Supplemental Figures

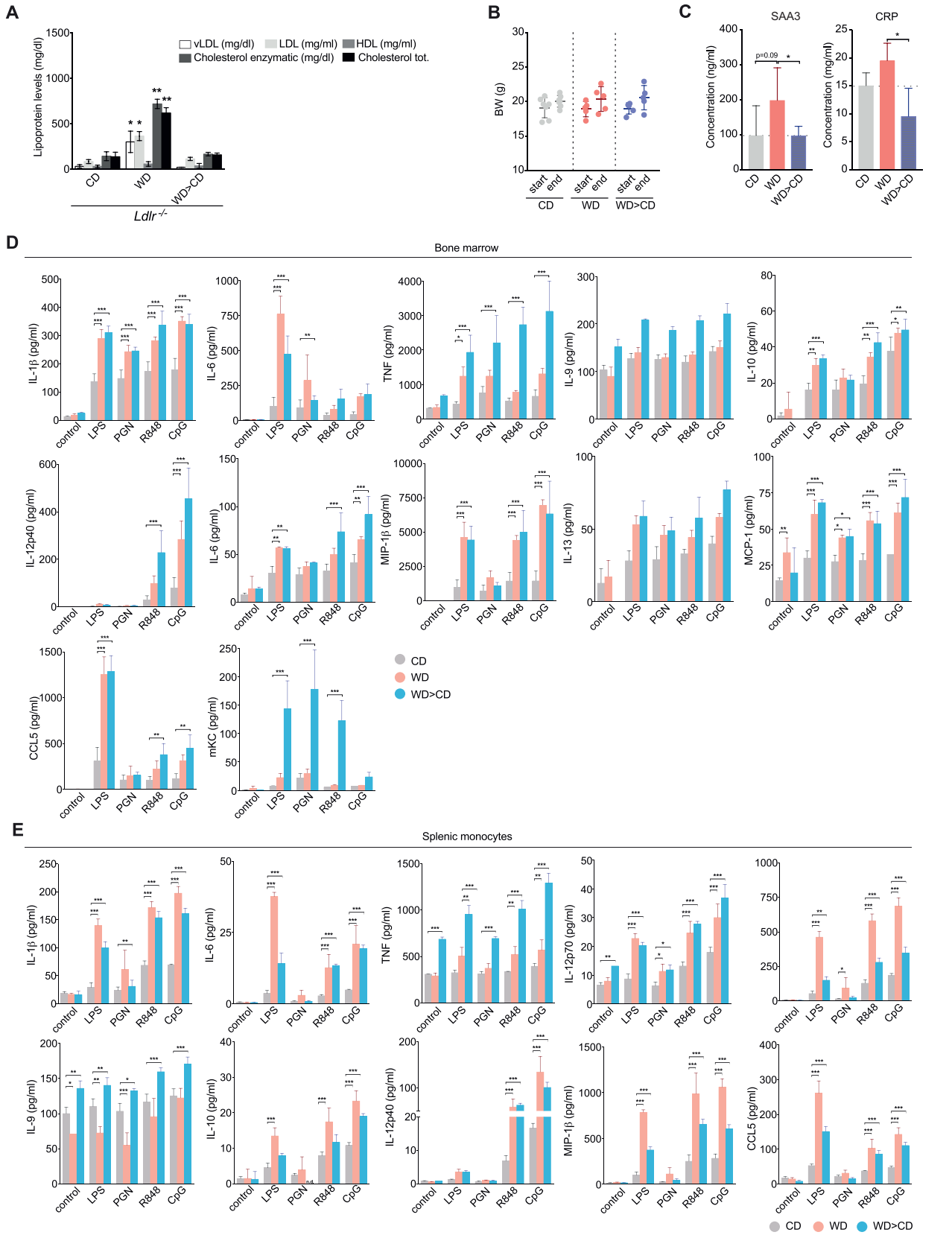

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Figure S1. Systemic and Cellular Responsiveness Are Altered upon WD Feeding, Related to Figure 1

(A) Systemic lipoprotein levels in female *Ldlr*$^{-/-}$ mice fed as shown.

(B) Body weights of female *Ldlr*$^{-/-}$ mice treated as indicated.

(C) Acute phase reactant levels in female *Ldlr*$^{-/-}$ mice treated as indicated.

(D and E) Cytokine and chemokine response of (D) bone marrow cells or (E) splenic CD11b^{+} monocytes isolated from female *Ldlr*$^{-/-}$ mice following diet manipulation and treated *ex vivo* with vehicle or different TLR stimuli for 6h as indicated.

n = 5 mice per group in (B) and n = 6-9 mice per group in (C); ± SEM, $p < 0.05$ versus CD (C), versus un-stimulated cells (D and E).

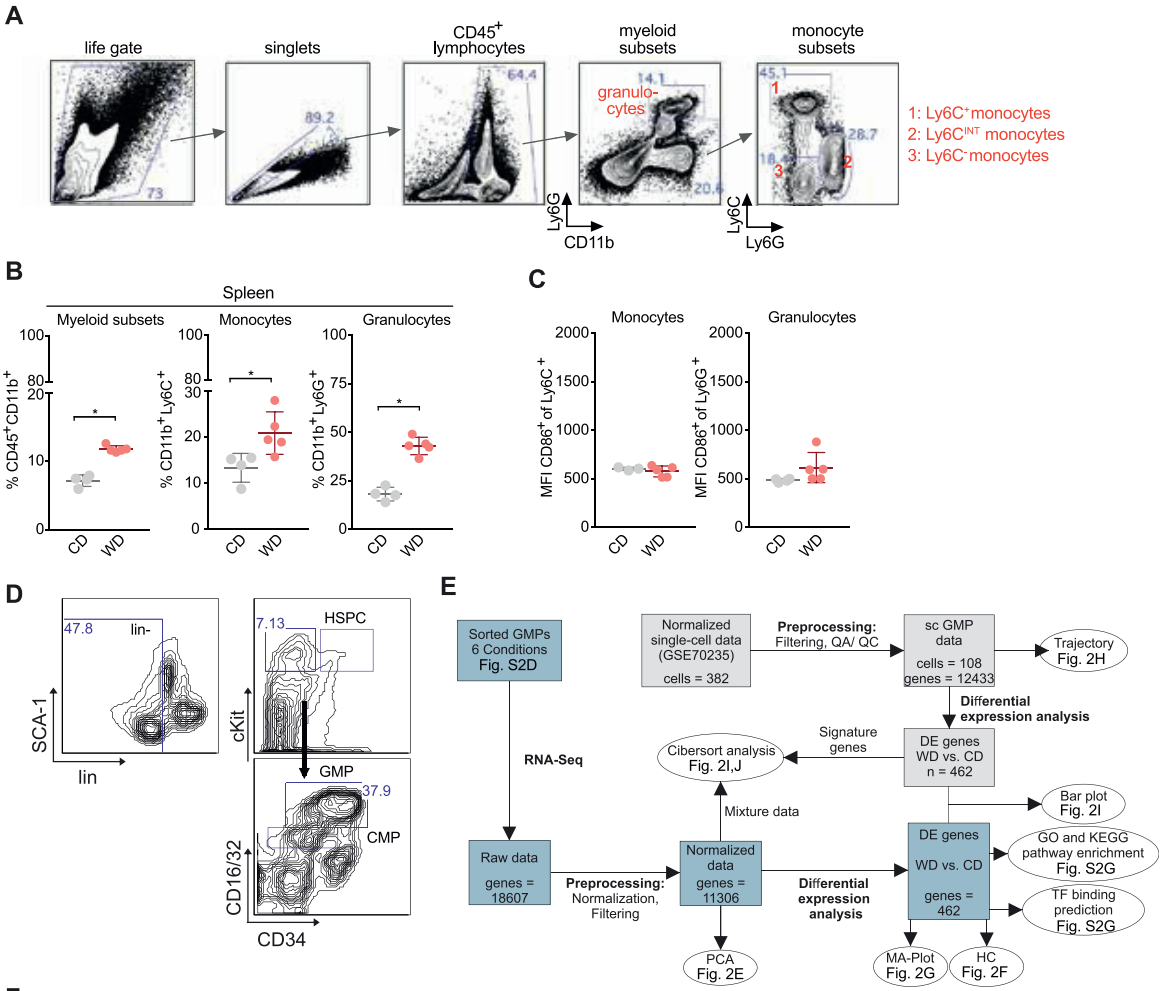

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Figure S2. WD Feeding Induces a Transcriptional Reprogramming in Bone Marrow Myeloid Precursor Cells, Related to Figure 2

(A) FACS gating strategy.

(B and C) Relative numbers (B) and activation status (C) of splenic myeloid subsets isolated from female *Ldlr*$^{-/-}$ mice treated as indicated.

(D) FACS sorting gating strategy for the different myeloid progenitor subsets.

(E) Schematic representation of the computational analysis as indicated.

(F) Functional enrichment analysis showing overrepresentation of genes upregulated in GMPs isolated from female *Ldlr*$^{-/-}$ mice treated as indicated in Gene Ontology terms or KEGG pathways.

(G) Transcription factor binding prediction analysis of significantly upregulated genes in GMPs isolated from female *Ldlr*$^{-/-}$ mice fed WD or CD.

Motif enrichment analysis was performed on 20kb area centered around the transcriptionally start site of upregulated genes. Log_2FC in genes expressed in GMPs and visualized for predicted transcriptional regulators. Boxes represent TFs with high motif similarity (FDR-adj. p value < 0.001). Colors indicate the normalized enrichment score of motif enrichment. n = 3-5 animals per group; ± SEM, $p < 0.05$ (B, C).

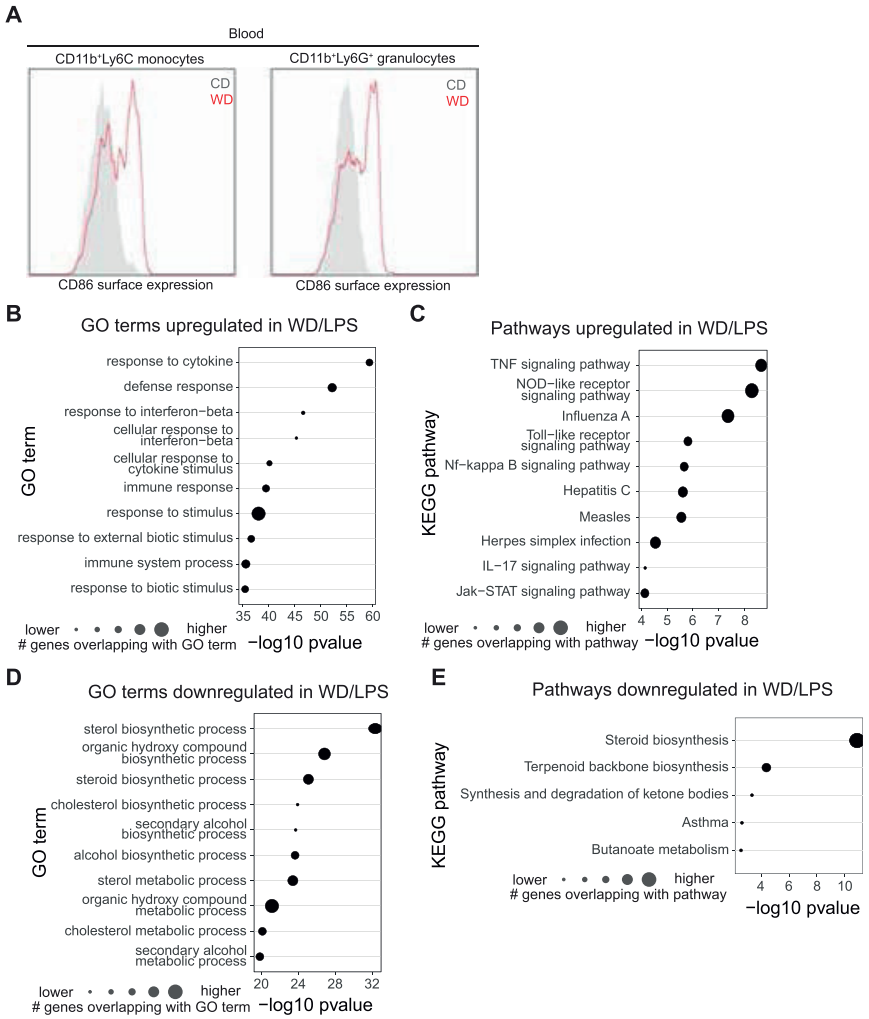

Figure S3. WD Priming Induces a Cellular Hyper-responsiveness upon LPS Challenge, Related to Figure 3

(A) Representative flow cytometry histogram analysis from myeloid cell subsets from CD and WD fed female *Ldlr*$^{-/-}$ mice.

(B–E) Functional enrichment analysis showing overrepresentation of genes upregulated (B and C) or downregulated (D and E) in GMPs isolated from mice treated as indicated.

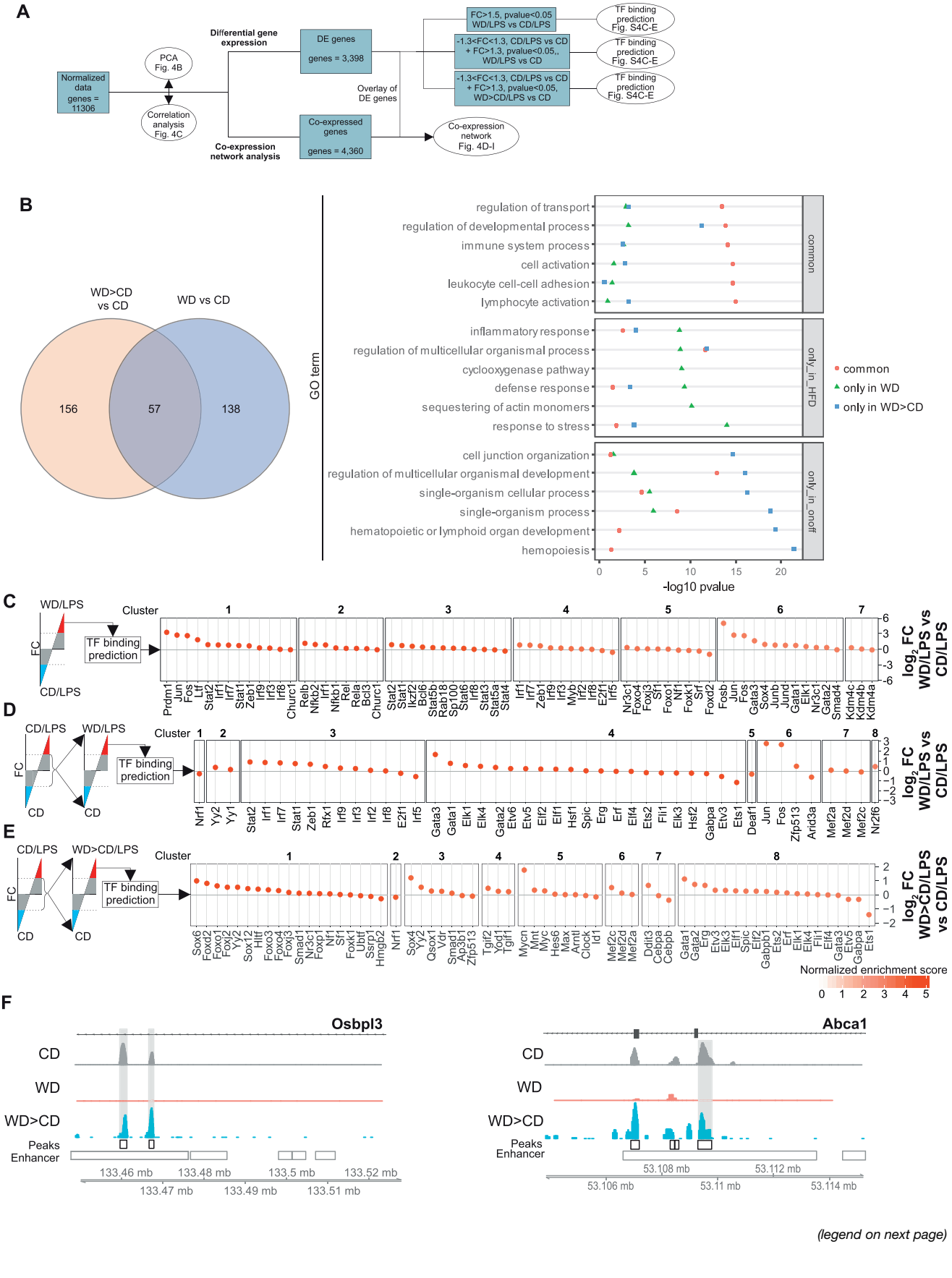

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Figure S4. WD Feeding Induces a Sustained Altered Transcriptional and Epigenetic Phenotype in Bone Marrow Myeloid Progenitors, Related to Figures 4 and 5

(A) Schematic describing the procedure of computational analysis of RNaseq data for Figure 4 and S4.

(B) Functional analysis of genes commonly upregulated in GMPs from mice treated as indicated. Top five enriched gene ontology terms of these gene lists are shown. DE genes: non-adjust. p value < 0.05, FC > 1.5.

(C–E) Transcription factor binding prediction of regulated genes in GMPs isolated from mice treated as indicated and selected genes as depicted in the schematics. Selection of input genes for analysis: (C) Genes upregulated in WD/LPS versus CD/LPS (FC > 1.5, non-adj. p value < 0.05), (D) Genes not regulated in LPS response under CD (−1.3 < FC < 1.3), but significantly upregulated in LPS response upon WD feeding in GMPs (FC > 1.3, non-adj. p value < 0.05) and (E) Genes not regulated in LPS response under CD (−1.3 < FC < 1.3), but significantly upregulated in LPS response upon WD > CD feeding in GMPs (FC > 1.3, non-adj. p value < 0.05). Motif enrichment analysis was performed on a 20kb area centered around the transcription start site of upregulated genes. Log_2 FC is visualized for predicted transcriptional regulators from conditions as indicated. Boxes represent TFs with high motif similarity (FDR-adj. p value < 0.001). Color indicates the normalized enrichment score of motif enrichment. Selected clusters are shown.

(F) Coverage of ATACseq signal for OSBPL3 (left panel) and ABCA1 loci (right panel).