**Supplemental Figure 1. Epistatic interaction between loci on chromosome 6 regulate red cell distribution width in blood.** Red cell distribution width based on genotype at SNP markers (A) rs13478633 and (B) rs13478641 on chromosome 6. Each dot represents one mouse. (C) QTL mapping results for main effects on chromosome 6. The LOD threshold for significance (p < 0.05) was calculated by permutation testing (n=10,000) and is indicated by a horizontal line. Mb position is indicated for both chromosomes 4 and 6 along the x-axis. No significant main effect QTLs were detected. (D) Red cell distribution width based on the combined genotypes at rs13478633 and rs13478641 on chromosome 6. (E) QTL mapping results for interaction effects on chromosome 6. The LOD threshold for significance (p < 0.05)) was calculated by permutation testing (n=10,000) and is indicated by a horizontal line. The most significant interaction QTLs were detected with peaks at rs13478633 (5.2 Mb) and rs13478641 (7.2 Mb). Mb position is indicated for Chromosome 6 along the x-axis. (F) Context-dependent effects of the BB and AB genotypes at rs13478633 and rs13478641. Mean and standard error are shown for each genotype combination. An “A” genotype indicates A/J-derived. A “B” genotype indicates C57BL/6J-derived.

**Supplemental Figure 2. Higher resolution mapping of main effect QTLs regulating the mRNA expression of *Extl1* and *Cadps2*.** The main effects for QTLs regulating the expression of *Extl1* to Chromosome 4 and *Cadps2* to Chromosome 6 are denoted by LOD peaks. In our previous study expression of these two genes mapped the chromosome 4 and chromosome 6 in their entirety (Chen *et al.* 2017), but in the current study we were able to map them to a single locus on each of the chromosomes as shown using N2 progeny. (A) The LOD score plot for the *Extl1* QTL is shown, with the LOD score peak located at rs13477965 (126.7 Mb). (B) The LOD score plot for the *Cadps2* QTL is shown, with the LOD score peak located at rs13478695 (32.3 Mb).

**Supplemental Figure 3. Higher resolution mapping of an interaction effect QTL pair regulating the mRNA Expression of *Tmem245*.** Using the N2 crosses, we mapped expression of *Tmem245* to interacting loci, one on chromosome 4 and one on chromosome 6. This provided increased mapping resolution in comparison to our previous study where we mapped interacting loci only to the entire chromosomes (Chen *et al.* 2017). The LOD score plot for the *Tmem245* interaction QTL is shown, with the LOD score peaks located at rs13477555 (10.2 Mb) on Chromosome 4 and rs3023840 (147.7 Mb) on Chromosome 6.