



# Article Identification and Expressional Analysis of Putative PRDI-BF1 and RIZ Homology Domain-Containing Transcription Factors in *Mulinia lateralis*

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**Simple Summary:** The formation of primordial germ cells (PGCs) is the basis of molluskan reproduction, but limited information is reported on this topic. PRDI-BF1 and RIZ homology domaincontaining proteins (PRDMs), especially PRDM1 (also known as BLIMP1) and PRDM14, have been reported to be essential for the formation of PGCs. In this study, we systematically characterized the putative PRDMs in a bivalve mollusk species, *Mulinia lateralis*, and analyzed their sequence structures, phylogenetic relationships, and expressional profiles. Furthermore, we analyzed the temporal–spatial expression patterns of *Ml-prdm1* and *Ml-prdm14* RNA in early embryos and larvae. Our study suggests that *Ml-prdm1* may function as an important regulator of PGC formation in *M. lateralis*.

Abstract: Mollusca represents one of the ancient bilaterian groups with high morphological diversity, while the formation mechanisms of the precursors of all germ cells, primordial germ cells (PGCs), have not yet been clarified in mollusks. PRDI-BF1 and RIZ homology domain-containing proteins (PRDMs) are a group of transcriptional repressors, and PRDM1 (also known as BLIMP1) and PRDM14 have been reported to be essential for the formation of PGCs. In the present study, we performed a genome-wide retrieval in Mulinia lateralis and identified 11 putative PRDMs, all of which possessed an N-terminal PR domain. Expressional profiles revealed that all these prdm genes showed specifically high expression levels in the given stages, implying that all PRDMs played important roles during early development stages. Specifically, Ml-prdm1 was highly expressed at the gastrula stage, the key period when PGCs arise, and was specifically localized in the cytoplasm of two or three cells of blastula, gastrula, or trochophore larvae, matching the typical characteristics of PGCs. These results suggested that *Ml-prdm1*-positive cells may be PGCs and that *Ml-prdm1* could be a candidate marker for tracing the formation of PGCs in *M. lateralis*. In addition, the expression profiles of *Ml-prdm14* hinted that it may not be associated with PGCs of *M. lateralis*. The present study provides insights into the evolution of the PRDM family in mollusks and offers a better understanding of the formation of PGCs in mollusks.

Keywords: Mulinia lateralis; PRDM gene family; PGCs; expression profiling

# 1. Introduction

Germline cells transmit genetic and epigenetic information across generations in all sexually reproducing animals to ensure the survival of the species [1,2]. Primordial germ



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**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). cells (PGCs) that separated from somatic cells during early embryogenesis are common precursors of both sperms and eggs [3,4], and the segregating of germ cells from somatic cells is the first diversification step in the evolution of metazoans [5]. Under the initial determination of germ cell fate, there are two generally accepted theories of PGC specification: preformation, in which the specification of PGCs is determined by maternally inherited determinants in early development, and epigenesis, in which PGCs arise by inductive signals in late development [3,6]. These two mechanisms are not mutually exclusive and are inevitably used simultaneously at a certain stage of germ cell development [6]. So far, the PGC specification modes are different among different species, and both theories are reported in mollusks [7–10].

PRDM proteins comprise an N-terminal PR (PRDI-BF1 and RIZ1 homology) domain derived from the SET (suppressor of variegation 3–9, enhancer of zeste, and trithorax) domain and a variable number of C-terminal Zn-finger repeats [11,12]. As important transcription factors, PRDMs modulate different cellular processes, including the regulation of germ cell development. For example, PRDM1 and PRDM14 are essential for PGC development in several species. Notably, PRDM1 is functionally conserved across vertebrates and invertebrates. In mice (Mus musculus), PRDM1 and PRDM14 have been identified as the key regulators of PGC specification. PRDM1 is a key transcriptional regulator and is primarily responsible for the repression of somatic genes in PGCs [13,14]. The deletion of *prdm1* led to the failure of normal proliferation and migration of mouse PGCs [13], and *prdm1* homozygous mutants lacked PGCs [15]. PRDM14 is critical for the reacquisition of potential pluripotency and successful epigenetic reprogramming during PGC specification [14,16]. Embryos with the complete deletion of *prdm14* generated impaired PGCs with reduced numbers and lower mobility [16]. In 11-week-old prdm14 mutant females and males, germ cells in the ovaries and testes were completely lacking [16]. The simultaneous overexpression of *prdm1*, *prdm14*, and *tfap2c* could rapidly and efficiently induce epiblastlike cells (EpiLCs) to enter a PGC state in vitro [17]. Notably, *prdm14* alone was sufficient to direct the PGC state in EpiLCs [17]. In humans (*Homo sapiens*), PRDM1 functions as a repressor of somatic genes, which might allow SOX17, the key regulator of PGC-like cells' (hPGCLCs) fate, to specify hPGCLCs [18]. The loss of *prdm14* significantly reduced the specification efficiency of hPGCLCs [19]. In chickens (Gallus gallus), both PRDM1 and PRDM14 play pivotal roles in the post-specification of PGC development and are involved in PGC self-renewal [20]. In crickets (*Gryllus bimaculatus*), prdm1 is required for PGC formation and/or maintenance [21]. PRDM2 plays a potential tumor suppressor role in the formation of testicular germ cell tumors (TGCTs), which derive from PGCs [22]. PRDM8 participates in the regulation of mouse testis development [23]. And PRDM9 is a key determinant of meiotic recombination hotspots in both humans and mice [24,25]. Moreover, PRDMs are also involved in the proliferation and differentiation of embryonic stem cells [26-29], hematopoietic stem cells [30-33], and neurons [34-39]. Systematic identifications, expressive analyses, and functional studies of the PRDM gene family have been well conducted in vertebrates, but little information is available on invertebrates, especially on mollusks. This lack of information has prevented the elucidation of the evolution and conservation of the PRDM family, as well as the PGC development mechanisms in mollusks.

Mollusks are one of the most diverse groups in the animal kingdom; most of them are aquaculture species with important economic value. As they are an ancestral bilaterian group, studies on PGC specification in mollusks can help to elucidate the evolution of metazoan germ cell specification. Furthermore, understanding the molecular mechanisms of germ cells will facilitate the development of propagation control techniques and promote the aquaculture industry [40–42]. However, studies on the origin and development of PGCs in mollusks are scarce, and currently only three genes, *vasa, nanos*, and *piwi*, are used in related studies [7–9,43,44].

In the present study, we systematically identified and characterized PRDMs in *M. lateralis*, a promising model organism for bivalve mollusks. We then conducted a functional domain prediction, and sequence, phylogenetic, and expression level analyses of PRDMs.

Moreover, we investigated the distribution of *Ml-prdm1* and *Ml-prdm14* transcripts in embryonic and larval stages. This study provided insights into the evolution of PRDMs and their potential involvement in PGC development in mollusks, laying a theoretical foundation for further functional investigations.

#### 2. Materials and Methods

# 2.1. Identification of M. lateralis PRDMs

To identify PRDM members (MI-PRDMs), we firstly searched the annotation files of the *M. lateralis* genome (unpublished data), and then combined the data with a proteinbased sequence alignment and a domain-based sequence analysis. For the sequence alignment, orthologous PRDM sequences of vertebrates and invertebrates downloaded from databases including NCBI (https://www.ncbi.nlm.nih.gov/, accessed on 20 October 2022) and Uniprot (https://www.uniprot.org/, accessed on 23 October 2022) (Table S1) were used as query sequences for blastp using BioEdit 7.0.9 software [45] with an E-value threshold of  $1 \times 10^{-5}$ . For the domain analysis, both hmmbuild and hmmsearch programs in HMMER v.3.0 [46] were used. Firstly, on the basis of sequence alignments with ClustalW (https://www.genome.jp/tools-bin/clustalw, accessed on 5 November 2022) among all MI-PRDMs identified by blastp, the hmmbuild was carried out to generate a hidden Markov model (HMM) profile. The hmmsearch program (E-value  $< 1 \times 10^{-5}$ ) was performed according to the HMM profiles for genome-wide domain analysis in *M. lateralis*. The candidate sequences obtained using these three methods were re-evaluated manually using CD-Search and Protein BLAST in the NCBI database with default parameters. Moreover, to better enrich the data on the PRDM gene family in shellfish for a more comprehensive phylogenetic analysis, the same identification procedure was applied to sequences from the Chlamys farreri genome [47].

#### 2.2. PRDMs Sequence Analysis

The isoelectric point (pI) and molecular weight (Mw) were predicted using the Expasy Compute pI/MW tool (https://www.expasy.org/, accessed on 12 November 2022). The functional domains of MI-PRDMs were visualized using IBS 1.0.3 [48] according to the prediction information from SMART (http://smart.embl-heidelberg.de/, accessed on 12 November 2022) and NCBI CD-Search. Multiple alignments of the PR domains among *M. lateralis*, *H. sapiens*, *M. musculus*, and *D. rerio* were performed using Clustal Omega on the EMBL-EBI website (https://www.ebi.ac.uk/, accessed on 12 November 2022), and the results were displayed using Jalview2.11.2.6 software [49].

## 2.3. Phylogenetic Analysis

The PR domains of sequences were extracted to perform a multiple sequence alignment using ClustalW with default parameters, and a phylogenetic tree was constructed using the maximum likelihood algorithm with default parameters in MEGA-X [50]. Finally, the tree was modified using the online software EvolView v3 (https://www.evolgenius.info/evolview, accessed on 10 March 2023).

#### 2.4. Gene Expression Analysis of M. lateralis prdms

The HeatMap function of TBtools [51] was used to conduct heatmap and clustering analyses of *M. lateralis prdm* genes based on the published RNASeq datasets of four developmental stages: blastula, gastrula, trochophore, and D-shaped larvae (NCBI accession numbers SRR17520079–SRR17520090) [52].

## 2.5. Collection of Embryos and Larvae

Adult *M. lateralis* were provided by the MOE Key Laboratory of Marine Genetics and Breeding. Mature males and females were stimulated with seawater at 27 °C to lay eggs or to release sperms after cooling in a dry and dark environment for 1.5 h. Artificial insemination was then carried out based on a ratio of 1 egg to 10 sperms, and the fertilized

eggs were incubated at 24 °C. Collected embryos and larvae were washed twice with PBS at room temperature and fixed with 4% paraformaldehyde overnight at 4 °C. Then, gradient dehydration was performed with serial methanol (25, 50, 75%, and 100%) after washing with PBS. Finally, the samples were stored in 100% methanol at -30 °C for whole-mount in situ hybridization analysis. Samples of the same developmental stages were also snap-frozen in liquid nitrogen and then stored at -80 °C for total RNA extraction.

#### 2.6. Quantitative RT-PCR Analysis of Ml-prdm1 and Ml-prdm14

The expression patterns of *Ml-prdm1* and *Ml-prdm14* during early development stages were detected. Briefly, the total RNA of the fertilized egg, multicellular embryo, blastula, gastrula, trochophore, D-shaped larva, and umbo larva were extracted with the MicroElute Total RNA Kit (Omega, Norcross, GA, USA). The RNA's integrity and quality were assessed by performing 1.2% agarose gel electrophoresis and spectrophotometry, and the first-strand cDNAs were reverse-transcribed using the SuperScript First-Strand Synthesis System (Invitrogen, Carlsbad, CA, USA). Quantitative RT-qPCR was conducted using the Light-Cycler 480 real-time fluorescence quantitative PCR instrument (Roche, Basel, Switzerland) with specific primers (Table 1), and *ef-1b* was utilized as an internal reference [52]. The  $2^{-\Delta\Delta Ct}$  method [53] was used to calculate relative gene expression with three biological replicates and three technical replicates. The statistical analysis was tested using one-way ANOVA followed by Duncan's test (SPSS 22.0, IBM Corp., Armonk, NY, USA), and the statistically significant difference was set as p < 0.05.

Table 1. Primer sequences used for quantitative RT-qPCR.

Gene Name	Forward Primer (5'-3')	Reverse Primer (5'-3')
Ml-prdm1	AGGAGAGGAAATGTTACAAGCA	GGCAGGAGTAGGTGGAGTCTTA
Ml-prdm14	ACTGACGCCTCGGTTTTATC	GTCGGACTCGGTGTTTCTGA
Ml-ef1b	GGGCATTACTTCACTCTAAAT	TGTGCTATCTGAGGGTCTACT

#### 2.7. Whole-Mount In Situ Hybridization of Ml-prdm1 and Ml-prdm14

Specific fragments of *Ml-prdm1* and *Ml-prdm14* were amplified using gastrula cDNA and gene-specific primers (Table 2) containing T7 or SP6 promoter sequences. The resultant PCR products were used as templates for in vitro transcription to synthesize digoxigenin-labeled RNA probes according to the manufacturer's instructions for the DIG RNA labeling kit (Roche, Mannheim, Germany). In addition, the labeled probes were precipitated using ethanol and lithium chloride, and dissolved in RNase-free water.

Table 2. Primer sequences used for the synthesis of RNA probes of in situ hybridization.

Gene Name	Forward Primer (5'-3')	Reverse Primer (5'-3')
Ml-prdm1	ATTTAGGTGACACTATAGAAGCG <sup>1</sup>	TAATACGACTCACTATAGGGAGACA <sup>2</sup>
	ATTTAGGTGACACTATAGAAGCG <sup>1</sup>	CATAGGAGGGTAAGGTGG TAATACGACTCACTATAGGGAGACA <sup>2</sup>
Ml-prdm14	GATTGGTTTCCCATTTC	TCGTGCTCCTCTGACTT

<sup>1</sup> The underlined sequence represents the SP6 promoter. <sup>2</sup> The underlined sequence represents the T7 promoter.

Whole-mount in situ hybridization was performed as previously described [54] with slight modifications. The rehydrated samples were treated with proteinase K (1  $\mu$ g/mL for embryos and 4  $\mu$ g/mL for trochophore larvae) at 37 °C for 20 min before incubation in TAE buffer. After treatment with acetic anhydride, samples were post-fixed in 4% paraformaldehyde for 30 min. Samples were pre-hybridized in hybridization buffer (50% deionized formamide, 5% dextran sulfate, 0.1% tween-20, 5 × SSC, 50  $\mu$ g/mL heparin, 500  $\mu$ g/mL yeast total RNA, 18 mM citric acid) at 60 °C for three hours, followed by being hybridized with 6  $\mu$ g/mL denatured RNA probe at 60 °C overnight and then washed in gradient saline sodium citrate buffer at 60 °C. After treatment in blocking buffer for 1 h,

samples were incubated with 1:2500 diluted alkaline phosphatase-conjugated digoxigenin antibody (Roche, Mannheim, Germany) overnight at 4 °C. Samples were finally incubated with NBT-BCIP in staining buffer (100 mM Tris-HCl, 100 mM NaCl, 10% PVA, 50 mM MgCl<sub>2</sub>, 0.1% Tween-20, pH 9.5) in darkness at 37 °C for color development.

# 3. Results

# 3.1. Identification and Sequence Analysis of M. lateralis Putative PRDMs

Eleven members of the PRDM family were identified in the genome of *M. lateralis*. All of these MI-PRDMs had one PR domain and several zinc fingers (0–20), and their protein lengths varied from 283 to 1969 aa (Figure 1; Table 3). The members identified with both SMART and NCBI CD-Search were named MI-PRDM, whereas those recognized by only one algorithm were designated as MI-PRDM-like. The predicted physical and chemical properties, molecular weights, and isoelectric points of all PRDM members were presented in Table 3.



Figure 1. Conserved domain identification of PRDM proteins of M. lateralis.

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Doma	in Number	PR Domain	рI	Mw (Da)
PR	Zinc Finger	Length	r-	Wive (Du)
1	5	122	6.96	95,462.42
1	11	122	6.04	221,527.46
1	4	135	5.74	98,698.34
1	3	118	7.96	84,010.47
1	10	121	8.54	81,667.44
1	12	119	6.25	165,430.32
1	3	120	9.2	32,469.99
1	0	98	8.54	60,496.27
1	6	124	8.91	59,197.42
1	20	118	5.96	181,519.82
1	9	49	6.76	98,759.51
	Doma PR 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	PR         Zinc Finger           1         5           1         11           1         4           1         3           1         10           1         12           1         6           1         20           1         9	Domain Number         PR Domain Length           PR         Zinc Finger         Length           1         5         122           1         11         122           1         4         135           1         3         118           1         10         121           1         3         120           1         6         124           1         20         118           1         9         49	Domain Number         PR Domain Length         PI           PR         Zinc Finger         Length         PI           1         5         122         6.96           1         11         122         6.04           1         4         135         5.74           1         3         118         7.96           1         10         121         8.54           1         12         119         6.25           1         3         120         9.2           1         0         98         8.54           1         6         124         8.91           1         20         118         5.96           1         9         49         6.76

Table 3. Summary of M. lateralis PRDMs properties.

Four highly conserved residues (G, I, and E-L) in both PR and SET domains [55] were observed in the PR domains of all the MI-PRDMs, except for the MI-PRDM16-like, of which the G and L were not conserved (Figure 2). In addition, six well-conserved and unique residues (W, A) and motifs (F-G-P, E-Q-N-L, Y/F-Y/F, L-V-W), which were almost exclusive to the PR domains [55–57], were partially or completely identified in MI-PRDMs (Figure 2). Notably, most of these residues and motifs were less conserved in MI-PRDM13-like and MI-PRDM16-like proteins. A multiple sequence alignment of 44 sequences between *M. lateralis* and three vertebrates showed that the identity of 14 residues was higher than 80%, and there was a residue (E) exhibiting great conservation in all sequences (Figure 3).

		G					F-	G-P																	
MI-PRDM13-like	DDMK1	r <mark>G</mark> V T	TKN/	Α					- s	Q٧	۱v	sc	KAF	RGK	PK	NL	G-					LR	LY	DEY	GPDL
MI-PRDM-4-like	FKDF	_ <mark>G</mark> vv	NCKI	D - 0	LS	ERT	RFC	<b>BP</b> M	VG	кн	VVN	ISQ	KD١	EE/	QE	NGF	QP	FL	KRK	- N	ЕТЕ	İVE	LL	EMY	DET
MI-PRDM14	DVVH	( <mark>G</mark> VI	CN	ктν	/ <mark> </mark> S	κ <mark>σ</mark> ν	KFC	3 P F	κg	R٧	INT	<b>SE</b>	- 1 1	(TN	DD	VSL	MW	ΕI	FQD	) (	GKL	.sh	FI	DG -	RRNA
MI-PRDM1		GVV	vsvi	D - Y	I P	R <mark>G</mark> T	RFC	<b>BP</b> L	NG	EII	FPE	EEP	LRF	RRE	SNF	٦I۶	LW	кı	FKD		NKV	/ск	FM	ονσ	DTSH
MI-PRDM9	PNAG	. GV I	TE	К - Е	E I P	ARV	MFC	3 PY	GG	vĸ	CYE	Q-	QM ·	A	HDS	S G Y	′C <mark>W</mark>	QI	нур		GKF	sн	FV	DAC	NKAN
MI-PRDM12	PGAG	. GV I	ST	s - v	/ I K	к <mark>с</mark> т	EMO	3 PY	PG	DL	vĸı	ГL -	- D -	V	TR	SDL	sw	ΕV	FSK	HD	MVL	.GF		ĪΤΑ	NAQF
MI-PRDM2	DKRR	GSI	ст	S - F		QGT	EFC	3 PY	κg	кı	VIC	οĸΝ	DD -	A	VD	PKF	sw	ĸν	FDL	ΤТ	FKY	LH	τv	DAS	CPAD
MI-PRDM16-like																									
MI-PRDM-8-like		GV	TAD	т - с	VD	YGR	IY	3 P F	ΡA	VGI	HIF	PQT	HF -			I <mark>G</mark> Y	'LT	AD	ERH	I - D	TGC	R	IN		SSLO
MI-PRDM15	GQGF	ر <mark>ور</mark> ۷	νακι	M - E	E I P	акн	QFC	3 P F	ΕA	KR.	ТΤН	IVF	DD -		1	r <mark>G</mark> F	FΤ	LK	VIG	- K	DGT	TI	CL	отт	DESE
MI-PRDM-10	DESE	GV F	ткі	R - A	AIP	KRT	QFC	3 P F	ΙA	EL	VPC	DE	sv.		1	RH	SF	PL	MVE	- Q	QGF	TL	FY	DTS	DENK
		-																						-	
MI-PRDM13-like	I-KSG	MY	< PA	RDI	FE	QNL		RS	RD	GH	VFI	RS	ткі	r I Q	E -	3 D E	LK	YW	FDD	KL	AR -				
MI-PRDM-4-like	CSWTN	AFIF	RLA	PSL	LE	QNC	τv	R-	DQ	DQI	F Y I	νT	KTE		E -	EE	LL	MW	FSA	EI	CYC				
MI-PRDM14	GNWMA	A F VI		RYA	٩QE	QNL	IA	1 <mark>Q</mark> -	VE	GD	VY	ΕV	CK	<mark>s</mark> i s	Q - 1		LL	vw	YGD	sY	LQF	: MG	VP	VA	
MI-PRDM1	SNWMH		VFS	Y <mark>s</mark> s	ssн	QNV	I AC	c <mark>a</mark> -	ID	YN	IYF	ΥT	IKF	PIP	P - 1	N T E	LL	vw	YCR	EY	ADF	۲ <b>L</b> -			
MI-PRDM9	SNWMF	2 V V		PSE	ENE	QNL	VAF	÷٥.	Υĸ	GS	IN	RS	Y <mark>K</mark> \	/ I E	s - 🤇	3 S E	LL	cw	YGN	IEY	GRE	LG			
MI-PRDM12	EHWL	/ <mark>Y</mark> V		RSE	ERE		DM\	/ <mark>a</mark> -	IG	тκ	IF	RA	RR	ΙE	v - v	GEE	LF	vw	YGK	SF	NLY	MG	ΙP		
MI-PRDM2	GNWMF	<mark>γ</mark> γα		RYF	EE	QN I	vsı	ra -	NG	TD	٧Y١	RA	LKC	DIE	A - 0	GEE	LL	тw	FE-						
MI-PRDM16-like	L F	X Y I P	ĸĸs	DNT	ГЕТ	SNL	MAN	/ <mark>Q</mark> -	LQ	NQ	LY	RA	IRE		A - E	DEE	ML	LΥ	ткр	RL	YNF	1			
MI-PRDM-8-like		YV		RTV		QNM	EA	<u>м</u> -	KD	GH	IFY	RT	LRI	IR	т - С	GEE	LL	vw	YSK	DF	AQI	L -			
MI-PRDM15	CNWLC		RAA	TTF	PED	RNC	IA	a-	IG	NN	IN	нт			v - 1	I E E	LL	vw	YAP	HF	AKK	(L -			
MI-PRDM-10	CNWMM		RPA	STY		QNC	VA	(Q -	HE	NE	IYP	τv	тк	o I S	EM	< T E	LK	vw	YAA	HY	AEF	RWG			
	W				E-	O-N-L	-				Y/F-)	(/F		1		F	-L L	-V-W							

**Figure 2.** Multiple sequence alignment of the PR domains in *M. lateralis*. Blue boxes indicate shared conserved residues in the PR and SET domains, and red boxes indicate exclusively conserved residues in the PR domains.

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		* ** 5 F-G-P		
MI-PRDM4-like	2 ARATLPPCFTLQQTAT SNFKDFI	WWCK-DCLSERTREGPM	V <mark>G</mark> KHVVMSQKD-YE-EQENGFQPFLKRK	67
Dr-PRDM4	2 ARLS <mark>LP</mark> RP <mark>L</mark> CLRISVTDEP	S <mark>VF</mark> SR-ES <mark>IP</mark> SRTCFGPM	VGQHCSSVELT-DWSDKDTPQI <mark>W</mark> KMFH	64
Mm-PRDM4	2 ARLSLPKQLVLRQSIVGTDVVGVLPL			71
MI-PRDM10	2 AWASLPPSLQIFRIDESEI	GVFTK-RAIPKRTCFGPF	IAELVPDDESV-TRHSFPLMVE	58
Dr-PRDM10	2 ARASLPLVL YIDR FLC	3 <mark>VF</mark> TK-RRI <mark>P</mark> KRTC <mark>FGP</mark> LI	EGPLVRQSELL-DTHIHLKLYMLDPE-KEG	62
Mm-PRDM10 Hs-PRDM10	2 ARASLPLVL YIDR FL( 2 ARASLPLVL YIDR FL(	SVESK-RRIPKRTOFGPVI	EGPLVRGSELK-DCYTHLKVSLDKGDRKDR	63
MI-PRDM15	2 ARLTLPSFVEVIDDGQGF	G <mark>VV</mark> AK - ME <mark>IP</mark> AKHQFGPFI	EAKRTTHVFDD-TGFFTLKVIG	58
Dr-PRDM15	3 ARSSLPDSLEIRLAEEGKI	SVFVL-RRLVRRTRFGPFI	EATRTSS-LQT-EGAFPLKIFQ	58
Hs-PRDM15	3 GRSSLPSNLEIRRLEDGAI	SVFAU - TQLVKRTQFGPFI	ESRRVAR-WER-ESAFPERVFQ	58
MI-PRDM13-like	e 1 LD PAVFDDMK	3 <mark>V</mark> TKN	VISCK	26
MI-PRDM8-like		SVOVT - OD I PAGT SEGPON	PAVG H I PQT HF I GYL	32
Mm-PRDM8	1 IQRG IWDGDAKAV - QQCL TD I F	SVYTT-CDIPENAIFGPC	VLSHTSLYDSIAFVALK	56
Hs-PRDM8	1 I QRG I WDGDAKAV - QQCL TD I F	SVYTT-CDIPENAIFGPC		56
Mm-PRDM16	16 EDIPIPPDFELR ESSIPGAGI	GIWA-KRKMEIGERFGPY	VVTPRAALKEADFGWEQMLNDHETSSQDSCT	84
Hs-PRDM16	16 EDIPI <mark>P</mark> ADFELR ESSIPGAGI	<mark>GV</mark> WA - KRKMEA <mark>G</mark> ERL <mark>GP</mark> C	VVVPRAAAKET DFG <mark>W</mark> EQILTDVEVSPQEGCI	84
MI-PRDM16-like	18 KGLVIRKTLVADVVH		K <mark>G</mark> RVINTSEIK-TNDDNSLMWEIFO	75
Dr-PRDM14	5 EGISILQTTCGSLSH	S <mark>AF</mark> ADKSTI <mark>P</mark> KGTRFGPF0	Q <mark>G</mark> KLVNTSEIK-TYDDNTLM <mark>W</mark> EIFE	62
Mm-PRDM14	5 EGLCLMQTSFGDVPHI		RGRVVNASEVK-AHRDNSRMWEIFE	61
Dr-PRDM14	1	IPAGLRIGPVI	PGIFKLGKYVS-DRKELGVKK	30
Mm-PRDM13	1	<mark>I P</mark> A <mark>G</mark> LRLGPVI	P <mark>G</mark> TFKLGKYLS-DRREPGPKK	30
Hs-PRDM13 MI-PRDM9	1	IPAGLRLGPVI	PGTFKLGKYLS-DRREPGPKK	30
MI-PRDM9	1 L T L PQG L V I G RSS I SHAGI	<mark>SVF</mark> NQGQTV <mark>PLG</mark> MHFGPFI	DGEEISE-EKALDSANSWVICR	58
Dr-PRDM9	1 LSLPPGLRISPSGIPEAGI	SVWNEASDL PVGLHFGPYI	EGQITED-EEAANSGYSWLITK	58
Hs-PRDM9	1 VPYEVYIS QSSVPGAG	SVEASDLPLGLAPGPT	PGDLVKTLDVTRSDLSWEVFS	55
Dr-PRDM12	1 <mark>L P</mark> SAVV I A QSSVPGEGI	GIFTKT-WIKAGTEMGPF:	S <mark>G</mark> RLLAPEHVD-LRKNNNLM <mark>W</mark> EVFN	58
Mm-PRDM12		GIFSKT-WIKAGTEMGPF		58
MI-PRDM2	1 <mark>P</mark> DG I RLG VSQVDKRRI	GSFCTS-PIAQGTEFGPYI	K <mark>G</mark> KIVIDKNDDAVDPKFS <mark>W</mark> KVFD	56
Dr-PRDM2	1 - WKGLPNSMKLE PSAVNPSR	SVWASR - LIPKGKREGPE	VGERKKRSQVTSNVYMWEVYF	58
Mm-PRDM2 Hs-PRDM2	1 - LRGLPEEVRLL PSAVDKTR	SVWATK - PILKGKKFGPF	VGDKKKRSQVKNNVYMWEVYY	58
MI-PRDM1	1	3 <mark>V</mark> WSVD - Y I PR <mark>G</mark> TRFGPLI	N <mark>G</mark> EIFPEEPLRRRESNR ICL <mark>W</mark> KIFK	42
Dr-PRDM1 Mm-PRDM1	1 ASLPRNLAFKHPA-DSKEV 1 ASLPRNLLFKYAANNSKEV	SVVSRE-YIPKGTREGPLY	VGESYTAENVP-KDANRKYFWR YS	60 61
Hs-PRDM1	1 ASLPRNLLFKYAT-NSEEV	SVMSKE - YIPKGTRFGPL	IGEIYTNDTVP-KNANRKYFWRIYS	60
MI-PRDM4-like	68NETEVELLEMYDET	VCSWTMFIRLAPSLLEQN	CTVYR DQD - QF <mark>YIVT</mark> KTE <mark>I</mark> R E <b>EELLMW</b> FSAELCYQLG	135
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4	68NETEVELLEMYDET 65NDIQEFCIVTTDEN 72	VCSWTMFIRLAPSLL <mark>EON</mark> ECNWMMFVRKARTTGEON	CTVYRDQD-QF <mark>YIVT</mark> KTE <mark>IREEELLMWF</mark> SAEICYQLG LVAYIDNG-KLYFCTTREIL-PDOELLFYFSRDYSRQLG	135 133
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 Hs-PRDM4	68 NET EVELLE MYDET 65 NDI QEFCIV TTDEH 72 TGV LEFCII TTDEN 72 NGV LEFCII TTDEN	VCSWTMFIRLAPSLLEON ECNWMMFVRKARTTGEON ECNWMMFVRKARNREEON ECNWMMFVRKARNREEON	CTVYR - DQD - QF <mark>YIVIK TE</mark> IR - E <mark>EEL MW</mark> FSAEICYQLG LVAYI - DNG - KLVFC TREIL - PDGELL FYFSRDYSROLG LVAYP - HDG - KIVFC SODIP - RESELL FYFSRDYSROLAQIG VAYP - HDG - KIVFC SODIP - RESELL FYFSRDYAQIG	135 133 140 140
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 Hs-PRDM4 MI-PRDM10 Dr-PRDM10	68NETEVELLEMYDET 65NDIQEFCIVTTDEH 72TGV-LEFCITTDEN 72NGV-LEFCITTDEN 59QGC-PTLFYDTSDEN	VCSWTMFIRLAPSLLEON ECNWMMFVRKARTTGEON ECNWMMFVRKARNREEON ECNWMMFVRKARNREEON KCNWMMFVRPASTYAEON	CTVYR - DQD - QFWIV KTEIR - EELLMWFSAEICYQLG LVAYI - DNG - KLYFFT TREIL - POQELLFYFSRDYSRQLG LVAYP - HDG - KIYFFT SQDIP - PESELLFYFSRDYSRQAQIG LVAYP - HDG - KIFFFT SQDIP - PENELLFYFSRDYAQQIG CVAYB - HEN - EINFTYTNDISEMKTEL YWWAAHYAERWG	135 133 140 140
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 Hs-PRDM4 MI-PRDM10 Dr-PRDM10 Mm-PRDM10	68	VCSWTMFIRLAPSLLEON CONVMMFVRKARTTGEON ECONVMMFVRKARNREEON CONVMMFVRKARNREEON KCNVMMFVRKARNREEON RCNVMMFVRPASTYAEON RCNVMMFVRPASHLEON	CTVYR - DQD - QFVIVIKTEIR - EELLMW SAEICYQLG LVAYI - DNG - KLYFCTTREIL - POOELLFY SRDYSROLG LVAYP - HDG - KIYFCTSQDIP - PESELLFY SRDYROQIG LVAYP - HDG - KIFFCTSQDIP - PESELLFY SRDYROQIG CVAYT - HEN - EIVFTVTROISEMKTEL XWYAASYAEFVN LVAYT YGS - DIFYTSIN NIQ - PROEL XWYAASYAEFVN	135 133 140 140 128 131
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 Hs-PRDM4 MI-PRDM10 Dr-PRDM10 Mm-PRDM10 Hs-PRDM10	68	VCSWTMFIRLAPSLLEON ECNWMFVRKARTTGEN ECNWMFVRKARNREEN KONWMFVRKARNREEN RCNWMFVRASTVAEN LCNWMFVRPADNHLEON LCNWMFVRPADNHLEON	CTVYR - DQD - QFYIVIKTEIR - EELLMW SAEICYQLG LVAYI - DNG - KLYFFITREIL - POELLFY SRDYSRQLG LVAYP - HDG - KIVFFISODIP - PESELLFY SRYAQQIG LVAYP - HDG - KIVFFISODIP - PESELLFY SRYAQQIG CVAYD - HEN - EIVFFITROISEMKTEL VWVAASYAFFIN LVAYG YGS - DIFYTSINNIQ - PKQEL VWVAASYAFFIN LVAYG - YGH - HVYYTTINNYE - PKQEL VWVAASYAFFIN	135 133 140 140 128 131 132
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 Hs-PRDM4 MI-PRDM10 Dr-PRDM10 Hs-PRDM10 MI-PRDM15 Dr-PRDM15	68	VCSWTMFIRLAPSLLEDN ECNWMMFVRKARNRECN ECNWMMFVRKARNRECN CCNWMFVRARNRECN CCNWMFVRARNECN CCNWMMFVRASTYAEDN LCNWMMFVRASTHLEON LCNWMMFVRASHLEON CCNWCVRASHLEON CCNWCVRASHLEON CCNWCVRASHLEON CCNWCVRASHLEON CCNWCVRASHLEON CONWCVRASHLEON	CTVYR - DQD - QFY IVYKTEIR - EELLMW SAEICYQLG LVAYI - DNG - KLYFC TREIL - PDOELLFY SRDYSRQLG LVAYP - HDG - KIYFC SQDIP - PESELLFY SRNYAQQIG LVAYP - HDG - KIYFC SQDIP - PESELLFY SRNYAQQIG LVAYP - HDG - KIYFC SRDYTO IP - PENELLFY SRDYAQQIG LVAYG - YGS - DIFYTSIKNIQ - PKOEL XWYAASYAEFVN LVAYG - YGH - HVYYT I NNE - PKQEL XWYAASYAEFVN LVAYG - IGN - NIYYH TRDIN - YFELL WYAAFYAFFX CIAYG - IGN - NIYYH TRDIN - YFELL WYAAFYAFFX CIAYG - IGN - NIYYH TRDIN - YFELL WYAAFYAFFX CIAYG - IGN - NIYYH TRDIN - YFELL WYAAFYAFFXKL	135 133 140 140 128 131 132 132 132
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 Hs-PRDM10 Dr-PRDM10 Mm-PRDM10 Ms-PRDM10 Mi-PRDM15 Dr-PRDM15 Mm-PRDM15	68         - NET - EVELLE - MYDET           65         - NDI - QEFCIV - TTDEH           72         - TGV - LEFCII - TTDEN           73         NGV - LEFCII - TDEH           74         - NGV - LEFCII - TDEH           75         - QGG - PTLFYD           76         - LFHCII - TDEH           76         - QGG - PTLFYD           77         - SDEH           78         - ERA - QOLWFD           79         - DLH - EDLWFE           79         - KDG - TTICLD           79         - KDG - SVUCFD           79         - KDG - NFVCFD           79         - TSNED	VCSWTMFIRLAPSLLEDN ECNWMMFVRARTTGEDN ECNWMFVRARTTGEDN ECNWMFVRARTTGEDN ECNWMFVRARTNEEDN CCNWMFVRASTVAEDN CCNWMFVRADNLLEDN LCNWMMFVRADNLLEDN LCNWMMFVRADNLLEDN CCNWMMVRATTFEDN CCNWMMVRATTFEDN CCNWMMVVRALFGAEDN	CTVYR - DQD - QFWIV KTEIR - EELL MW SAEICYQLG LVAYI - DNG - KLVFF TREIL - PDGELL FY SRDYSRQLG LVAYP - HDG - KIVFF TSGDIP - PESELL FY SRDYSRQLG CVAYP - HDG - KIFFF TSGDIP - PESELL FY SRDYAQQIG CVAYB - HEN - EIVFT VTGDISEMKTEL VWYAAHYAERWG LVAYG - VG - HFYT TKDISEMKTEL VWYAAHYAERWG LVAYG - YGH - HVYYT I KNUG PKOCL VWYAASYAEFVN LVAYG - YGH - HVYYT I KNUG PKOCL VWYAASYAFFVN CAYG - YGH - HVYYT I KNUG PKOCL VWYAASYAFFVN CIAYG - YGH - HVYYT I KNUG PKOCL VWYAASYAFFVN LVAYG - YGH - HVYYT I KNUG PKOCL VWYAASYAFFVN CIAYG - IGS - DYFT SGDVL - PGTEL VWYAFFAKKL LTAYG - GDD - DYFN SGDVL - PGTEL VWYAFYAKKM	135 133 140 128 131 132 132 126 126
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 HS-PRDM4 MI-PRDM10 Dr-PRDM10 MI-PRDM10 MI-PRDM15 Mm-PRDM15 HS-PRDM15 HS-PRDM12 MI PRDM12	68      NETEVELLEMYDET         65       -NDIQEFCIVTTDEH         72       -TGV-LEFCIITTDEN         72       -NGV-LEFCIITTDEN         59       -QGC-PTLFYD       -TSDEN         63       -ERA-QDLWFD       -LSDEE         64       -DLH-EDLWFE       -LSDET         64       -DLH-EDLWFE       LSDET         59       -KDG-SVVCFD       -TSNED         59       -KDG-HVCFD       -TSNED         59       -KDG-HPVCFD       -TSNED         59       -KDG-HPVCFD       -TSNED         59       -KDG-HPVCFD       -TSNED	VCSWTMFIRLAPSLLEDN ECNWWMFVRARTTGEDN ECNWMFVRARTTGEDN ECNWMFVRARTTGEDN CONWMFVRARTTGEDN CONWMFVRASTYAEON CONWMFVRASTYAEON CONWMFVRASTHEON LCNWMFVRASHLEDN LCNWMFVRASHTHEON OCNWMFVRASHTHEON OCNWMFVRASTTFEOR	CTVYR - DQD - QFVIV KTEIR - EELL MW SAEICYQLG LVAYI - DNG - KUYFD TREIL - PDGELL FY SRDYSRQLG LVAYP - HDG - KIYFD SQDIP - PESELL FY SRDYSRQLG CVAYB - HEG - KIFFD SODIP - PESELL FY SRDYAQQIG CVAYG - HEN - EIVFTYT KOISEMKTEL YWYAABYAERWG LVAYG - YGS - DIFYTY SINIQ - PKGEL YWYAABYAERWG LVAYG - YGH - HVYYT INME - PKGEL YWYAASYAFFYN LVAYG - YGH - HVYYT INME - PKGEL YWYAAFYAKK LTAYG - GDD - DYFN SODYL - PGTEL RYWYAFYAKKM LTAYG - HSS - DYYFT SRDIP - OF LWWAAFYAKKM	135 133 140 140 128 131 132 132 126 126 126
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 Hs-PRDM10 Dr-PRDM10 Mm-PRDM10 MI-PRDM15 Dr-PRDM15 Dr-PRDM15 Hs-PRDM15 Hs-PRDM15 MI-PRDM13-like MI-PRDM3-like	68	V CSWTMFIRLAPSLLEDN ECNWMMFVRARTTGEDN ECNWMFVRARTTGEDN ECNWMFVRARTTGEDN CCNWMFVRARTTGEDN KCIWMMFVRASTYAEDN CCLWMMFVRASTYAEDN CCLWMMFVRASHTEDN LCNWMFVRASHTEDN CCNWMFVRASHTEDN DCCNWMFVRASTTDHKHEN DCCNWMFVRASTTDHKHEN DCCNWMFVRASTTDHKHEN DCCNWMFVRAST	CTVYR - DQD - QFW IV KTEIR - EELL MW SAEICYQLG LVAYI - DNG - KUYFCT TREIL - PDGELL FY SRD SRD G LVAYP - HDG - KIYFC SQDIP - PESELL FY SRD YAQQIG CVAYD - HEN - EIVFT VTRDISEMKTEL FY SRD YAQQIG CVAYD - HEN - EIVFT VTRDISEMKTEL YW AAH YAERWG LVAYG - YGS - DIFYTSINIQ - PRGEL YWY AASYAEFVN LVAYG - YGH - HYYTI IN ME PRGEL YWY AASYAFYN LVAYG - YGH - HYYTI IN ME PRGEL YWY AASYAFYN LVAYG - YGH - HYYTI IN ME PRGEL YWY AASYAFYN LVAYG - YGH - HYYTI IN ME PRGEL YWY AASYAFYN LVAYG - YGH - HYYTI SND Y PRGEL YWY AASYAFYN LYAYG - YGH - HYYTI SND Y PRGEL YWY AASYAFYN LYAYG - YGH - HYYTI SND Y PRGEL YWY AAFYAKKM LTAYG - HGS DVYFTI SRD P OF EL YWY AAFYAKKM LTAYG - HGS DVYFTI SRD P OF EL YWY AAFYAKKM LLYAY - SRDCHYFIRST IN GEGEL YWY AAFYAKKM LLYAYG - GOD - HIFYR IN SRD P OF EL WWY AAFYAKKM LLYAYG - HGS - DYYFTI SRD P OF EL WWY AAFYAKKM LLYAYG - HGS - DYYFTI SRD P OF EL WWY AAFYAKKM	135 133 140 140 128 131 132 128 128 128 128 128 128 128 108
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 Hs-PRDM10 Dr-PRDM10 Mm-PRDM10 MI-PRDM15 Dr-PRDM15 Mm-PRDM15 Hs-PRDM15 Mm-PRDM15 MI-PRDM13-like Dr-PRDM3-like Dr-PRDM8-like	68	VCSWTMFIRLAPSLLEON ECNWMMFVRAARNEEON ECNWMMFVRAARNEEON CCNWMMFVRAARNEEON CCNMMFVRAARNEEON CCNMMFVRAARNEEON CCNMMFVRAARNEEON LCNWMFVRAANLEON LCNWMFVRAANLEON CCNMMFVRAANLEON CCNMMMVRAAEFGHAN DCNMMMVRAAEFGHAN DCNMMMVRAAEFGHAN DLIKSGWYKAARDIFEON	CTVYR - DQD - QFV IV KTEIR - EELL MW SAEICYQLG LVAYI - DNG - KUYFCTTREIL - PDGELLFY SRDYSRQLG LVAYP - HDG - KIYFCTSQDIP - BESELLFY SRDYAQQIG CVAYD - HEN - EIYFTYTRDISEMKTEL - YW AAHYAERWG LVAYG - YGS - DIFYTSINIQ - PRGELVWY AASYAEFVN LVAYG - YGH - HYYTTINN - PRGELVWY AASYAFFVN LVAYG - YGH - HYYTTINN - PRGELVWY AAFYAKKM LTAYG - HGS - DWFFTSGDIP - PGTELRVW AAFYAKKM LDIYR - SRDGHVFINSTN - PRGELVWY AAFYAKKM LDIYR - SRDGHYFINSTN - RGELVWY AAFYAKKM LDIYR - SRDGHYFINSTN - RGEELVWY BOLLAR MEAYM - KGG - QLHFRW LRINR - TGEELVWY AGELSHLL	135 133 140 128 131 132 132 126 126 126 126 126 126 133
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 MI-PRDM10 Dr-PRDM10 MI-PRDM10 MI-PRDM15 MI-PRDM15 MI-PRDM15 MI-PRDM13-like Dr-PRDM8 MI-PRDM8-like Dr-PRDM8 Mm-PRDM8	68	VCSWTMFIRLAPSLLED CONVMMEVRAARNEED ECNVMMEVRAARNEED ECNVMMEVRAARNEED CONVMMEVRAARNEED CONVMMEVRAARNEED CONVMMEVRAARNEED CONVMMEVRAAD CONVMMEVRAAD CONVMMEVRAAD CONVMMEVRAAD CONVMMEVRAALEPG CONVMMEVRAAEHON CONVMMEVRAAEHON CONVMMEVRAAEHON CONVMMEVRAAEHON CONVMMEVRAAEHON CONVMMEVRAAEHON CONVMMEVRAAEHON CONVMMEVRAAEHON CONVMMEVRAAEHON CONVMMEVRAAEHON CONVMENT CONVMENT CONVMENT CONVMENT CONVMENT CONVMENT CONVMENT CONVMENT CONV	CTVYR - DQD - QFYIV KTEIR - EELL MW SAE ICYQLG LYAYI - DNG - KLYFC TREIL - PDGELL FY SRD'SRQLG LYAYP - HDG - KIYFC SQD IP - PESELL FY SRD YSRQLG CYAYB - HEG - KIFFC SQD IP - PESELL FY SRD YAQQIG CYAYB - HEG - KIFFC SQD IP - PESELL FY SRD YAQQIG CYAYB - GO - HEY FY TY DISEMTTEL XWY AAHYAERWG LYAYG - YGH - HYYTT IN NU - PKOCL XWY AASYAEFVN LYAYG - YGH - HYYTT IN NU - PKOCL XWY AASYAFFVN CIAYG - YGH - HYYTT IN NU - PKOCL XWY AASYAFFVN CIAYG - YGH - HYYTT IN NU - PKOCL XWY AASYAFFVN CIAYG - YGH - HYYTT IN NU - PKOCL XWY AASYAFFVN CIAYG - YGH - HYYTT IN NU - PKOCL XWY AASYAFFVN CIAYG - YGH - HYYTT IN NU - PKOCL XWY AASYAFFVN CIAYG - YGH - HYYTT IN NU - PKOCL XWY AASYAFFVN CIAYG - YGH - HYYTT IN NU - PKOCL XWY AASYAFFVN CIAYG - HGS - DYFTT SRD IP - PGTEL XWY AAFYAKKM LTAYG - HGS - DYFTT SRD IP - PGTEL XWY AAFYAKKM LTAYG - HGS - DYFTT SRD IP - PGTEL XWY AAFYAKKM LTAYG - HGG - DYFTT SRD IP - PGTEL XWY AAFYAKKM LTAYG - HGG - UFFT IN IN TO HET LU YW AAFYAKKM LTAYG - HGG - UFFT THA TIG ELL VWY GELSHLAR MEAYM - KDG - HFYR TLAIN ROW - KDEELL VWY GKELTEL LAYI - KGG - UFFR TIROV - SCHUL WY GKELTEL L LAYI - KNG - UFFR SRD IP A KDEL VWY GKELTEL LAYI - KNG - UFFR SRD IP A KDEL VWY GKELTEL L	135 140 140 128 131 132 126 126 126 126 126 126 126 126 126 12
MI-PRDM4-like Dr-PRDM4 Mm-PRDM4 MI-PRDM10 Dr-PRDM10 MI-PRDM10 MI-PRDM15 Dr-PRDM15 MI-PRDM15 MI-PRDM15 MI-PRDM3-like Dr-PRDM8 MS-PRDM8 MS-PRDM8 Dr-PRDM8	68         - NET - EVELLE - MYDET           65         NDI - QEFCIV - TTDEH           72         TGV - LEFCII - TTDEN           73         NGV - LEFCII - TTDEN           74         NGV - LEFCII - TTDEN           75         - CAGA - PTLFYD           76         - CHWFD - LSDET           76         - DLH - EDLWFE - LSDET           76         - DLH - EDLWFE - LSDET           79         - KDG - TTICLD - TTNED           70         - KDG - HPVCFD - TSNED           70         - KDG - HPVCFD - TSNED           77         - SF - DKRTVRUG - LTYD - EVCP           71         - SF - DKRTVPY FRVD TSAANGSS           77         - ST - DKRTVPY I FRVD TSAANGSS           75         - ST - DKRTVPY I FRVD TSAANGSS           75         - ST - DKRTVPY I FRVD TSAANGSS	VCSWTMFIRLAPSLLEDN ECNWMMFVRARNTGEDN ECNWMFVRARNTGEDN ECNWMFVRARNREDN CCWMFVRARNEEDN CCWMFVRASTAEN CCWMFVRASTAEN CCWMFVRADNLEDN CCMMMFVRADNLEDN CCMMMFVRADNLEDN CCMMMFVRAATTPEONE CCMMMFVRAATTPEONE CCMMMFVRAATTPEONE CCMMMFVRAATTPEONE DCMMMFVRAATTPEONE DCMMMFVRAATTPEONE DCMMFVRAATTPEONE CCMMFVRAATTPEONE	CTVYR - DQD - QFWIV KTEIR - EELL MW SAE ICYQLG LYAYI - DNG - KUYFC TREIL - PDGELL FY SRD SRD G LYAYP - HDG - KIYFC SRD IP - PESELL FY SRD YSRD G CYAYB - HEG - KIFFC SRD IP - PESELL FY SRD YAQ IG CYAYB - HEG - KIFFC SRD IP - PESELL FY SRD YAQ IG CYAYB YGH - HYYTYT I KNIG - PKOEL YWYAAFYAERWN LYAYG YGH - HYYYTT I KNIG - PKOEL YWYAAFYAEFWN LYAYG YGH - HYYYTT I KNIG - PKOEL YWYAASYAEFWN LYAYG YGH - HYYYTT I KNIG - PKOEL YWYAASYAFFWN LYAYG GD - DYFTS KOIP AG TER YWYAAFYAKKL LYAYG GD - DYFTS KOIP AG TER YWYAAFYAKKL LYAYG GS - DYFTS KOIP AG TER YWYAAFYAKKL LYAYG GS - DYFTS KOIP AG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - PG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - PG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - PG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - PG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - PG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - PG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAFYAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAFYAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAFYAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAFYAFYAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAFYAFYAKKL LYAYG - HGS - DYFTS ROIP - NG TER YWYAFYAFYAFYAFYAFYAFYAFYAFYAFYAFYAFYAFYAFY	135 140 140 128 131 132 126 126 126 126 126 126 133 133 133 224
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EDLG - SEKFCV - ANQAG           81         - D - G - KLSHFI D - GKG           82         - D - G - KLSHFI D - GKG           81         - N - G - RLSHFI D - GKG           81         - N - G - KLSHFI D - GKG           82         - D - G - KLSHFI D - GKG           83         - N - G - RLSHFI D - GKG           84         - GN - GYSYI D - AEKDT           85 <td>VCSWTMFIRLAPSLLEDN CSWTMFVRARTTGEDN ECNWMMFVRARTTGEDN ECNWMFVRARTTGEDN CCNWMFVRARTTGEDN CCWMMFVRARTTGEDN CCWMMFVRARTSEDN CCWMMFVRARDNHLEDN CCWMMFVRADNHLEDN CCWMMFVRADNHLEDN CCWMMFVRADNHLEDN CCWMMFVRADNHLEDN CCWMMFVRADTHEDN CCWMMFVRADTFEDN CCWMMFVRADTFEDN CCWMMFVRADTFEDN CCWMFVRATTFEDN CCWMFVCARTFEDN CCWMFVCARTFEDN CCWMFVCARTFEDN</td> <td>CTVYR - DQD - QFW IV KTEIR - EELL MW SAE ICYQLG VAYI - DNG - KUYFC TREIL - PDGELL FY SRD SRD G UAYP - HDG - KIYFC TREIL - PDGELL FY SRD SRD G CAYB - HDG - KIFFC SADIP - PENELL FY SRD YAQ IG CAYB - HEN - EIVFT VRD ISEM TEL YW AAHYAERWG UAYP - HDG - KIFFC SADIP - PENELL FY SRD YAQ I CAYB - YGH - HVYTT I NWE - PKGEL YW AASYAEFVN UAYG - YGH - HVYTT I NWE - PKGEL YW AASYAFFVN UAYG - YGH - HVYTT I NWE - PKGEL YW AASYAFFVN UAYG - YGH - HVYTT I NWE - PKGEL YW AASYAFFVN UAYG - YGH - HVYTT I NWE - PKGEL YW AASYAFFVN UAYG - YGH - HVYTT I NWE - PKGEL YW AASYAFFVN UAYG - GDD - DYFN SODY - PGTEL YW AAFYAKKL LTAYG - GS - DYFT SRD IP - PGTEL YW AAFYAKKL LTAYG - GS - DYFT SRD IP - PGTEL YW AAFYAKKL LTAYG - GG - DYFT SRD IP - PGTEL YW AAFYAKKL LTAYG - GG - QUHFT SRD IP - PGTEL YW AAFYAKKL LTAYG - GG - QUHFT SRD IP - PGTEL YW AAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW AAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW AAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW YAAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW YAAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW YAAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW YAAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW YAAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW YGKD FALL LAWG ISGN YK Y IKDIE - DGEL VW YGKELTELL LAWG ISGN YKY Y KO I CH E PGEL VW YGKELTELL LAWG IGGN YYK Y KO I CH E PGEL VW YGKELTELL LAWG IGGN IYYA I RDIE - IGGEL VW YGKELTELL LAWG LQN - QUYYA I REIG - ADERL VY WGKELTELL LAWG HGG - QIYY YA I REIG - ADERL VW YGKELTELL LAWG HGG - QIYY YA I REIG - ADERL VW YGKE YLG LAWG HGG - QIYY YA I REIG - ADERL VW YGKE YLG LAWG HGG - QIYY YA I REIG - ADERL VW YGKE YLG LAWG HGG - QIYY YA I REIG - ADERL VW YGKE YLG LAWG HGG - QIYY YA I REIG - ADERL VW YGK YLG LAWG - YGG - NYKY YK IG SG CEL VW YGKY YLG LAND - YGG - YGY YR YLG SG CEL VW YGKY YN SNSLAWF LA I ADD GG - QI FY ALROVO - PGEL VW YGK YN SALAWF LAND - YGG - NYKY YK YG YG YGG YGEL CWY YGG YGG YGEL VAFG YKR SI YYR YG YGW I F SG CEL VWY YGG YGG YGEL YAFG - YKR - NYK YG YGW I F SG CEL VWY AAFY AGG</td> <td><math display="block">\begin{array}{c} 135\\ 133\\ 140\\ 128\\ 131\\ 132\\ 126\\ 126\\ 126\\ 126\\ 133\\ 132\\ 224\\ 163\\ 133\\ 132\\ 133\\ 132\\ 133\\ 102\\ 133\\ 102\\ 102\\ 127\\ 128\\ 128\\ 128\\ 128\\ 128\\ 128\\ 128\\ 128</math></td>	VCSWTMFIRLAPSLLEDN CSWTMFVRARTTGEDN ECNWMMFVRARTTGEDN ECNWMFVRARTTGEDN CCNWMFVRARTTGEDN CCWMMFVRARTTGEDN CCWMMFVRARTSEDN CCWMMFVRARDNHLEDN CCWMMFVRADNHLEDN CCWMMFVRADNHLEDN CCWMMFVRADNHLEDN CCWMMFVRADNHLEDN CCWMMFVRADTHEDN CCWMMFVRADTFEDN CCWMMFVRADTFEDN CCWMMFVRADTFEDN CCWMFVRATTFEDN CCWMFVCARTFEDN CCWMFVCARTFEDN CCWMFVCARTFEDN	CTVYR - 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HGS - DYYFT SRD IP - PGTEL YW YAAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW YAAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW YAAFYAKKL LTAYG - HGS - DYYFT SRD IP - PGTEL YW YGKD FALL LAWG ISGN YK Y IKDIE - DGEL VW YGKELTELL LAWG ISGN YKY Y KO I CH E PGEL VW YGKELTELL LAWG IGGN YYK Y KO I CH E PGEL VW YGKELTELL LAWG IGGN IYYA I RDIE - IGGEL VW YGKELTELL LAWG LQN - QUYYA I REIG - ADERL VY WGKELTELL LAWG HGG - QIYY YA I REIG - ADERL VW YGKELTELL LAWG HGG - QIYY YA I REIG - ADERL VW YGKE YLG LAWG HGG - QIYY YA I REIG - ADERL VW YGKE YLG LAWG HGG - QIYY YA I REIG - ADERL VW YGKE YLG LAWG HGG - QIYY YA I REIG - ADERL VW YGKE YLG LAWG HGG - QIYY YA I REIG - ADERL VW YGK YLG LAWG - YGG - NYKY YK IG SG CEL VW YGKY YLG LAND - YGG - YGY YR YLG SG CEL VW YGKY YN SNSLAWF LA I ADD GG - QI FY ALROVO - PGEL VW YGK YN SALAWF LAND - YGG - NYKY YK YG YG YGG YGEL CWY YGG YGG YGEL VAFG YKR SI YYR YG YGW I F SG CEL VWY YGG YGG YGEL YAFG - YKR - NYK YG YGW I F SG CEL VWY AAFY AGG	$\begin{array}{c} 135\\ 133\\ 140\\ 128\\ 131\\ 132\\ 126\\ 126\\ 126\\ 126\\ 133\\ 132\\ 224\\ 163\\ 133\\ 132\\ 133\\ 132\\ 133\\ 102\\ 133\\ 102\\ 102\\ 127\\ 128\\ 128\\ 128\\ 128\\ 128\\ 128\\ 128\\ 128$
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Figure 3. Multiple sequence alignment of the PR domains in different species. Asterisks indicate residues with more than 80% identity, blue boxes indicate shared conserved residues in the PR and SET domains, and red boxes indicate exclusively conserved residues in the PR domains.

## 3.2. Phylogenetic Analysis of Putative M. lateralis PRDMs

The putative PRDM proteins of *M. lateralis* were further confirmed using phylogenetic analysis (Figure 4). In the phylogenetic tree constructed, MI-PRDM1 and MI-PRDM14 displayed the closest phylogenetic relationships with other bivalves. MI-PRDM9 and MI-PRDM15 displayed the closest phylogenetic relationships with C. farreri. MI-PRDM10 exhibited the closest clustering relationship with Crassostrea gigas and MI-PRDM4 clustered with *Crassostrea virginica* and *C. gigas*. In short, *M. lateralis* PRDMs were closely clustered with different molluskan PRDMs and then grouped with vertebrate PRDMs in each family member clade.



**Figure 4.** Phylogenetic analysis of M. lateralis PRDM proteins. Hs: *Homo sapiens;* Mm: *M. musculus;* Gg: *G. gallus;* XI: *Xenopus laevis;* Dr: *Danio rerio;* Sa: *Sparus aurata;* My: *M. yessoensis;* Mc: *Mytilus coruscus;* Cv: *C. virginica;* Cg: *C. gigas;* Pm: *Pecten maximus;* Mg: *Mytilus galloprovincialis;* Pc: *Pomacea canaliculate;* Cf: *C. farreri.* Blue dots indicate M. lateralis PRDMs.

## 3.3. Temporal Expression Pattern of Putative M. lateralis prdms during Early Development Stages

*M. lateralis prdms* exhibited dynamic expression patterns during embryonic and larval stages, which were obtained from the published RNASeq datasets (NCBI accession numbers SRR17520079–SRR17520090) (Figure 5). Three family members (*Ml-prdm9, Ml-prdm13-like, Ml-prdm16-like*) were highly expressed in the blastula; two family members (*Ml-prdm1, Ml-prdm2*) showed the highest expression levels in the gastrula stage; and the highest expression of five members (*Ml-prdm14, Ml-prdm10, Ml-prdm4-like, Ml-prdm12, and Ml-prdm15*) occurred in the trochophore larva stage, whereas only *Ml-prdm8-like* had the highest expression level in the D-shaped larva stage. According to the heatmap, the expression profiles of *Ml-prdm1* and *Ml-prdm14* exhibited a similar trend: the expression level initially increased and then subsequently decreased. However, the highest expression of *Ml-prdm1* occurred earlier than that of *Ml-prdm14*.



Figure 5. Expression profiles of prdm genes during early development stages of M. lateralis.

With the RT-qPCR analysis, it was shown that *Ml-prdm1* started to express at the multicellular stage and reached a peak value when developed to the gastrula stage. The expression decreased at the trochophore larva stage and declined sharply after that (Figure 6). A similar pattern could be seen in *Ml-prdm14*, with the exception that the trochophore larva occupied the highest expression level and the D-shaped larva was second to that.

#### 3.4. Spatial Expression Pattern of M. lateralis prdm1 and prdm14 in Embryo and Larva

To reveal the potential relevance of PRDMs to PGC specification, the spatial distribution of *Ml-prdm1* and *Ml-prdm14* mRNA from fertilized egg to trochophore larva was investigated by carrying out whole-mount in situ hybridization. According to the results, no signals of *Ml-prdm1* or *Ml-prdm14* transcripts were detected in fertilized eggs and multicellular embryos. The signals of *Ml-prdm1* were initially detected in the blastula, but those of *Ml-prdm14* were observed firstly in the gastrula, which was consistent with the temporal expression pattern that *Ml-prdm14* exhibited, with higher expression in later stages compared to *Ml-prdm1*. The signals of *Ml-prdm1* were specifically concentrated in the cytoplasm of two adjacent cells in the blastula and gastrula (Figures 7 and S1). And then, in the trochophore larva, *Ml-prdm1* transcripts were localized in three cells in the middle of the body, and the signals were still mainly located in the cytoplasm. In contrast, the positive signals of *Ml-prdm14* appeared as two or three dots scattered in cell clusters at the edge of the gastrula or trochophore larva, respectively (Figure 7). These

two genes displayed quite distinct expression patterns, implying that they may have different functions.



**Figure 6.** Expression of *Ml-prdm1* and *Ml-prdm14* during early development stages of *M. lateralis*. (**A**,**B**) represented *Ml-prdm1* and *Ml-prdm14*, respectively. Genes expression level of trochophore or gastrula was set as standard 1, respectively, and the expression levels in other stages were indicated as relative fold-change. All data were represented as mean  $\pm$  SD (n = 3). Different letters indicated statistically significant differences (p < 0.05).



**Figure 7.** The localization of *Ml-prdm1* and *Ml-prdm14* transcripts in early development stages of *M. lateralis* detected by whole-mount in situ hybridization.

# 4. Discussion

The number of *prdm* genes identified per species is significantly different, ranging from 2 in the sponge *Oscarella carmela* to 19 in teleosteans [55]. Such differences of gene numbers also exist within each main animal lineage [55]. In lophotrochozoans, 6 to 8 genes can be found in platyhelminthes, whereas in mollusks, the number of *prdm* genes ranges from 8 in *Pinctada fucata* to 13 in *C. gigas* [55]. In the present study, we identified 11 putative PRDMs in both the *M. lateralis* and *C. farreri* genomes. The identified MI-PRDM13-like lacked zinc fingers in this study because of the non-integral nature of its DNA sequence in the genome. However, its deduced amino acid sequences and PR domain were conserved with the PRDM13 of other species, and this member was retained in the present study.

In vertebrates, several PRDM proteins have been shown to possess intrinsic HM-Tase activity similar to that of SET proteins [23,31,58–61], whereas others that lack this intrinsic activity can participate in epigenetic regulation by interacting with enzymes capable of methylating histones or catalyzing other post-translational modifications of chromatin [30,62–64]. Four highly conserved residues shared in the PR and SET domains as well as six well-conserved and unique residues and motifs that are exclusive to the PR domains [55–57] were identified in MI-PRDMs (Figure 2). Furthermore, fourteen residues showed an identity of higher than 80% between *M. lateralis* and vertebrates (Figure 3). These conserved residues and motifs suggest that MI-PRDMs may exert molecular functions similar to those of their vertebrate homologous proteins.

PRDMs are transcriptional factors that regulate many fundamental aspects of cellular differentiation [65]. Transcriptomic analysis revealed that *M. lateralis prdm* genes exhibited dynamic expression patterns during embryonic and larval development (Figure 5). It is worth mentioning that nearly half of the *M. lateralis prdm* genes had the highest expression levels in the trochophore larva, including *Ml-prdm4-like*, *Ml-prdm10*, *Ml-prdm12*, *Ml-prdm14*, and *Ml-prdm15*. In many mollusks, the trochophore stage is the beginning of neurogenesis [66–69]. It has been reported that *prdm4*, *prdm12*, and *prdm14* are involved in vertebrate neurological development [36,70–72]. Therefore, we can presume that these members of the PRDM gene family may have important functions in larval nervous system development.

It was speculated that *Ml-prdm1*-positive cells are putative PGCs or their progenitors in *M. lateralis*. PGCs in mollusks can be recognized in mesodermal tissues around the time of gastrulation [73,74]. In the transcriptomic and quantitative RT-PCR analysis results, we observed the highest expression of *Ml-prdm1* at the gastrula stage (Figures 5 and 6), suggesting that *Ml-prdm1* may be involved in PGC formation in *M. lateralis*. The specific expression patterns of *prdm1* orthologs have been revealed in many organisms, including Drosophila melanogaster [75], G. bimaculatus [21], Petromyzon marinus [76], Strongylocentrotus purpuratus [77], D. rerio [78], X. laevis [79], Ambystoma mexicanum [80], G. gallus [81], and *M. musculus* [13,82], and *prdm1* was identified as the PGC marker in most of these animals. Usually, a subset of cells labeled by marker genes, such as vasa and nanos, are identified as putative PGCs or their precursors in mollusks. Although the expression patterns of these markers throughout embryonic development are not completely the same, the bivalve blastula and gastrula shared a similar subcellular localization of markers, which were restricted to two cells or cell clumps [7–9,43]. In the present study, *Ml-prdm1* exhibited a restricted expression in the embryos and larvae of *M. lateralis*. In the blastula and gastrula, we observed two hybridization signals restricted to only two cells (Figure 7). In the trochophore larva, hybridization signals specifically appeared in three cells without any signals elsewhere (Figure 7). The distribution of *Ml-prdm1* transcripts around the gastrula stage was remarkably similar to some of the putative PGC markers, especially *nanos*, in other bivalves [8,9]. In addition, *Ml-prdm1*-positive cells exhibited slow cell cycles from the blastula to the trochophore larva, and this was also consistent with observations in other mollusks in which PGCs were mitotically quiescent for a period [73,74]. Therefore, we hypothesized that *Ml-prdm1* is a candidate PGC marker gene.

In mice, the expression of *Ml-prdm1* preceded *Ml-prdm14* [16,83,84], and a similar expression pattern was detected in the present study. However, the expression of *prdm14* 

has been detected in presumptive *prdm1*-positive cells representing PGCs and their precursors in mice [16,85]. In contrast, the spatial expression patterns of these two genes in *M. lateralis* were completely different and did not seem to be co-expressed (Figure 7). It has been reported that *prdm14* in *G. bimaculatus* is absent, although *prdm1* has been shown to play an essential role in PGC development, indicating the different roles of *prdm14* [21]. Moreover, we failed to identify an ortholog of the vertebrate *tfap2c* gene either in the transcriptome or in the genome, which is another regulator cooperating with *prdm1* in the specification of murine PGCs [1,84]. Therefore, we assumed that *Ml-prdm14* was probably not expressed in *M. lateralis* PGCs and was dispensable for their specification. This distinction suggested the divergence of the molecular network for PGC formation between vertebrates and invertebrates. Further functional validations should be performed to elucidate the mechanisms of PGC formation in mollusks.

## 5. Conclusions

In the present study, we identified 11 PRDM gene family members in *M. lateralis* based on genome-wide screening. The functional domain compositions, sequence identities, phylogenetic relationships, and expression profiles of the *M. lateralis* PRDMs were uncovered. Furthermore, we investigated the distribution of *Ml-prdm1* and *Ml-prdm14* transcripts during the early developmental stages, ranging from fertilized eggs to trochophore larvae. The results suggested that *Ml-prdm1* may present functional conservation in terms of PGC specification similar to that in vertebrates. This study provides insights into the evolution of PRDMs in mollusks and offers clues for the further investigation of *prdm1* in the formation of PGCs in mollusks.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biology12081059/s1, Table S1: Accession numbers of PRDM protein sequences. Figure S1: The visualization of *Ml-prdm1* expressing cells in early development stages of *M. lateralis*.

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