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Distinct Consequences of *BCOR* and *BCORL1* Mutations in Myeloid Neoplasms and Bone Marrow Failure

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ABSTRACT

BCOR and *BCORL1 (BCOR/L1)* mutations are observed in both myeloid neoplasms (MN) and bone marrow failure syndromes (BMF), but their clinical significance may differ. We analyzed 11 340 patients and identified 418 *BCOR/L1*-mutated patients, focusing on differences between MN and BMF. Compared with MN, BMF was associated with younger age, a higher frequency of normal karyotype, a greater proportion of missense mutations, and significantly lower variant allele frequencies (VAFs). We next compared *BCOR/L1*-mutated cases with wild-type cases. In MN, *BCOR/L1* mutations were associated with older age, inferior survival, and a higher number of co-occurring mutations, whereas in BMF, they were associated with a higher prevalence of PNH clones. Single-cell DNA sequencing and VAF-based analysis demonstrated that *BCOR/L1* mutations were usually secondary in MN but primary events in BMF. Longitudinal sequencing revealed that *BCOR/L1*-mutant clones often contracted or disappeared over time, even in progression, suggesting limited clonal fitness of *BCOR/L1* mutations themselves; instead, progression was associated with increased mutational burden, particularly in *RUNX1*. Prognostically, *BCOR/L1* mutations were associated with inferior survival in MN, whereas in BMF they were not associated with prognosis and tended to correlate with a favorable response to immunosuppressive therapy. RNA-sequencing analyses showed reduced BCOR/L1 expression in BMF, and BCOR knockout was associated with reduced HLA class I expression. Our findings suggest that *BCOR/L1* mutations are secondary events in MN and co-occurring mutations may influence disease progression and prognosis, whereas in BMF they appear to be ancestral events acquired independently of progression to MN, potentially through immune privilege-related mechanisms.

Valeria Visconte and Jaroslaw P. Maciejewski contributed equally to this study.

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1 | Introduction

The homologous *BCOR* and *BCORL1* (*BCOR/L1*) genes act as epigenetic regulators and components of the polycomb repressive complex (PRC1.1) [1]. In fact, polycomb group genes such as PCGF1 bind to the C-terminal PUFD domain of BCOR to form together with KDM2B and RING1A/B the noncanonical PRC1.1 complex [1]. PRC1.1 catalyzes the ubiquitination of histone H2A at lysine 119 (H2AK119ub), which is linked to PRC2-mediated histone H3K27 methylation. In addition, KDM2B, a component of PRC1.1, directly demethylates histone H3K36me2 via its JmjC domain [1].

Somatic *BCOR* mutations are found in approximately 5% of patients with acute myeloid leukemia (AML) and in 5% of patients with myelodysplastic syndromes (MDS). *BCORL1* mutations are present in about 5% of AML and 1% of MDS patients [1–3]. In AML, *BCOR* mutations are classified as an adverse risk factor in the European Leukemia Net 2022 (ELN2022) guidelines [1, 3–6]. The poor prognosis ascribed to *BCOR/L1* mutations has been attributed to the chemotherapy resistance observed in murine models and further explained by activation of stemness and pro-oncogenic signaling pathways due to a marked reduction of PRC1.1 abundance and function [7, 8].

Increased stem and progenitor cell fitness is also consistent with the observation that *BCOR* mutations are detected in approximately 10% of patients with aplastic anemia (AA), a frequency significantly higher than would be expected from age-related clonal hematopoiesis alone [9, 10]. Notably, however, *BCOR/L1* mutations in AA are associated with a favorable prognosis, including a good response to immunosuppressive therapy (IST), and are inversely associated with progression to myeloid neoplasia (MN) [9, 11]. Furthermore, in a longitudinal next-generation sequencing (NGS) study of 237 patients with AA undergoing IST, somatic mutations were detected in 41% of patients after IST. Whereas mutations in genes such as *ASXL1* were associated with clonal expansion, clones harboring *BCOR* or *PIGA* mutations tended to decrease in size or remain stable [12]. Collectively, these findings suggest that *BCOR* mutations which are known to promote disease progression in MN, may be acquired for distinct biological reasons in the context of bone marrow failure (BMF). It remains unclear whether this observation can be explained by a somatic genetic rescue mechanism or instead reflects a selective advantage within the hematopoietic stem cell compartment in AA.

Clinical observations in MN and BMF suggest that identical *BCOR/L1* mutations can have markedly different roles depending on disease context. This study was conducted to clarify the genetic, clinical characteristics, and disease-specific roles of *BCOR/L1* mutations.

2 | Methods

2.1 | Patients

This research was conducted under the Institutional Review Boards of Cleveland Clinic Foundation (CCF) (IRB #5024) and participating institutions, and all samples were collected after written informed consent in accordance with the Declaration of Helsinki. Samples were collected from the following cohorts: CCF, Munich Leukemia Laboratory (MLL), St. Jude Children's Research Hospital, and publicly available datasets (Supplementary Table 1) [2, 13–18]. We also used the Beat AML cohort, MLL cohort, GSE80062 [19], and GSE167869 [8] for RNA expression data. Single-cell DNA sequencing (scDNA-seq) data was provided by The MD Anderson Cancer Center, the Lewis Katz School of Medicine at Temple University, and St. Jude Children's Research Hospital. Beat AML data was used for drug sensitivity analyses [14], and cellular-level gene expression was analyzed using the *Normal hematopoiesis with AMLs* dataset available through BloodSpot [20].

2.2 | Disease Definition and Clonal Hierarchy Criteria

MN was defined as AML, MDS, myelodysplastic/myeloproliferative neoplasm (MDS/MPN), and myeloproliferative neoplasm (MPN), while BMF was defined as AA, paroxysmal nocturnal hemoglobinuria (PNH), and clonal hematopoiesis of indeterminate potential/clonal cytopenia of undetermined significance (CHIP/CCUS). Bi-allelic mutations were defined as the presence of ≥ 2 mutations in *BCOR/L1* genes within the same patient. All diseases with $<5\%$ BM blasts were classified as low risk (LR), whereas those with $\geq 5\%$ BM blasts were classified as high risk (HR); for MN, except for AML, these categories were defined as LR-cMN (chronic myeloid neoplasm) and HR-cMN, respectively. The breakdown of patients in the HR and LR groups is provided in Supplementary Table 2. Disease progression ("progressed") was defined as an increase in BM blasts to $\geq 5\%$ or progression from BMF or CHIP/CCUS to MN. For *BCOR/L1* variant allele frequency (VAF) $<10\%$ as low VAF, and $\geq 10\%$ as high VAF. For genes located on the X chromosome, VAF values were adjusted to 50% in male patients. Furthermore, primary and secondary *BCOR/L1* mutations were defined based on the difference between the VAF of *BCOR/L1* and the highest VAF among co-occurring mutations: cases with a difference of $\geq 5\%$ or without any co-occurring mutations were classified as primary, those with a difference of $\leq -5\%$ were classified as secondary, and those with a difference between -5% and $<5\%$ were classified as unknown according to VAF-based analysis [21, 22].

2.3 | Genetic Studies

For the data collected at CCF, whole-exome or target sequencing was performed on paired tumor and germline DNAs (purified CD3-lymphocytes) (Supplementary Table 3). Libraries were captured using SureSelect Human All Exon 50 Mb or V4 Kit (Agilent Technologies), and captured targets were sequenced using a HiSeq 2000/2500/X (Illumina). Reads were aligned to the human genome (hg19) using BWA. Data were validated using a TruSeq Custom Amplicon Kit (Illumina). Variants were annotated using Annovar and filtered by in-house bioanalytic pipeline [23]. Variants in patients from the MLL and St. Jude cohorts were called as previously reported [18, 24]. Open-source data derived from whole-exome sequencing from Beat AML and TCGA, and targeted capture sequencing patients from The German-Austrian AML study, the King's College Hospital, Penn-CHOP Comprehensive BMFS Center, and RACE cohort. The gene sequencing methods of publicly shared data were previously described [2, 13–17].

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scDNA-seq data from collaborating institutions were analyzed using SCITE or BSCITE as previously described [25, 26]. For BMF cases, H5 files were generated according to published methods [18]. Genotypes with DP < 10, GQ < 30, or 0 < AF < 20% were treated as missing, whereas genotypes with AF ≥ 20% were considered mutation-positive. Cells with a genotype present fraction < 0.50 were excluded, as were variants present in > 40% of cells, < 1% of cells, or fewer than 30 mutated cells. The clonal hierarchy was inferred using SCITE. For phylogenetic tree visualization, pathologic variants included Tier 1 or 2 by VarSome [27] and literature-reported disease-associated Tier 3 variants.

RNA expression analyses were conducted using the Beat AML and MLL cohorts, as well as public datasets (GSE80062 and GSE167869) [8, 19]. Cellular composition was estimated using CIBERSORTx [28], and gene expression values were further adjusted using linear models that included the estimated proportions of BCOR-expressing cell populations, including neutrophils, monocytes, and hematopoietic stem cells, as covariates.

2.4 | Statistical Analysis

For univariate analyses, continuous variables were analyzed using the Mann–Whitney *U* test (or the Kruskal–Wallis test for comparisons involving ≥ 3 groups), and categorical variables were analyzed using Fisher's exact test. Survival analyses were performed using the log-rank test. For multivariate analyses, continuous variables were dichotomized at the median and analyzed using logistic regression. Variable selection was performed using a stepwise method based on the Akaike Information Criterion. For prognostic analyses, Cox proportional hazards models were applied, with hematopoietic stem cell transplantation treated as a time-dependent covariate. In addition, when assessing correlations, both *p* values and Pearson correlation coefficients (*r* values) were calculated. All statistical analyses were performed using RStudio (version 2023.09.1+494) and GraphPad Prism (version 10.6.1).

3 | Results

3.1 | Study Cohort

In total, 11 340 patients diagnosed with AML, MDS, MDS/MPN, MPN, CHIP/CCUS, AA, and PNH were included in this study based on sample and clinical information availability (Table 1), and 116 healthy controls were included in bulk RNA-sequencing analysis. Bulk RNA-sequencing analysis was performed in a total of 1319 individuals (BeatAML: AML, 401; healthy control, 21; and sorted-CD34, 12; MLL: AML, 5; HR-cMN, 308; LR-cMN, 472; BMF, 36; healthy controls, 64).

3.2 | BCOR/L1 Mutational and Expression Analysis in Hematologic Disease

Since *BCOR/L1* are located on the X chromosome, we compared BCOR/L1 mRNA expression levels between males and females using bulk RNA-sequencing, but found no significant difference, suggesting complete lyonization. When we compared BCOR/L1 expression between control blood and sorted-CD34+ cells, BCOR expression tended to be higher in CD34+ cells ($p = 0.063$) (Supplementary Figure1A,B). Comparison of BCOR/L1 expression across different hematopoietic cell types showed that BCOR was predominantly expressed in multipotent progenitors and common myeloid progenitors, whereas BCORL1 expression was observed mainly in mature myeloid, myeloid progenitor, and B-cell populations (Supplementary Figure 1B). Therefore, in addition to batch effect correction, adjustment for cellular composition was also applied in all comparisons (Supplementary Figure 2A–C).

Mutational analysis, as summarized in Supplementary Table S2, identified 497 *BCOR/L1* alterations in 444 of 11 340 patients. After exclusion of germline alterations (Supplementary Figure 3), 470 somatic mutations were identified in 418 patients. Mutations were scattered through the gene without any canonical position (Figure 1A). Furthermore, the pathogenicity of somatic missense variants was assessed using PRECISE (MutFunc), and all variants with a score of 0.6 or higher were observed exclusively in patients with MN (Supplementary Table S4) [29]. *BCOR/L1* mutations were significantly more frequent in males (male 4.0% vs. female 3.4%, $p = 0.036$) (Table 1); among the affected cases, 377 mono-allelic and 41 cases with > 1 mutation were identified. As both men and women were affected (Male:Female ratio of 1.5, OR: 0.96, SE: 0.33), we concluded that most of the double mutant cases correspond to clonal mosaicism. Looking at co-occurring events, *IDH1* mutations ($p = 0.013$) were significantly more frequent in bi-allelic cases, while *EZH2* mutations tended to be less frequent in bi-allelic cases ($p = 0.060$) (Supplementary Table 5).

Cytogenetic analysis showed that *BCOR/L1* mutations were significantly less common in core-binding factor AML (CBF-AML; $p < 0.001$), t(15;17; $p < 0.0001$), and *KMT2A*-rearranged patients ($p = 0.003$) versus those with normal karyotype (Figure 1C). When analyzed irrespective of diagnosis, mutations in *DNMT3A* and *ASXL1* tended to co-occur with *BCOR/L1*, whereas *FLT3* mutations, complex karyotypes, and *NPM1* mutations were less frequently observed. Multivariate analysis further demonstrated that *U2AF1* ($p = 0.02$), *DNMT3A* ($p < 0.001$), *PTPN11* ($p = 0.03$), *WT1* ($p = 0.03$), and *RUNX1* ($p < 0.0001$) were significantly associated with *BCOR/L1* mutations (Figure 1D,E). *BCOR/L1* mutations in MN most frequently co-occurred with *RUNX1* mutations; indeed, 167/418 patients harbored both *BCOR/L1* and *RUNX1* mutations. Among the 418 cases with *BCOR/L1* mutations, *RUNX1* mutations were classified as germline or somatic, with 21 and 103 cases identified, respectively (Supplementary Figure 3, Supplementary Figure 4A). However, no differences in clinical characteristics, mutational profiles, or prognosis were observed (Supplementary Table 6, Supplementary Figure 4B). When subcategorized according to the functional impact [30, 31], the distribution of *BCOR/L1* mutations was not different (Supplementary Table 7, Supplementary Figure 4C). In general, VAF of *BCOR/L1* was significantly lower in the HR than in the LR and in females than in males, whereas no significant difference in VAF was observed between missense (MS) + in frame (IF) and frameshift (FS) + nonsense (NS) + splice site (SP) groups (Figure 1F). Using drug sensitivity (Beat AML dataset) [14], *BCOR/L1*-mutated AML showed higher sensitivity to the PARP inhibitor XAV-939, RAF265, and crizotinib compared with wild-type AML (Figure 1G).

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TABLE 1 | Patients' clinical characteristics.

Characteristics			Number	*BCOR* mutations (%)*	*BCORL1* mutations (%)*
Number of patients			11 340	3.5	1.3
Age	Median (range)		67 (2–100)		
	< 67		4761	2.2	1.2
	≥ 67		5013	4.3	1.2
	NA		1566	2.4	1.1
Sex	Male		6147	3.8	1.4
	Female		5191	3.1	1.2
	NA		2	0.0	0.0
Disease	AML (63.8)	pAML	5775	3.1	3.1
		sAML	1431	4.4	1.8
		NA	30	3.3	0.00
	MDS (14.6)	IB	533	8.1	1.5
		LB	582	3.1	0.3
		MDS-5q	141	1.4	0.0
		MDS-SF3B1	282	2.5	0.0
		MDS-biTP53	4	25.0	0.0
		Others**	109	0.0	0.0
	MDS/MPN (6.3)	CMML	313	3.2	0.0
		MDS/MPN with neutrophilia	28	7.1	7.1
		MDS/MPN with SF3B1 and thrombocytosis	85	2.4	0.0
		MDS/MPN not otherwise specified	153	2.6	0.0
		Others**	131	2.04	0.0
	MPN (5.3)	CML	109	0.0	0.0
		CNL	5	20.0	0.0
		ET	151	3.3	0.7
		PV	149	0.0	0.7
		PMF	67	3.0	3.0
		MPN-NOS	56	0.0	0.0
		Other**	62	0.0	0.0
	CHIP/CCUS (1.9)	CHIP	87	1.1	1.10
		CCUS	132	6.1	2.3
	AA/PNH (8.2)	AA	859	5.8	1.0
		PNH	66	3.3	1.7

Abbreviations: AA, aplastic anemia; AML, acute myeloid leukemia; CCUS, Clonal Cytopenia of Undetermined Significance; CHIP, Clonal Hematopoiesis of Indeterminate Potential; CMML, chronic myelomonocytic leukemia; CML, chronic myelogenous; CNL, chronic neutrophilic leukemia; ET, essential thrombocythemia; IB, increased blasts; LB, low blasts; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; NA, not available; pAML, primary acute myeloid leukemia; PMF, primary myelofibrosis; PNH, paroxysmal nocturnal hemoglobinuria; PV, polycythemia vera; sAML, secondary acute myeloid leukemia.
*_BCOR_ was evaluated in 11 024 cases, and _BCORL1_ was evaluated in 5137 cases.
**Others are cases without any subtype classification provided.

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Analysis of public datasets (GSE80062) showed that BCOR/L1 expression was reduced in BMF compared with healthy controls and that BCOR/L1 expression was lower in PNH clones than in non-PNH clones (Figure 1H). In addition, multivariable analysis comparing the low (BCOR bottom 25% expression) with normal and high BCOR/L expressors (top 75%), female, MN, *IDH2*, and

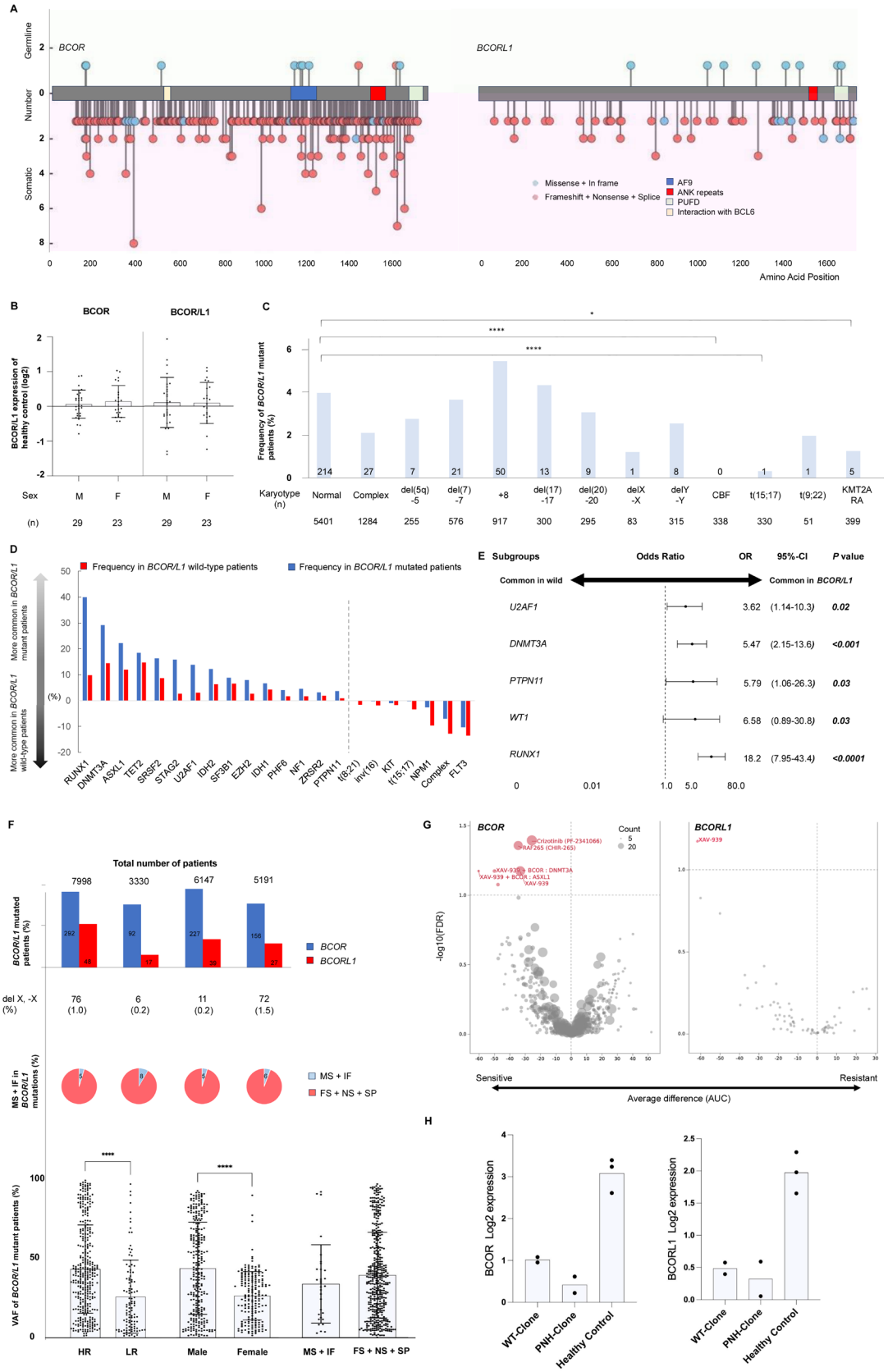

FIGURE 1 | Legend on next page.

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FIGURE 1 | Characteristics of *BCOR/L1*-mutated patients. (A) Lollipop plot in *BCOR/L1* mutations. (B) Comparison of BCOR/L1 expression between healthy males and females based on MLL RNA sequencing data. (C) *BCOR/L1* mutated frequency across chromosomal abnormalities. (D) Characteristics of gene mutations in *BCOR/L1*-mutated and wild-type patients. Only genes with $p < 0.05$ are shown. (E) Forest plot of co-mutated genes and karyotype between *BCOR/L1*-mutated and wild-type cases. Variables with $p < 0.05$ were included in the multivariate analysis. (F) *BCOR/L1* mutated frequency, VAF, and type of mutations (HR vs. LR, male vs. female, and MS + IF vs. FS + NS + SP). (G) Drug sensitivity in *BCOR/L1*-mutated versus wild-type patients based on Beat AML [2]. (H) Comparison of BCOR/L1 expression among healthy controls, PNH clones, and non-PNH clones in aplastic anemia (GSE80062). BCOR/L1, BCOR and BCORL1; F, female; FS, frameshift; HR, high risk; IF, in frame; LR, low risk; M, male; SP, splice; VAF, variant allele frequency.

SF3B1 mutations were significantly less frequent, whereas *PHF6* and *PTPN11* mutations were overrepresented. For BCORL1, ≥ 3 gene mutations, *SRSF2*, and *TET2* mutations were significantly less frequent in BCORL1 bottom 25%, while trisomy 8 was more common (Supplementary Table 8).

3.3 | Comparison of Mutational Landscape of BCOR/L1 Mutant MN and BMF Patients

We then compared the clinical features, topography, demographics, and genetics of *BCOR/L1* mutant cases in BMF and MN. When the frequency of *BCOR/L1* mutations was compared across disease categories, *BCOR* mutations were frequent in secondary AML (sAML) (4.4%), MDS (4.3%), and AA/PNH (5.6%), whereas *BCORL1* mutations were common in primary AML (pAML) (3.1%). In CHIP/CCUS, *BCOR/L1* mutations were detected in 4.1% and 1.8% of cases, respectively. BMF showed lower clonal burden than pAML ($p < 0.0001$), sAML ($p < 0.0001$), MDS ($p = 0.006$), and MDS/MPN ($p = 0.012$). When cases were compared after stratification into MN and BMF, BMF showed a trend toward a higher frequency of MS + IF than MN ($p = 0.062$), while VAF was significantly lower in BMF ($p < 0.0001$) (Figure 2A). *BCOR/L1*-mutated patients were most frequent in patients aged ≥ 71 years in MN, while in BMF they were most common in the 31–40-year age group (Figure 2B). In multivariate analysis, MN was significantly associated with the presence of co-occurring mutations ≥ 3 ($p < 0.0001$), whereas BMF was significantly associated with a normal karyotype ($p = 0.003$) and delY/-Y ($p < 0.001$). Sex was not a significant factor (Figure 2C). Focusing on co-occurring mutations in MN and BMF, *BCOR/L1*-mutated cases were accompanied by additional mutations in 93% of MN and 53% of BMF cases. The top three affected genes in MN were *RUNX1*, *DNMT3A*, and *ASXL1*, whereas those in BMF were *DNMT3A*, *PIGA*, and *ASXL1* (Figure 3A). Compared with wild-type cases, in MN, *BCOR* mutations tended to co-occur with *RUNX1*, *STAG2*, *U2AF1*, and *BCORL1* mutations, while *BCORL1* mutations were more likely to co-occur with *RUNX1* and *BCOR* mutations. Conversely, in BMF, *BCOR* mutations were more likely to co-occur with *U2AF1* and *STAG2* mutations, whereas *BCORL1* mutations were more likely to co-occur with *STAG2* mutations (Figure 3B).

3.4 | Comparison of Clinical Outcomes of BCOR/L1 Mutant MN Versus BMF

Patients with BMF were younger than those with MN and more frequently had a normal karyotype (Table 2). Survival analysis focusing on AML and HR-cMN was performed for MN. In AML, univariate analysis showed that *BCOR* mutations were associated with shorter overall survival (OS), whereas *BCORL1* mutations were rather linked to longer OS; however, neither mutation was identified as an independent prognostic factor in multivariate analysis. In HR-cMN, *BCOR* mutations were associated with shorter OS in univariate analysis and multivariate analysis (Supplementary Table 9). In *BCOR/L1*-mutated AML, age ≥ 68 years, male, sAML, and a complex karyotype were associated with shorter OS, whereas 3 + 7-based chemotherapy was associated with longer OS. In multivariate analysis, age ≥ 68 years and co-occurring *KDM6A* mutations were independently associated with shorter OS (Supplementary Table 10). In *BCOR/L1*-mutated HR-cMN, *ASXL1* and *EZH2* mutations were independently associated with shorter OS (Supplementary Table 11). In contrast, in BMF (AA/PNH only), age ≥ 44 years and *DNMT3A* mutations were associated with shorter OS, whereas PNH and *PIGA* mutations heralded a significantly longer OS. In multivariate analysis, age ≥ 44 years and *PIGA* mutations were identified as prognostic factors. Similar results were observed for progression-free survival (PFS), and *BCOR/L1* mutations were not associated with either OS or PFS (Supplementary Table 12).

Taken together, in MN, *BCOR/L1* mutations tended to be more frequently observed in males ($p = 0.067$), were more frequent in patients aged ≥ 68 years ($p < 0.001$), were associated with shorter OS ($p < 0.001$), and occurred in the context of ≥ 3 mutations ($p < 0.0001$). In contrast, in BMF, *BCOR/L1* mutations were significantly associated with the presence of a PNH clone ($p < 0.001$) and showed a trend toward a better response to IST, although this did not reach statistical significance ($p = 0.150$). In addition, patients with *BCOR/L1* mutations in BMF (AA/PNH only) tended to have ≥ 2 co-occurring mutations ($p = 0.051$; Figure 2D).

3.5 | Expression Analysis in MN and BMF

When we compared BCOR/L1 mRNA levels among MN, BMF, and healthy controls, BCOR/L1 expression was significantly decreased in BMF compared with both healthy controls and MN (Figure 3C). Given the selection of *BCOR/L1* mutations in BMF, we compared the expression of immune-related genes (Supplementary Table 13) between *BCOR/L1*-mutated and wild-type cases in MN and BMF. In the public dataset comparing BCOR knockout and WT cells (GSE167869), HLA Class I gene expression was decreased and VSIR increased in BCOR knockout cells. However, no individual immune-related gene showed

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consistent alterations across all cohorts, nor did their expression correlate with the clonal burden (Supplementary Tables 14, 15). Pathway-level comparison between *BCOR/L1*-mutated and wild-type patients showed that enhanced activation-related pathways, such as MHC Class II antigen presentation, were more pronounced in BMF versus MN (Supplementary Figure 2D).

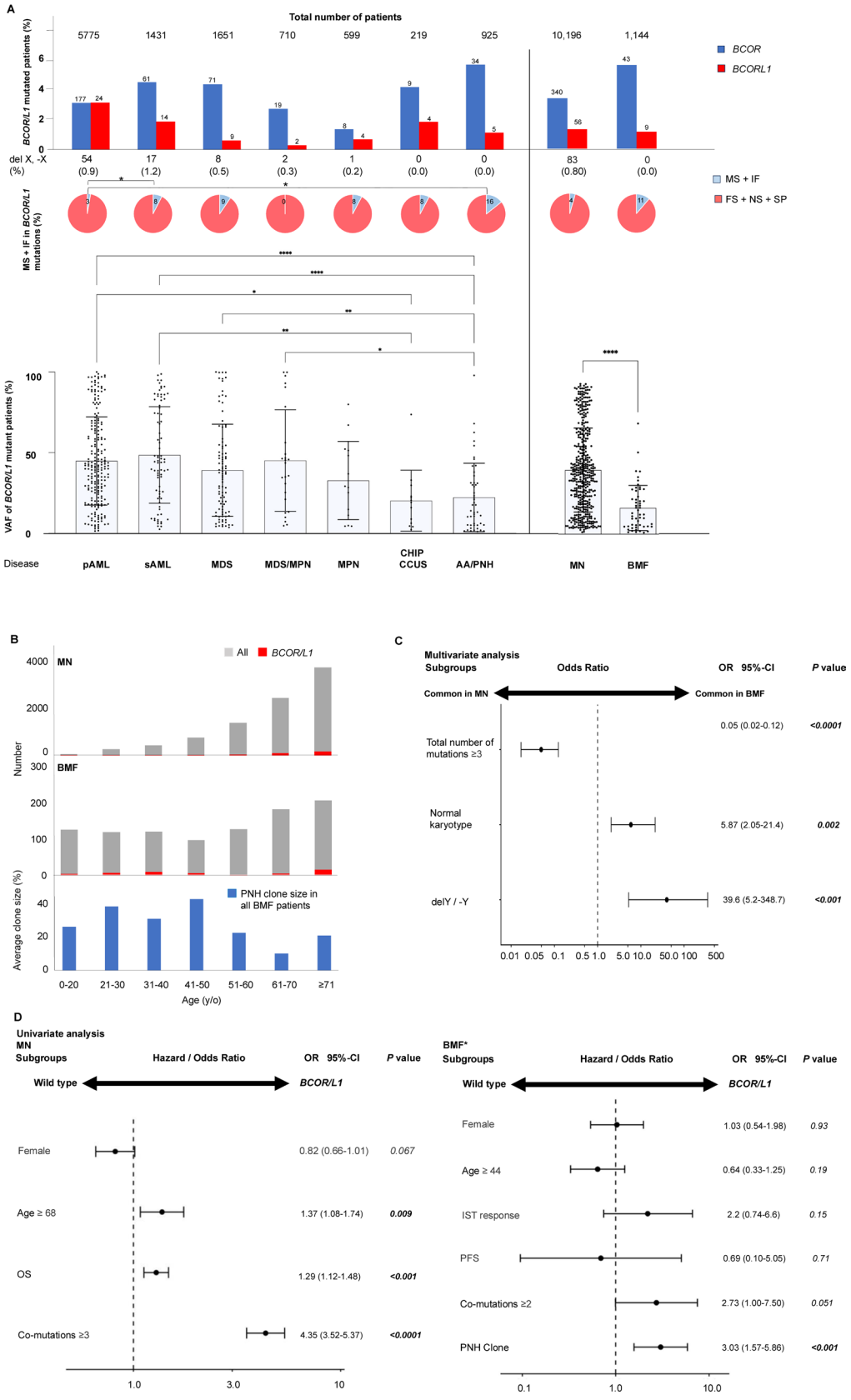

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FIGURE 2 | Distribution of *BCOR/L1* mutations in MN and BMF. (A) *BCOR/L1* mutated frequency, VAF, and type of mutations among disease types. (B) *BCOR/L1* mutation frequency across different ages. (C) Forest plot between MN and BMF. Univariable analyses were performed for the following variables: Age ≥ 70 years, sex, *BCOR/L1* mutation type (MS + IF vs. FS + NS + SP), normal karyotype, complex karyotype, del(5q)/−5, trisomy 8, del(20q)/−20, del(17p)/−17, del(7q)/−7, del(X)/−X, del(Y)/−Y, t(8;21), inv (16), and the presence of ≥ 3 gene mutations. Variables with $p < 0.10$ were included in the multivariate analysis. (D) Clinical characteristics between *BCOR/L1*-mutated and wild patients in MN and BMF patients. *For this analysis, BMF was limited to AA and PNH. AML, acute myeloid leukemia; BMF, bone marrow failure; BCOR/L1, BCOR and BCORL1; CHIP, Clonal Hematopoiesis of Indeterminate Potential; CCUS, Clonal Cytopenia of Undetermined Significance; FS, frameshift; HR, high risk; IF, in frame; IST, immune suppressive therapy; LR, low risk; MDS, myelodysplastic syndrome; MN, myeloid neoplasm; MS, missense; MPN, myeloproliferative neoplasms; NS, nonsense; OS, overall survival; pAML, primary acute myeloid leukemia; PFS, progression free survival; PNH, paroxysmal nocturnal hemoglobinuria; sAML, secondary acute myeloid leukemia; SP, splice; VAF, variant allele frequency.

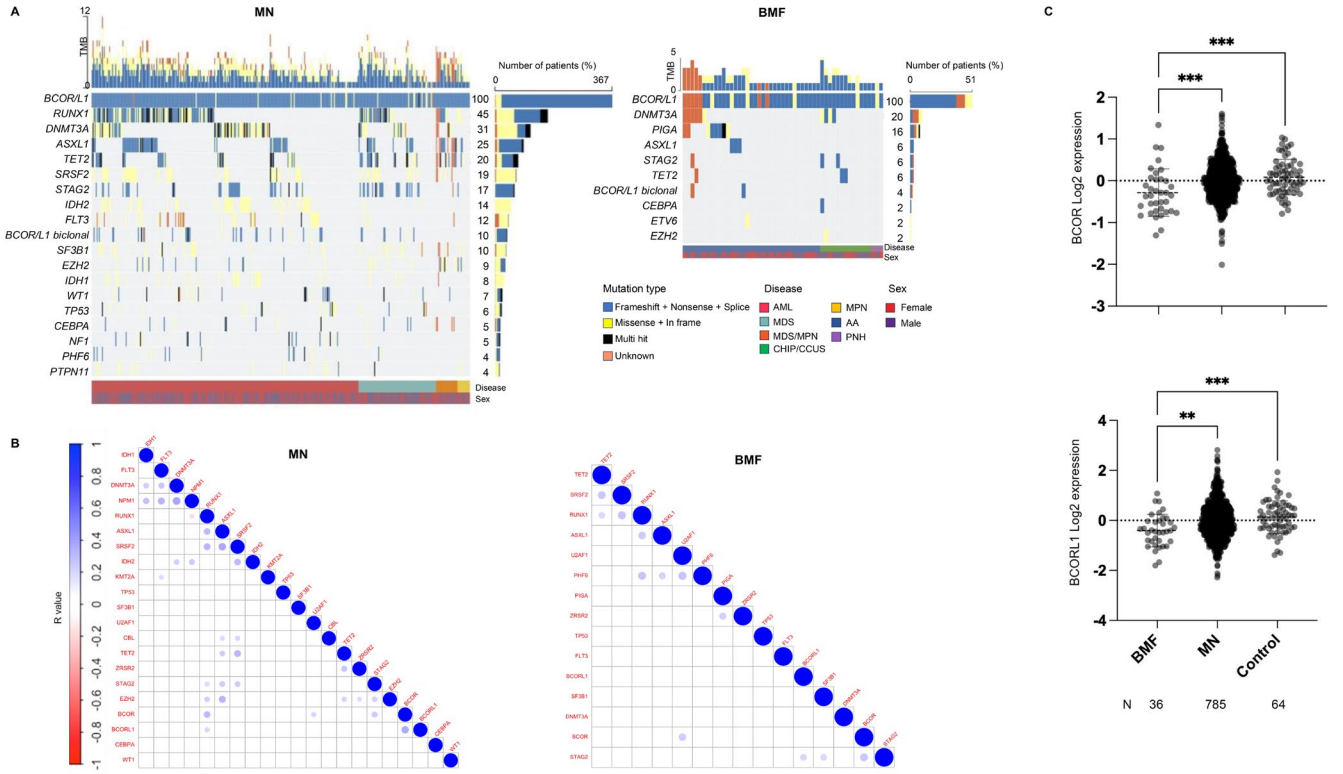

FIGURE 3 | Co-occurring mutations and expression analysis between MN and BMF. (A) Waterfall plot between MN and BMF. (B) Characteristics of co-mutations among MN and BMF. We analyzed the top 20 genes of MN, including *BCOR/L1*, as well as the top 15 of BMF. Only p value < 0.05 and r value > 0.1 or −0.1 > were shown. (C) Comparison of BCOR/L1 expression among BMF, MN, and control groups after adjustment for batch effect and cell composition (MLL). AML, acute myeloid leukemia; BMF, bone marrow failure; BCOR/L1, BCOR and BCORL1; CHIP, Clonal Hematopoiesis of Indeterminate Potential; CCUS, Clonal Cytopenia of Undetermined Significance; FS, frameshift; IF, in frame; MDS, myelodysplastic syndrome; MN, myeloid neoplasm; MS, missense; MPN, myeloproliferative neoplasms; NS, nonsense; PNH, paroxysmal nocturnal hemoglobinuria; SP, splice; VAF, variant allele frequency; WT, wild-type.

3.6 | Comparison of Clonal Architecture Between MN and BMF Using scDNA-Seq

Using a VAF-based analysis [21, 22], we subclassified *BCOR/L1* mutations as primary or secondary events. In MN, 60 patients (16%) were classified as primary and 226 patients (59.5%) as secondary, whereas in BMF, 22 cases (58%) were primary and 9 cases (24%) were secondary, indicating that primary *BCOR/L1* mutations were significantly more frequent in BMF ($p < 0.0001$) (Figure 4A). Next, scDNA-seq revealed that, in all AML cases, *BCOR/L1* mutations were not primary events but rather secondary events showing a linear pattern of clonal evolution (Figure 4B–E). In two patients, *BCOR/L1* mutations co-occurred with *RUNX1* mutations, and *RUNX1* was inferred to have been acquired earlier than *BCOR/L1* (Figure 4B,D). In contrast, among AA patients, *BCOR/L1* was identified as a primary event in one case (Figure 4F), whereas in another case, *BCOR* mutation was classified as a secondary event but was acquired early in the clonal ontogenesis (Figure 4G). Taken together, these findings suggest that *BCOR/L1* mutations are acquired as late secondary events in MN, whereas in BMF they occur as primary or early clonal events.

3.7 | Longitudinal Dynamics of BCOR/L1-Mutated Clones Between MN and BMF

Among the 418 patients with *BCOR/L1* mutations, 64 underwent longitudinal NGS analysis. Of these, 14 patients (14 mutations) were classified as BMF, and 50 patients (64 mutations) were classified as MN (Figure 5A). In treatment-refractory MN

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TABLE 2 | Clinical characteristics of *BCOR/L1*- mutated MN and BMF.

	MN ($n=367$)	BMF ($n=51$)	*p value*
Age at diagnosis, median years old (range)*	71.0 [19.0, 94.0]	37.0 [2.0, 91.0]	***<0.001***
Sex, male	221 (60.2)	27 (52.9)	*0.362*
Date at diagnosis, median year (range)**	2015 [2003, 2025]	2022.5 [1980, 2025]	***0.017***
BCOR/L1 mutation			*0.068*
BCOR	311 (84.7)	42 (82.4)	
BCORL1	27 (7.4)	8 (15.7)	
BCOR & BCORL1	29 (7.9)	1 (2.0)	
BCOR/L1 mutation type***			***0.045***
Frameshift	172 (47.0)	20 (44.4)	
Nonsense	113 (30.9)	11 (24.4)	
Splice	26 (7.1)	6 (13.3)	
Inframe	3 (0.8)	0 (0.0)	
Missense	13 (3.6)	6 (13.3)	
Multihit	39 (10.7)	2 (4.4)	
BCOR/L1 VAF	40.60 [1.40, 100.00]	14.00 [1.06, 73.70]	***<0.001***
Type of disease			
AML	259 (70.6)	0 (0.0)	***<0.001***
MDS	75 (20.4)	0 (0.0)	
MDS/MPN	21 (5.7)	0 (0.0)	
MPN	12 (3.3)	0 (0.0)	
CHIP/CCUS	0 (0.0)	13 (25.5)	
AA	0 (0.0)	35 (68.6)	
PNH	0 (0.0)	3 (5.9)	
Karyotype****			***0.002***
Normal	189 (54.0)	25 (73.5)	
Complex	27 (7.7)	0 (0.0)	
Del7/7q	13 (3.7)	2 (5.9)	
Other mutations	121 (34.6)	7 (20.6)	

Note: Bold values indicate statistically significant results ($p<0.05$).
Abbreviations: AA, aplastic anemia; BMF, bone marrow failure; CHIP, Clonal Hematopoiesis of Indeterminate Potential; CCUS, Clonal Cytopenia of Undetermined Significance; MDS, myelodysplastic syndrome; MDS/MPN, myelodysplastic myeloproliferative neoplasms; MN, myeloid neoplasms; MPN, myeloproliferative neoplasms; PNH, paroxysmal nocturnal hemoglobinuria; VAF, variant allele frequency.
*Age information was unavailable for 33 cases.
**Date at diagnosis information was unavailable for 98 cases.
***_BCOR/L1_ mutation type was unknown for 7 cases.
****Karyotype of 34 patients are unknown.

cases harboring *BCOR/L1* mutations, expansion of the *BCOR/L1*-mutant clone was not observed; rather, a decrease or disappearance of the clone was noted in 42% of patients (Figure 5B). Although only three BMF cases progressed to MN, one showed disappearance of the *BCOR/L1*-mutant clone at progression, and clonal disappearance or decrease was also observed in 55% of the non-progressed cases (Figure 5C). At progression, patients acquired an average of 1.8 new mutations, including *RUNX1* mutations, suggesting that acquisition of additional, rather than *BCOR/L1* mutations themselves, may be associated with disease progression (Figure 5D).

Among 94 patients with *BCOR/L1*-mutated BMF or LR-cMN who could be evaluated longitudinally, we compared the non-progressors to progressors. The latter included more patients with LR-cMN and showed significantly higher VAF, a greater number of coexisting mutations, and enrichment for *ASXL1, EZH2, RUNX1*, and *TET2* (Supplementary Table 16). FISH plot analysis

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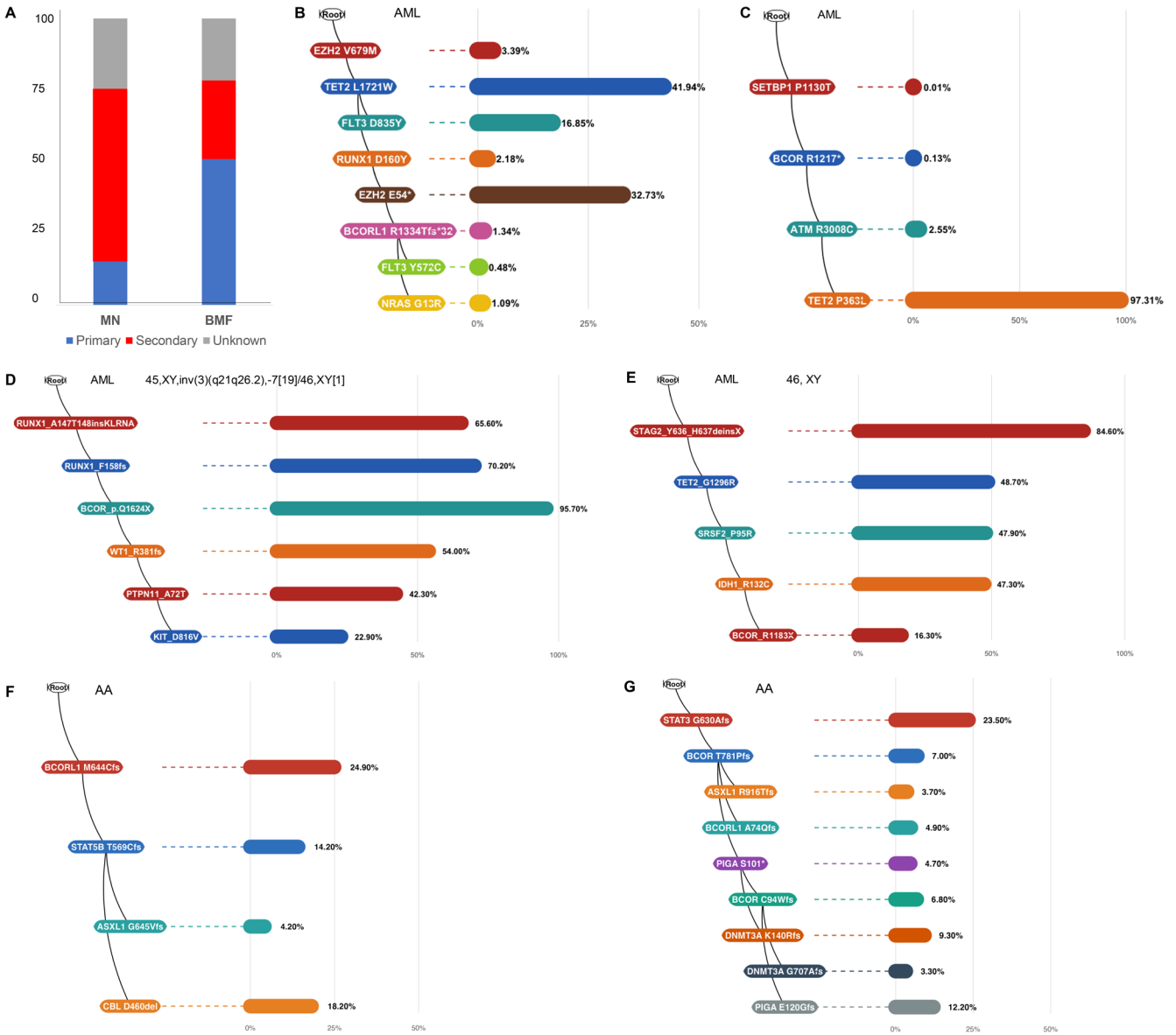

FIGURE 4 | Comparison of clonal architecture between MN and BMF using scDNA-seq. (A) Comparison of *BCOR/L1* mutations as primary versus secondary events in MN and BMF with VAF-based analysis. (B) AML. SCITE-based phylogenetic tree from scDNA-seq [26]. (C) AML. SCITE-based phylogenetic tree from scDNA-seq [26]. (D) AML. BSCITE-based phylogenetic tree from scDNA-seq [25]. (E) AML. BSCITE-based phylogenetic tree from scDNA-seq [25]. (F) AA. SCITE-based phylogenetic tree from scDNA-seq. (G) AA. SCITE-based phylogenetic tree from scDNA-seq. AA, aplastic anemia; AML, acute myeloid leukemia; BMF, bone marrow failure; MN, myeloid neoplasm; scDNA-seq, single-cell DNA sequencing.

of two exemplary relapsed AML cases also showed that while new somatic hits were acquired, *BCOR/L1* mutations were no longer detectable at relapse (Figure 5E,F). Similarly, in a *BCOR/L1*-mutated AA case with AML evolution, the *BCOR* mutation was no longer detectable at the AML stage, whereas new mutations in *RUNX1*, *CSF3R*, *ASXL1*, and *U2AF1* emerged. Following therapy at relapse, an additional *PHF6* mutation was acquired (Figure 5G). In another two responders to IST, the *BCOR* mutation became undetectable over time, with concomitant expansion of the *PIGA*- or *DNMT3A*-mutated clone (Figure 5H,I).

4 | Discussion

In this study, we conducted the largest analysis of *BCOR/L1* mutations across hematologic disease. The contrasting presence of *BCOR/L1* mutations in MN and BMF is striking. Leveraging a very large cohort of carriers of these mutations, we focused on the comparison between BMF and MN to find explanation for the distinctively different impact of identical lesions on disease biology.

First, because *BCOR/L1* genes are located on the X chromosome, we studied sex differences but while *BCOR/L1*-mutated MN was slightly enriched in males, no significant sex difference was observed in BMF, and BCOR/L1 expression did not differ based on gender in both disease groups, likely due to mostly complete lyonization [32]. Consequently, there was no increased frequency of females in BMF versus MN that could explain the protective role of the heterozygous versus hemizygous configuration in BMF. However, clonality of the *BCOR/L1* mutations was indeed lower in BMF versus MN, which also showed a higher number

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of co-mutations and lower proportion of missense mutations. In MN, *RUNX1* was the most frequent co-occurring mutation and remained significantly associated with *BCOR/L1* mutations after multivariable analysis. In addition, missense mutations in MN tended to exhibit higher predicted pathogenicity. These observations are consistent with lesser pathogenicity of these lesions in BMF also described by others [6, 9], but the causal or temporal relationship cannot be deciphered. Nevertheless, loss of function

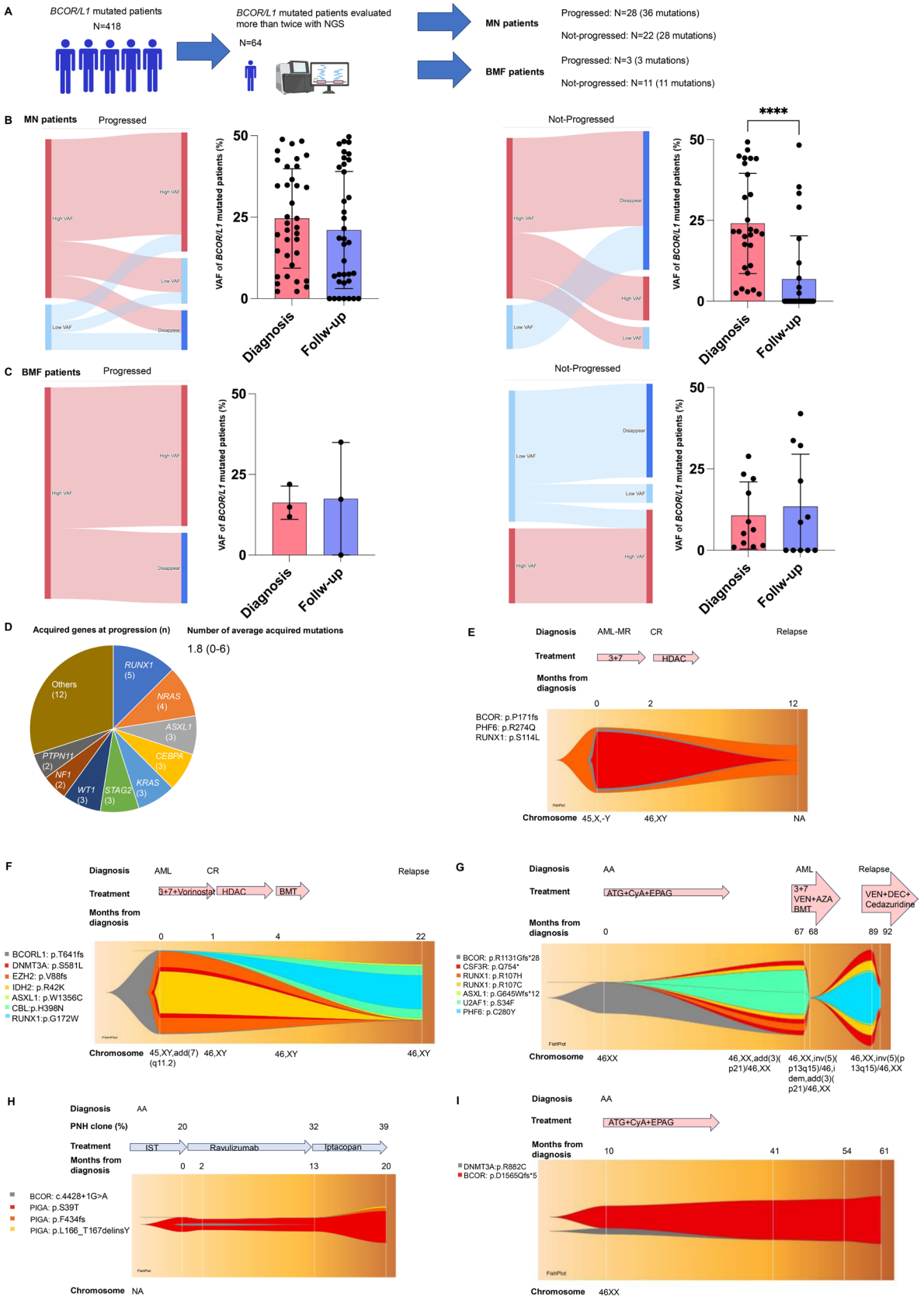

FIGURE 5 | Legend on next page.

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FIGURE 5 | Longitudinal analysis of *BCOR/L1*-mutated MN and BMF and fish plots of representative cases. (A) Description of each group in a series of *BCOR/L1* mutated patients. (B) Progressed and Not-Progressed MN patients. (C) Progressed and Not-Progressed BMF patients. (D) Acquired genes at progression. (E) A 35-year-old male with AML who lost the *BCOR* mutation at relapse. (F) A 52-year-old male with AML who lost the *BCOR* mutation at relapse. (G) A 23-year-old female with AA who lost the *BCOR* mutation upon progression to AML. (H) A 14-year-old male patient with AA in whom the *BCOR* mutation disappeared during treatment, accompanied by an expansion of the *PIGA*-mutated clone. (I) A 26-year-old female patient with AA in whom the *BCOR* mutation disappeared during treatment, accompanied by an expansion of the *DNMT3A*-mutated clone. AA, aplastic anemia; AML, acute myeloid leukemia. BMF, bone marrow failure; MN, myeloid neoplasm.

experiments in mouse models showing that *BCOR/L1* alterations alone are insufficient to induce leukemia and that co-occurring mutations are required for disease development [33, 34] are in agreement with our clinical findings. BCOR inactivation may indeed play a similar role in association with *RUNX1* mutations, wherein EZH2 loss of function variants through mutations and deletions has been shown to facilitate progression to MDS [35]. Of note is that unlike *BCOR*, *RUNX1* mutations have been associated with progression of AA to MDS [36].

Another explanation as to the low pathogenicity yet selective pressure of *BCOR/L1* mutation in BMF could be their position within the clonal hierarchy. Both VAF-based analysis [21, 22] and scDNA-seq indicated that these mutations are most likely secondary events in MN, leaving out in BMF the MN-categorical founder hit. When longitudinal changes in *BCOR/L1*-mutant clone size were evaluated, approximately half of the cases showed a decrease or disappearance of the clone, even among cases with disease progression. Consequently, the auxiliary MN-promoting role of BCOR is missing and rather selection pressure is related to factors unique to BMF pathogenesis. We conclude in MN, intra-clonal selection and subclonal competition did not appear to favor *BCOR/L1* mutations as the final evolution pathway may eliminate that subclone. Indeed, Robertson et al. calculated gene-specific fitness using longitudinal NGS data from CHIP patients and reported that the fitness of *BCOR/L1* mutations was intermediate; however, the total number of cases was very small, with only five mutant patients [37]. In BMF, *BCOR/L1*-mutant clones remain stable or decrease in size, while *DNMT3A* and *ASXL1* mutations have been reported to show a tendency toward clonal expansion over time [9, 12, 38]. A deep NGS study of MN highlighted another possibility by demonstration that the fraction of *BCOR* mutations in CD34 + CD38− early hematopoietic progenitor cells was lower than of other mutations. These findings suggest that *BCOR* mutations may not arise initially at the level of multipotent hematopoietic stem cells but may instead be acquired at a later stage [3]. In contrast, because only approximately 20% of BMF cases harbor multiple co-occurring mutations, *BCOR/L1* mutations may represent primary events in the majority of BMF cases [9].

Our results suggest that *BCOR/L1* mutations are associated with progression in MN together with co-occurring mutations, whereas they may play a different role in BMF. In the prognostic analysis, *BCOR* mutations were associated with poor prognosis in both AML and HR-cMN in univariate analyses, and this association remained significant in multivariate analysis in HR-cMN. Among *BCOR/L1*-mutated cases, co-occurring *KDM6A* and *EZH2* mutations were associated with poor prognosis, whereas *RUNX1* mutations showed no significant impact on prognosis. *KDM6A* is involved in the removal of H3K27me3 and plays a role opposite to the transcriptional repression mediated by *BCOR* and *EZH2*, and it has also been reported to be associated with resistance to chemotherapy [39]. In contrast, in BMF, although the difference was not significant, *BCOR/L1* mutations tended to be associated with a favorable response to IST and were not associated with progression to MN, OS, and PFS. Previous reports have also shown that *BCOR/L1* mutations in BMF are associated with favorable prognosis, good responses to IST, and a low risk of progression to MN [9, 11, 12, 38].

Despite these differences, the most intriguing question is whether *BCOR/L1* mutations induce immune selection similar to that of *PIGA* [38, 40]. We have extensively investigated these issues by studying whether decreased expression of immune regulatory proteins in *BCOR/L1* mutant cases may lead to "immune-privileged" state. When we analyzed the expression of immune surface regulators in BCOR knockout cell line, we indeed noted a decreased expression of HLA class and increased expression of VSIR. However, this observation was not reproduced by an analysis of bulk RNA sequencing in primary patients, whereby no consistent relationship between *BCOR* mutations and HLA expression was found.

In summary, in our large study leveraging a variety of technologies, we show that in BMF, *BCOR/L1* mutations may have lower pathogenicity as they can be less deleterious. They can occur in women and occur without the genetic context seen in AML. Consequently, they lead to low clonal burden and often can vanish due to being outcompeted by normal cells or other mutant clones. These observations do suggest that other mechanisms, for example "immune privilege", can lead to clonal expansion of *BCOR/L1* in BMF as standalone hits.

Author Contributions

Atsushi Marumo (Marumo) collected and analyzed clinical and molecular data, interpreted the results, and wrote the manuscript. Arda Durmaz analyzed molecular data. Christopher Haddad, Aashray Mandala (Mandala), Felipe de Almeida Sartori, Akram Abushamma, Serhan Unlu, Xiaorong Gu, Zachary Brady, Matteo D'Addona, Kartik Lakhotiya, Luca Guarnera, Mark D. Orland, Carlos Bravo-Perez, and Carmelo Gurnari collected and contributed to manuscript editing. Masanori Yoshida, Monika M. Toma, Koichi Takahashi, Tomasz Skorski, Stephan Hutter, Torsten Haferlach, and Marcin Wlodarski provided data and contributed to manuscript editing. Valeria Visconte and Jaroslaw P. Maciejewski conceived, supervised, designed the study and contributed to manuscript preparation as well as figure and table design. All authors critically reviewed the manuscript and approved the final version for submission.

Acknowledgments

The authors have nothing to report.

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Ethics Statement

This study was approved by Institutional Review Boards of Cleveland Clinic Foundation (CCF) (IRB #5024) and participating institutions.

Consent

All samples were collected after written informed consent in accordance with the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1: Supplementary** Summary of sources of patients. **Table S2: Supplementary** Classification of disease subtypes into HR and LR. **Table S3: Supplementary** List of genes on the target sequencing panel. **Table S4: Supplementary** Features of *BCOR/L1* missense mutations. **Table S5: Supplementary** Comparison between bi-allelic and mono-allelic mutations of *BCOR/L1*. **Table S6: Supplementary** Comparison of germline and somatic *RUNX1* mutations in *BCOR/L1*-mutated patients. **Table S7: Supplementary** Criteria of classification in *RUNX1* function. **Table S8: Supplementary** Features of factors associated with decreased BCOR/L1 expression. **Table S9: Supplementary** Survival analysis in AML and High Risk-cMN. **Table S10: Supplementary** Survival analysis in *BCOR/L1*-mutated AML. **Table S11: Supplementary** Survival analysis in *BCOR/L1*-mutated High Risk-cMN. **Table S12: Supplementary** Survival analysis in *BCOR/L1*-mutated BMF. **Table S13: Supplementary** Candidate genes in RNA sequencing. **Table S14: Supplementary** Comparison of *BCOR/L1*-mutated and wild-type cases within each cohort using RNA sequencing. **Table S15: Supplementary** Identification of genes correlated with *BCOR/L1* VAF in each cohort. **Table S16: Supplementary** Comparison of *BCOR/L1*-mutated BMF and LR-cMN between Progressed and Not-Progressed. **Figure S1: Supplementary** Comparative analysis of BCOR/L1 expression across different cell types. **Figure S2: Supplementary** The process of batch effect removal in MLL RNA sequencing data. **Figure S3: Supplementary** Criteria to distinguish germline versus somatic variants. **Figure S4: Supplementary** Relationship between *BCOR/L1* and germline or somatic *RUNX1* mutations.

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