**Supplementary Information for:** Inherited myeloproliferative neoplasm risk impacts hematopoietic stem cells

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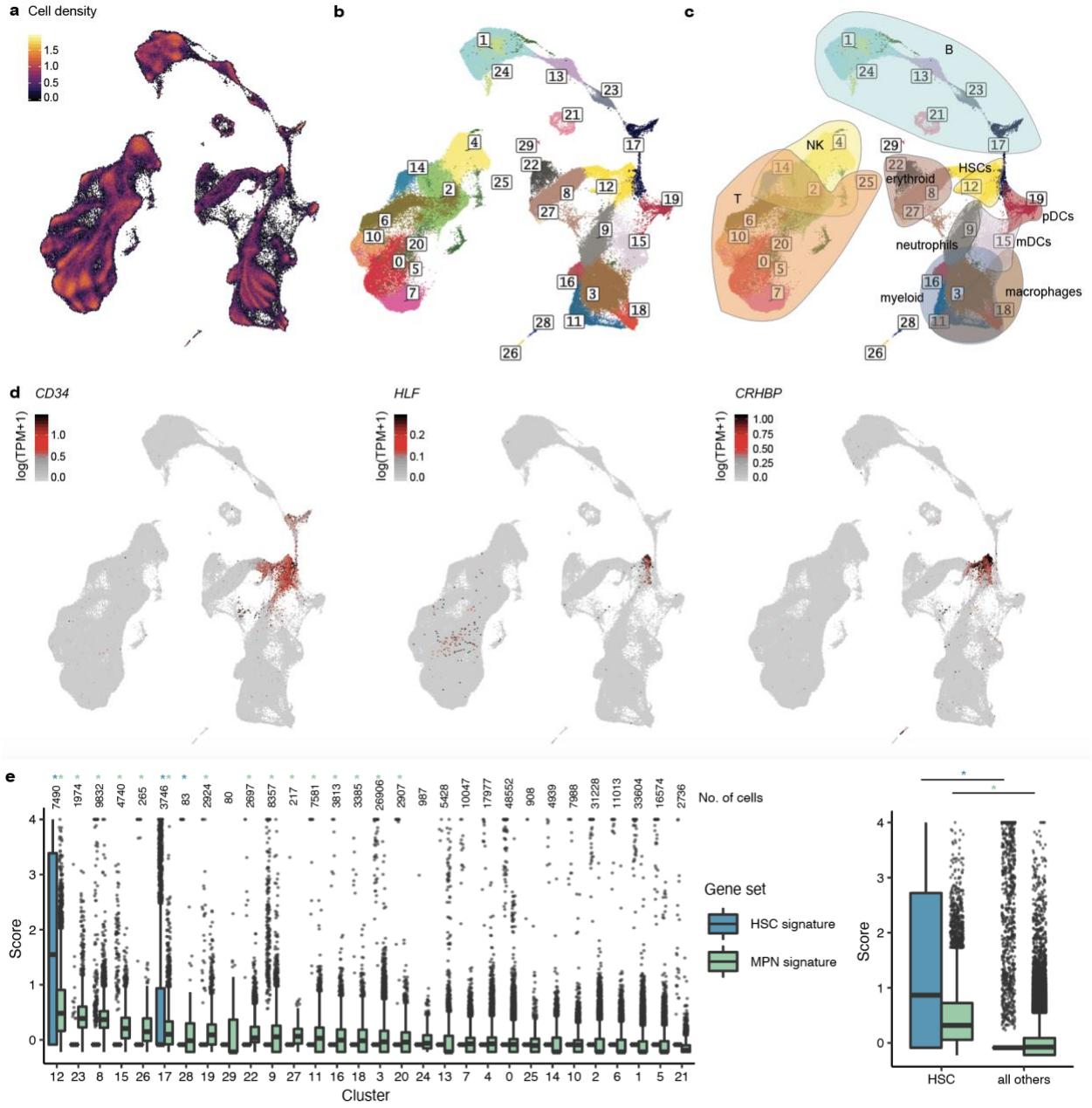
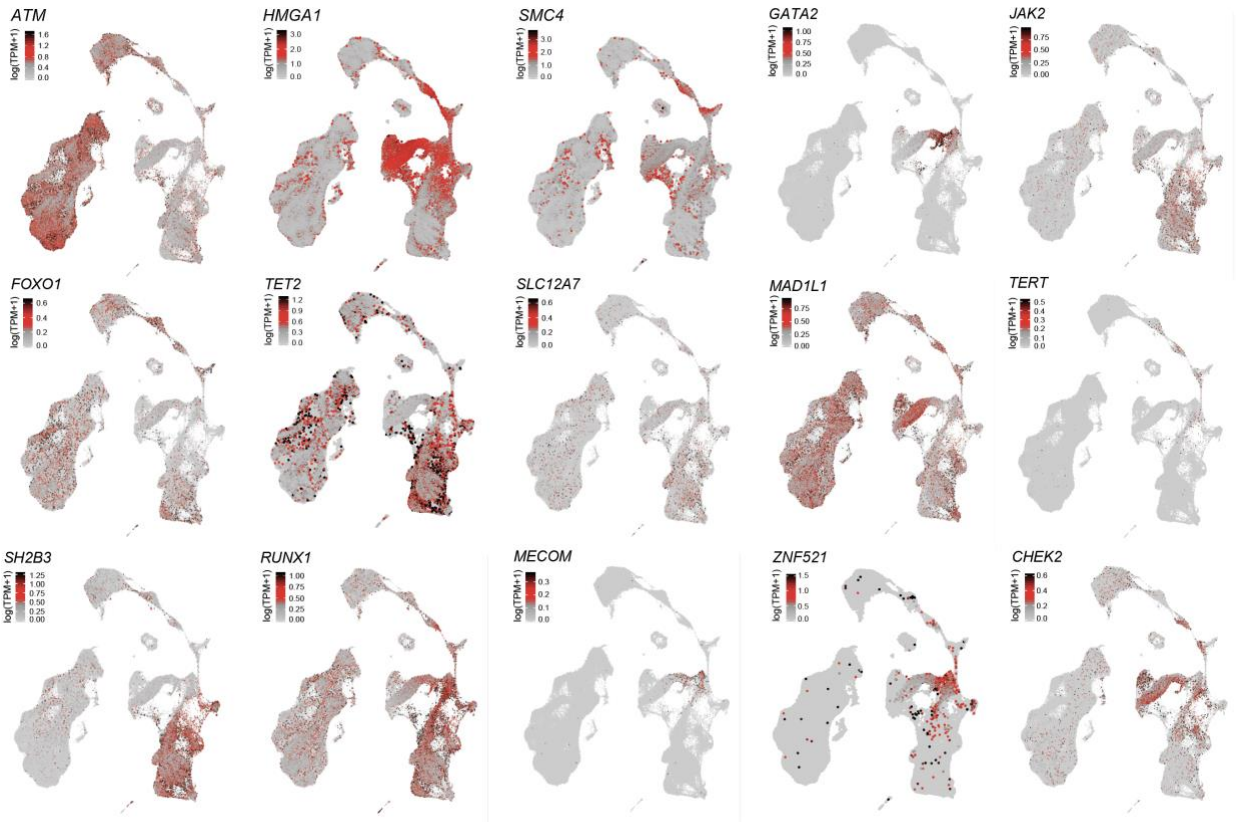
## Supplementary Figures

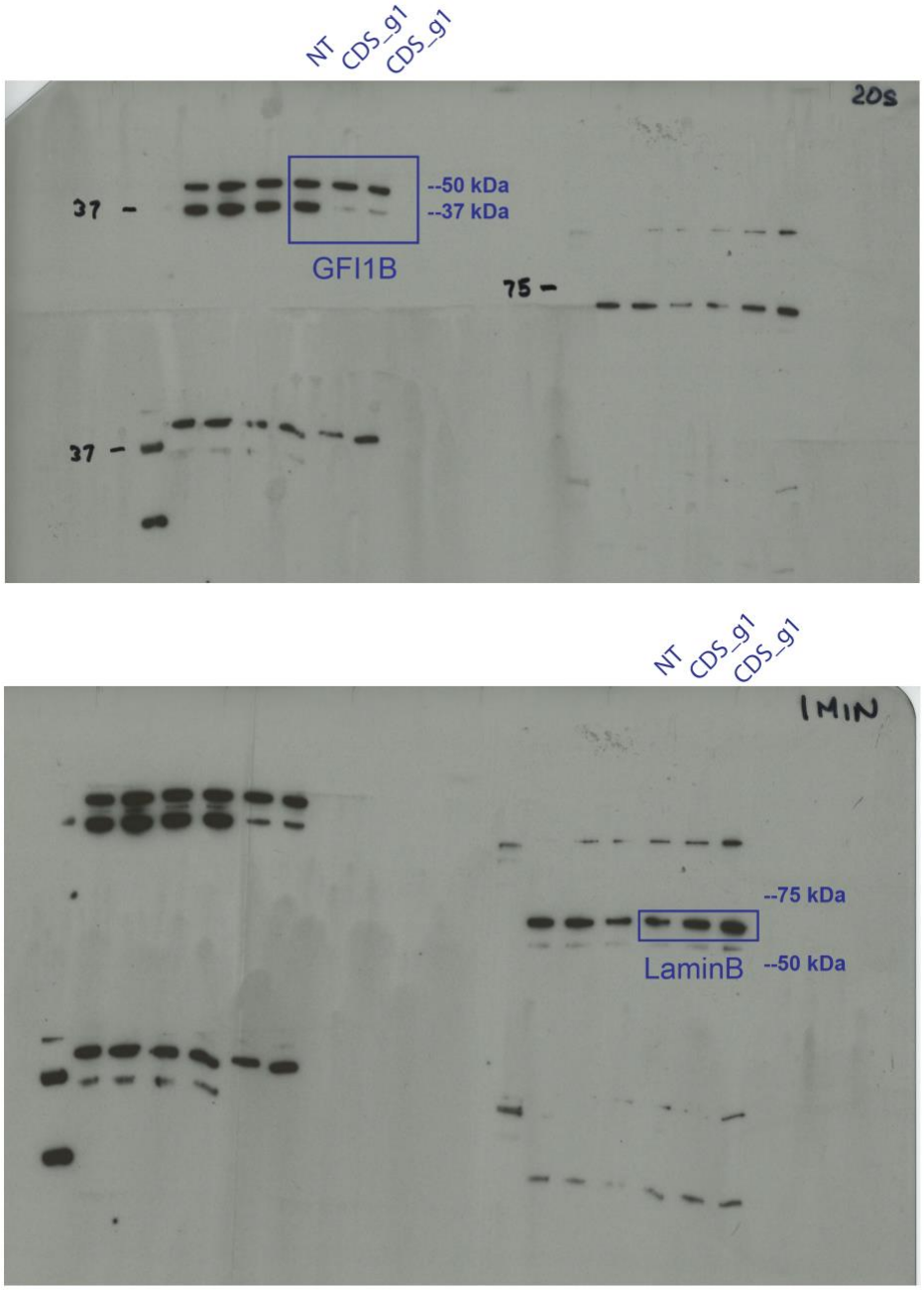



**Supplementary Figure 1.** Inference of cell types within 278,978 single cells from human bone marrow. **a-c,** UMAP projections of hematopoietic single cells, colored by (**a**) cell density, (**b**) Louvain community clusters, and (**c**) Louvain community clusters with overlays of annotated major hematopoietic lineages inferred from marker genes: B cells marked by *CD79A*, T cells marked by *CD3D*, natural killer (NK) cells marked by *GZMH* and *NKG7*, myeloid cells marked by *FCN1* and *MAFB*, macrophages marked by *CD68* and *CLEC10A*, myeloid dendritic cells (mDCs) marked by *FCER1A*, plasmacytoid dendritic cells (pDCs) marked by IL3RA, neutrophils marked by *ELANE*, and erythroid cells marked by *GYPA*. **d,** UMAP projections colored by the expression (log(transcripts

per million + 1)) of the three gene markers used to annotate HSCs (*CD34*, *HLF*, *CRHBP*). **e,** Left: The distribution of the HSC (blue) and MPN (green) gene scores across all Louvain clusters, ordered from left to right by decreasing average MPN signature score; Right: HSC and MPN gene scores in the combined HSC-significant clusters (12, 17, 28) vs. all other cells. False-discovery rate (FDR)-corrected *$P$<0.001 (one-tailed Mann-Whitney U-test), with the * color coded corresponding to the gene signature.




**Supplementary Figure 2.** UMAP projections of hematopoietic single cells (n = 278,978), colored by expression of 15 MPN target genes. Color bars represent log(transcripts per million + 1).




**Supplementary Figure 3.** Uncropped protein blots from **Extended Data Fig. 8e**. Western blot measuring GFI1B protein expression 5 days following CRISPR/Cas9 targeting with non-targeting control (NT), or coding regions of GFI1B (g1, g2). LaminB expression used as loading control. LaminB controls was probed on the same blot as the GFI1B.

## Supplementary Note

*Novel MPN risk loci*

In our study, we detected seven previously unreported loci associated with MPN risk at genome-wide significance ($p < 5 \times 10^{-8}$). Here, we present each of these risk loci and nominate potential biological mechanisms based on bioinformatic functional analyses and literature mining.

The first novel association is in locus 3q21.3. The lead SNP rs9864772 (RAF = 0.608, p-value = $2.06 \times 10^{-8}$) localizes to a distal enhancer for *GATA2*, which encodes a hematopoietic transcription factor that has been shown to play a causal role in inv(3)/t(3;3) AML[1]. Moreover, Gata2 has a critical role in HSC development, self-renewal, and maintenance in mice[2,3], and human germline mutations in *GATA2* compromise HSC function and differentiation[4].

There are two novel, conditionally independent associations in locus 3q25.33, represented by lead SNPs rs77249081 (RAF = 0.0096, p-value = $5.54 \times 10^{-10}$) and rs74676712 (RAF = 0.114; p-value = $3.64 \times 10^{-11}$), located ~650 kb apart. The nearest gene to rs74676712 is *KPNA4*. *KPNA4* encodes importin subunit alpha-4, which has been shown to mediate nuclear localization of STAT3, a downstream mediator of JAK2-mediated signaling[5], as well as other nuclear factors. Importantly, JAK2 itself has been shown to have critical nuclear roles in hematopoietic cells[6], suggesting a potential role for importins in this localization as well.

A fourth locus at 6p21.31, represented by lead SNP rs116466979 (RAF = 0.045; p-value = $1.86 \times 10^{-12}$), is located near *HMGA1*. *HMGA1*, a non-histone chromatin remodeling oncogene, has been shown to be overexpressed in both murine models and patients with polycythemia vera, and higher levels associate disease progression to myelofibrosis and acute myeloid leukemia[7,8]. Interestingly, genetic mutations in the functionally related *HMGA2* gene have also been associated with patients with myeloid neoplasia[9] and hematopoietic stem cell expansion in MPNs[10].

The fifth region, locus 13q14.11 is represented by the lead SNP rs8002412 (RAF = 0.18; joint p-value = $5.23 \times 10^{-10}$) near the *FOXO1* gene. Previous work has shown that expression of *FOXO1* in human CD34+ cells promotes a preleukemic state with enhanced self-renewal and dysregulated differentiation[11]. Moreover, FoxO1 deletion, in tandem with other FoxO transcription factors, in mice compromises HSC survival[12].

The sixth association is found in locus 18q11.2, represented by lead SNP rs9946154 (RAF = 0.644, p-value = $1.50 \times 10^{-8}$) within an intron of *ZNF521*. Our gene mapping analysis nominated *ZNF521* as the most likely target gene in this locus through four distinct biological criteria (**Extended Data Fig. 7**). *ZNF521* is a transcription co-factor that is highly expressed in hematopoietic progenitors, and has been shown to regulate the proliferation and repopulation of hematopoietic progenitors[13-15].

The seventh association is located in locus 21q22.12 within an intron of *RUNX1*. *RUNX1* encodes for runt-related transcription factor 1 and is required for HSC development, HSC homeostasis, lymphoid development, and platelet production. Somatic mutations and chromosomal rearrangements involving *RUNX1* are frequently observed in acute myeloid leukemia[16], myelodysplastic syndrome (MDS)[17], chronic myelomonocytic leukemia[18], and MPNs[19]. Rare germline missense mutations in the gene have been linked to familial platelet disorders with increased risk of myeloid malignancy[20].

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