (median = 57.5% vs/3%, respectively, with p value = 0.000), and both serum albumin and hemoglobin levels were lower (p = 0.002 and 0.047, respectively) (Table 4).

Table 3 Comparison of FAM72D expression level between group I (Newly diagnosed and relapsed) and group II (In remission)

Parameter	Group I *n* = 30	Group II *n* = 30	P value	Significance
FAM72D Median (IQR)	1.905 (0.671–4.563)	0.747 (0.260–1.101)	**0.000**	**HS**

Bold value indicates statistically significant

IQR = interquartile range, HS = highly significant (p < 0.01)

Mann–Whitney test

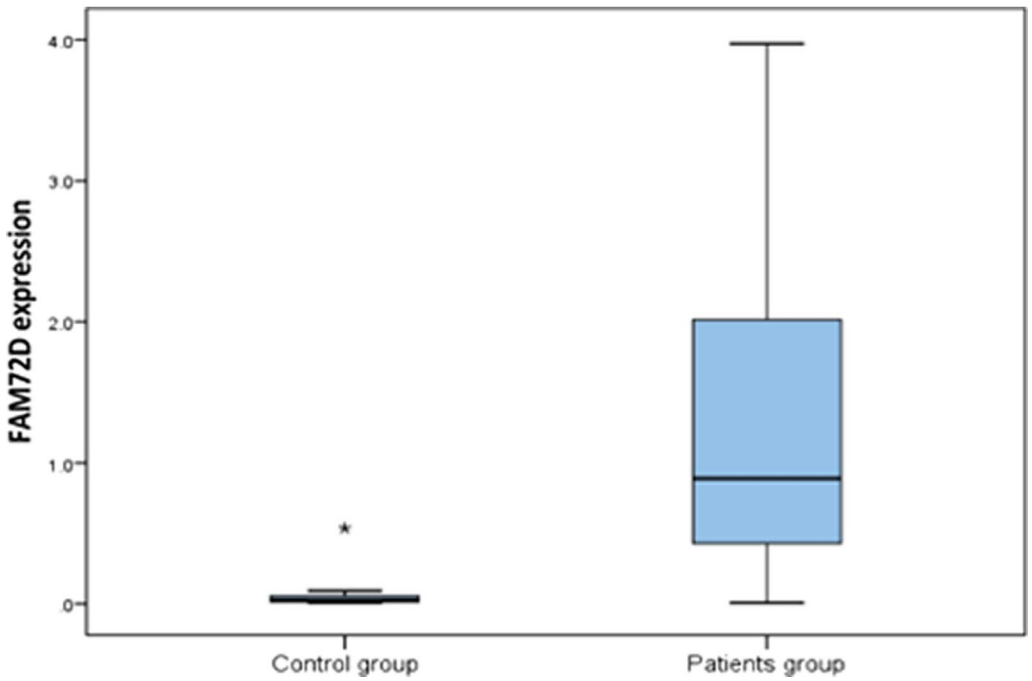

Fig. 1 Comparison of FAM72D expression level between the patients and control group

A significant positive correlation was found between FAM72D expression level and each of BMPCs count, M band, and β2 microglobulin ($p = 0.000$, $p = 0.002$, $p = 0.024$, respectively). In contrast, significant negative correlations were present between FAM72D expression level and both serum albumin and hemoglobin levels ($p = 0.000$, $p = 0.035$, respectively).

To determine the performance of FAM72D expression level in discriminating between remitted and relapsed patients, a cut-off value was established according to the ROC curve. A cut-off value of > 1.547 was found to have a sensitivity of 56.67% and a specificity of 93.33% (Fig. 2).

Finally, univariate logistic regression analysis showed that the risk of relapse is 18.3 folds when the FAM72D level is greater than 1.547.

Discussion

Despite the relative uniformity of its dominant plasma cells which represent the terminal stage of normal B-cell differentiation, plasma cell myeloma is considered a complex neoplasm. Trisomies of odd-numbered chromosomes, occurring at the early premalignant stages, are considered primary cytogenetic abnormalities and are potentially involved in disease pathogenesis [10]. Moreover, t(4;14), t(14;16) and del (17p) have been incorporated in the revised international staging system (RISS) as high-risk factors which strengthen the importance of cytogenetic abnormalities as prognostic factors in newly diagnosed myeloma patients [11]. Furthermore, the gain or amplification of chromosome arm 1q21 (1q21+) occurs in 40% of patients at diagnosis and is considered a secondary genomic event with more amplification as the tumor progresses denoting that it is one of the most frequent adverse chromosomal aberrations in PCM [12].

FAM72 is a gene located on chromosome 1 with four paralogues (A-D) in humans [7]. It may promote the occurrence and development of cancers in tissues and is involved in cancer cell division, proliferation, and differentiation. Additionally, high levels of FAM72 are associated with hypomethylation and affect the prognosis of various cancers [13]. This is consistent with Feng et al., study data that showed that the FAM72 gene family precipitate cancer development and progression in both mice and humans, and its expression correlates with a higher mutation load in many tumor types as well as poorer survival [14].

To our knowledge, only one research studied the role of FAM72D in PCM [15]**.** So, we performed this study to highlight the role of FAM72D in PCM patients and correlate its expression level with clinical and laboratory markers used in the diagnosis and prognosis of PCM.

The significantly higher FAM72D expression level in the patients than in the control group demonstrated in our study was in accordance with Qu and his colleagues who suggested that there may be an association between FAM72D and tumorigenesis, playing a crucial role in this

Table 4 Comparison between different patients as regards the levels of FAM72D expression

Parameter		FAM72D ≥ 1 *n* = 28	FAM72D < 1 *n* = 32	p-value	Significance
Age (years)	Mean ± SD	54.11 ± 9.45	55.66 ± 9.61	0.533	NS#
Gender n (%)	Male	16 (57.1)	20 (62.5)	0.673	NS*
	Female	12 (42.9)	12 (37.5)		
Bone aches n (%)	Yes	22 (78.6)	16 (50.0)	**0.022**	**S***
	No	6 (21.4)	16 (50.0)		
Anemic symptoms n (%)	Yes	22 (78.6)	17 (53.1)	**0.039**	**S***
	No	6 (21.4)	15 (46.9)		
Renal impairment n (%)	Yes	8 (28.6)	6 (18.8)	0.370	NS*
	No	20 (71.4)	26 (81.3)		
International staging system n (%)	I	12 (42.9)	19 (59.4)	0.209	NS*
	II	5 (17.9)	7 (21.9)		
	III	11 (39.3)	6 (18.8)		
TLC ($X10^3$/μl)	Mean ± SD	6.16 ± 3.14	6.43 ± 1.97	0.695	NS#
Hb (g/dl)	Mean ± SD	10.24 ± 2.09	11.32 ± 2.05	**0.047**	**S#**
PLT ($X10^3$/μl)	Mean ± SD	242.04 ± 112.53	247.53 ± 105.94	0.846	NS#
Serum albumin (g/dl)	Mean ± SD	3.11 ± 0.53	3.56 ± 0.57	**0.002**	**HS#**
M band (g/dl) n (%)	Absent	25 (89.3)	23 (71.9)	0.093	NS*
	Present	3 (10.7)	9 (28.1)		
S.creatinine (mg/dl)	Median (IQR)	1.05 (0.8–5)	0.9 (0.8–1.2)	0.340	NS**
β2 microglobulin (mg/L)	Median (IQR)	4 (2.7–8.25)	2.9 (2.3–4.55)	0.076	NS**
BMPCs (%)	Median (IQR)	57.5 (4.75–82.5)	3 (1.75–21)	**0.000**	**HS****

Bold values indicate statistically significant

TLC = total leucocyte count, SD = Standard deviation, *n* = number, Hb = hemoglobin, PLT = platelet, M band = monoclonal band, IQR = Interquartile range, BMPCs = bone marrow plasma cells

HS = highly significant (*p* value < 0.01), S = significant (*p* value < 0.05), NS = non- significant (*p*-value > 0.05)

* Chi-square test

Independent t-test **Mann–Whitney test

process. Also, FAM72D upregulation in nearly all tumor tissues compared to normal tissues highlights its significance in cancer development [16].

Our study revealed that the highest level of FAM72D mRNA median expression was in the newly diagnosed/relapsed group of patients. This finding was in agreement with Chatonnet et al., (2020) who observed that the FAM72D, located in the 1q21 region amplified in high-risk myeloma patients, was associated with poor prognosis [15].

Moreover, we found a positive correlation between FAM72D expression and BMPC count, M band, and β2 microglobulin, denoting that FAM72D may be a proliferation marker for myeloma. This finding goes with the results of Chatonnet et al. [15], who found a significant correlation between FAM72 expression and plasma cell labeling index. Also, Hanamura et al. [17] found that amplification of 1q21 and possibly overexpression of its genes occurs in parallel with disease progression from MGUS to relapsed PCM. Finally, FAM72D expression was associated with proliferation in hepatocellular carcinoma [18]. This proliferation effect of FAM72 could be due to that FAM72D coexpressed genes were significantly associated with the M phase of the cell cycle

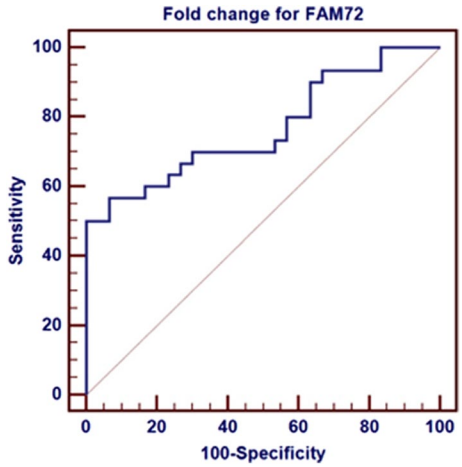

Fig. 2 ROC curve of FAM72D expression level as a predictor of relapse

which regulation comes from the interaction between FOXM1 and FAM72A to D. Loss of function of FOXM1 or FAM72 leads to significant mitotic abnormalities. In addition, overexpression of FAM72 resulted in enhanced growth and response to IL6 which is a main PCM growth factor [15].

All these facts go with the poor prognostic effect of FAM72D which was further demonstrated by univariate logistic regression analysis which showed that the risk of relapse is 18.3 folds when the FAM72D level is greater than 1.547. Moreover, high expression levels of FAM72D were associated with resistance to bortezomib [15].

Conclusion

Our study is considered one of the rarest studies that tried to clarify the role of FAM72D in PCM development and proliferation. Their routine inclusion in the genetic work-up of patients with PCM may be beneficial for better characterization and subclassification of this disease category and for selecting patients who are expected to benefit the most from new treatment strategies.

Abbreviations

+1q	Gain or amplifications of the long arm of chromosome 1
AUC	Area under curve
BMPCs	Bone marrow plasma cell
CBC	Complete blood count
cDNA	Complementary DNA
CT	Cycle threshold
HS	Highly significant
FAM72	Family with sequence similarity 72
IGH	Immunoglobulin heavy chain
IPT	Immunophenotyping
IMWG	International myeloma working group
IQR	Inter-quartile range
MGUS	Monoclonal gammopathy of undetermined significance
mRNA	Messenger ribonucleic acid
NDMM	Newly diagnosed multiple myeloma
NPV	Negative predictive value
NS	Non-significant
PCM	Plasma cell myeloma
PPV	Positive predictive value
ROC	Receiver operating characteristic curve
S	Significant
TLC	Total leucocytic count

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Author contributions

All authors have read and approved the final manuscript submission. MF and DE conceptualized and designed the study. DS contributed to data interpretation and manuscript writing. RA performed the technical work. MM and NH select cases and collect clinical data.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Informed written consent was obtained from all enrolled subjects. The study was approved by the Scientific and Ethical Committee, Ain-Shams University (FMASU MD 252/ 2020) and was in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Mikhael J, Bhutani M, Cole C (2023) Multiple myeloma for the primary care provider: a practical review to promote earlier diagnosis among diverse populations. Am J Med 136:33–41
2. Wilson L, Rennoldson M (2020) Are pain and fatigue in multiple myeloma related to psychosocial factors? A Syst Rev Cancer Nurs 43(3):E121–E131
3. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin D, Pineros M et al (2019) Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 144(8):1941–1953
4. Morgan G, Walker B, Davies F (2012) The genetic architecture of multiple myeloma. Nat Rev Cancer 12(5):335–348
5. Barwick B, Gupta V, Vertino P, Boise L (2019) Cell of origin and genetic alterations in the pathogenesis of multiple myeloma. Front Immunol 10:1121
6. D'Agostino M, Cairns D, Lahuerta J, Wester R, Bertsch U, Waage A et al (2022) Second revision of the international staging system (R2-ISS) for overall survival in multiple myeloma: a European myeloma network (EMN) report within the HARMONY project. J Clin Oncol 40(29):3406–3418
7. Ho N, Kim P, Kutzner A, Heese K (2017) Cognitive functions: human versus animal—4:1 advantage |-FAM72-SRGAP2-|. J Mol Neurosci 61:603–606
8. Ho N, Rahane C, Pramanik S, Kim P, Kutzner A, Heese K (2021) FAM72, glioblastoma multiforme (GBM) and beyond. Cancers 13(5):1025

9. Rajkumar S, Dimopoulos M, Palumbo A, Blade J, Merlini G, Mateos M et al (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15:e538–e548
10. Rajan A, Rajkumar S (2015) Interpretation of cytogenetic results in multiple myeloma for clinical practice. Blood Cancer J 5(10):e365
11. D'Agostino M, Cairns DA, Lahuerta JJ, Wester R, Bertsch U, Waage A et al (2022) Second revision of the international staging system (R2-ISS) for overall survival in multiple myeloma: a european myeloma network (EMN) report within the HARMONY project. J Clin Oncol 40(29):3406–3418
12. Hanamura I (2021) Gain/amplification of chromosome Arm 1q21 in multiple myeloma. Cancers (Basel) 13(2):256
13. Rahane C, Kutzner A, Heese K (2019) cancer tissue-specific FAM72 expression profile defines a novel glioblastoma multiform (GBM) gene-mutation signature. J Neurooncol 141(1):57–70
14. Feng Y, Thakur B, Bruce J, Mamand S, Shirdarreh M, Wong M et al (2023) The FAM72 gene family promotes cancer development by disabling the base excision repair system [abstract]. In: Proceedings of the American association for cancer research annual meeting 2023; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2023; 83(7_Suppl): Abstract nr 1217
15. Chatonnet F, Pignarre A, Sérandour A, Caron G, Avner S, Robert N et al (2020) The hydroxymethylome of multiple myeloma identifies FAM72D as a 1q21 marker linked to proliferation. Haematologica 105(3):774–783
16. Qu G, Li D, Xue F, Zhu M, Guo W, Xu W (2022) The pan-cancer analysis reveals FAM72D as a potential therapeutic target and closely linked to immune infiltration and prognosis in hepatocellular carcinoma. https://doi.org/10.21203/rs.3.rs-2335487/v1
17. Hanamura I, Stewart J, Huang Y, Zhan F, Santra M, Sawyer J et al (2006) Frequent gain of chromosome 1q21 in plasma- cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. Blood 108(5):1724–1732
18. Yao Z, Jia C, Tai Y, Liang H, Zhong Z, Xiong Z et al (2020) Serum exosomal long noncoding RNAs lnc-FAM72D-3 and lnc EPC1-4 as diagnostic biomarkers for hepatocellular carcinoma. Aging 12(12):11843–11863

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