Supplemental Results

TWAS fine mapping via Conditional Analysis. TWAS conditional analysis was also used to fine map TWAS loci in which multiple genes achieved the Bonferroni adjusted significance threshold (see Supplemental Table S2). For example, erythropoietin (*EPO*) (GRCh37 chr7:100,720,800-100,723,700) encodes the primary regulator of red blood cell production and has been well studied for its impact on blood cells through its causal role in familial erythrocytosis [MIM: 617907] and Diamond-Blackfan anemia-like [MIM: 617911].[32] The 1Mb region surrounding *EPO* also contains 28 distinct GWAS variants across 21 different blood cell traits. In our marginal TWAS analysis, 13 gene-trait associations were significant at this locus including *EPO* ($p = 2\times10^{-12}$), with the TWAS sentinel gene being solute carrier family 12 member 9 (*SLC12A9*) ($p = 2.51\times10^{-29}$). However, despite the well-studied links to blood cell genetics, the *EPO* gene was not included in the 95% FINEMAP credible set. Yet after we condition the TWAS predicted expression on the distinct red blood cell signals at this locus, *EPO* was the only conditionally significant gene at the locus ($p = 2.19\times10^{-6}$). The association between *SLC12A9* and hemoglobin was completely attenuated after conditioning ($p = 0.71$). This suggests that while the genetic link between *EPO* and blood cell traits are well established, the full set of causal variants and overall genetic architecture underlying the association remains elusive.

Supplemental Figures

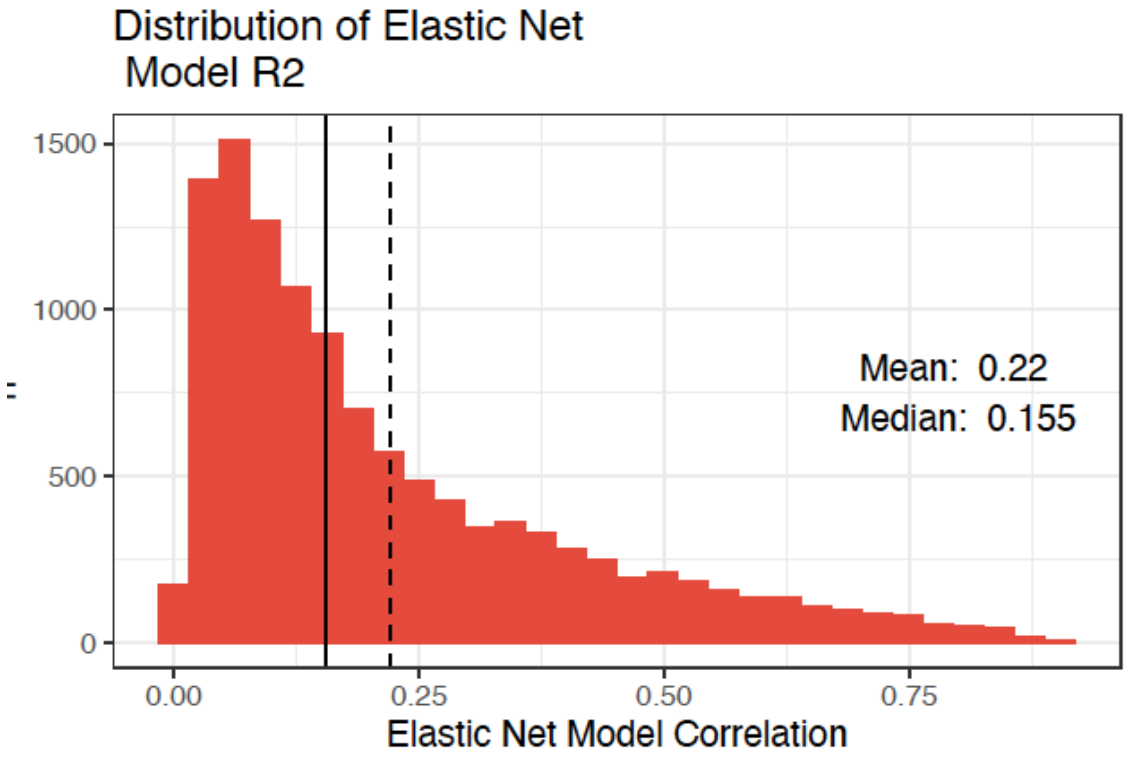

Figure S1 - Distribution of Model R2 of gene expression prediction models trained with Elastic Net.

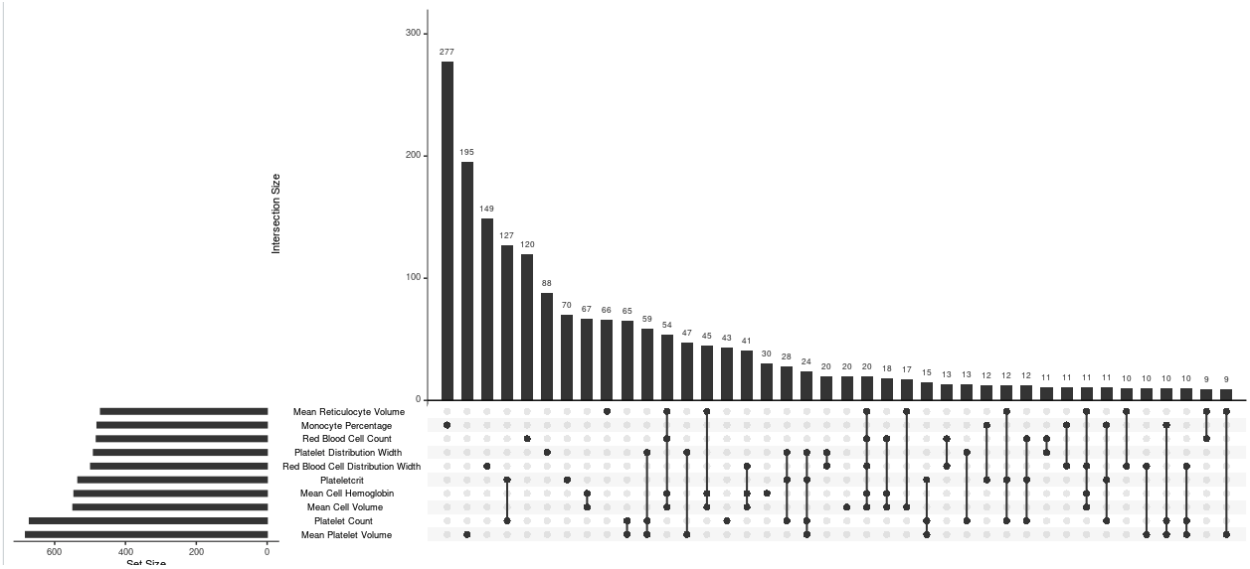

Figure S2 - Upset Plot of marginal analysis genes by phenotype.

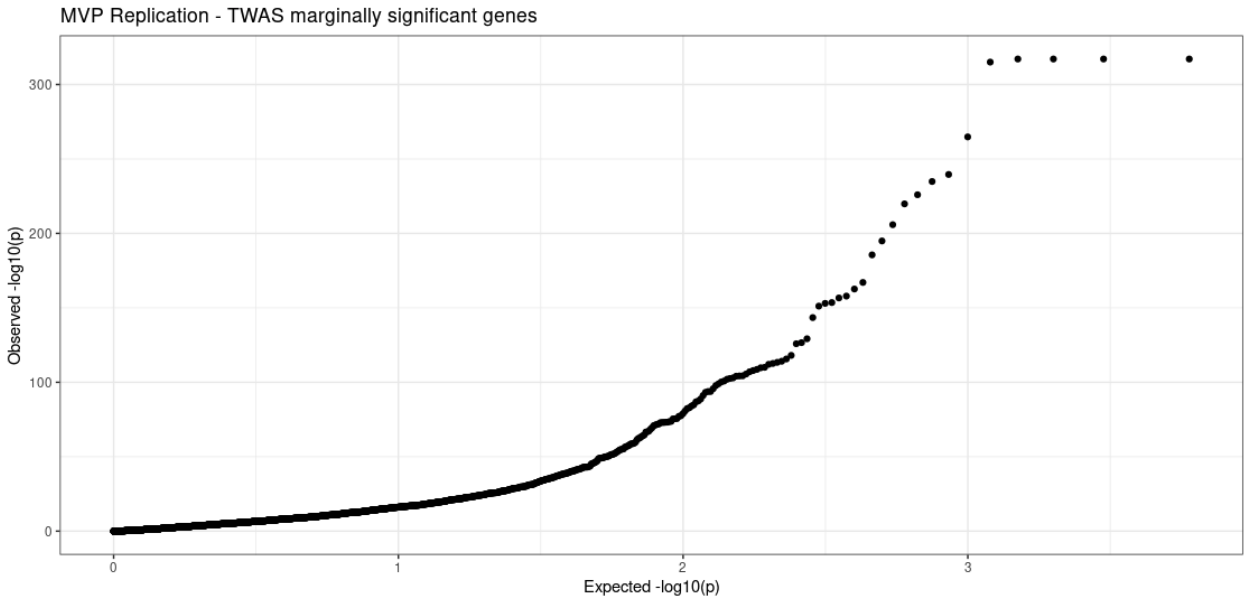

Figure S3 - QQPlot of -log10 p-values from MVP Replication of marginally significant TWAS genes.

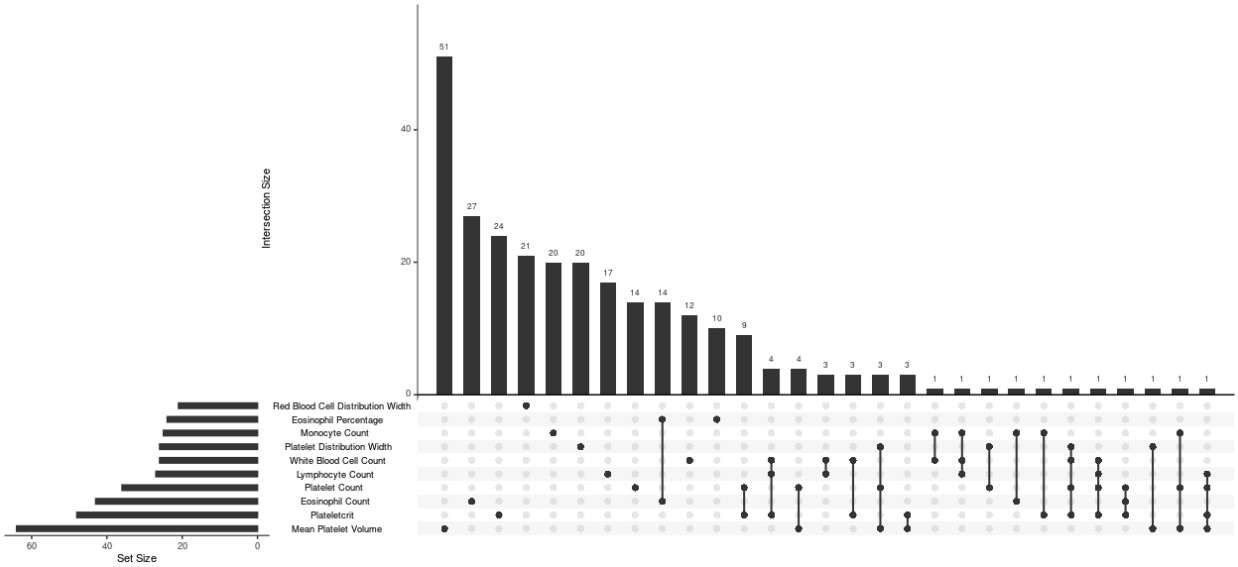

Figure S4 - Upset Plot of conditional analysis genes by phenotype.

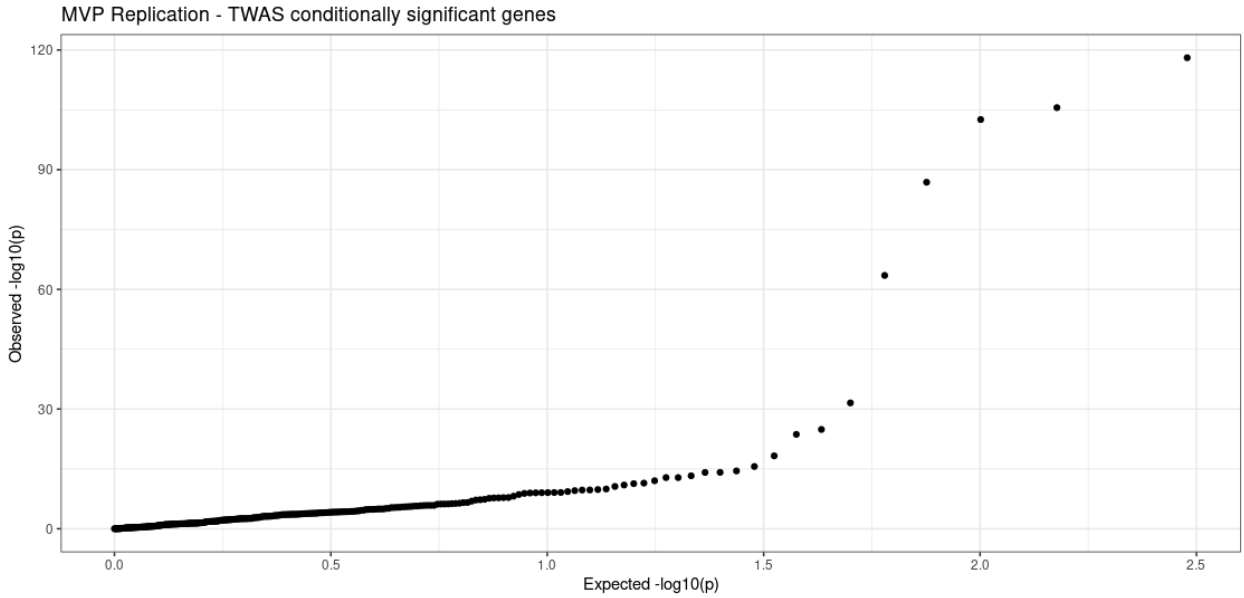

Figure S5 - QQPlot of -log10 p-values from MVP Replication of conditionally significant TWAS genes.

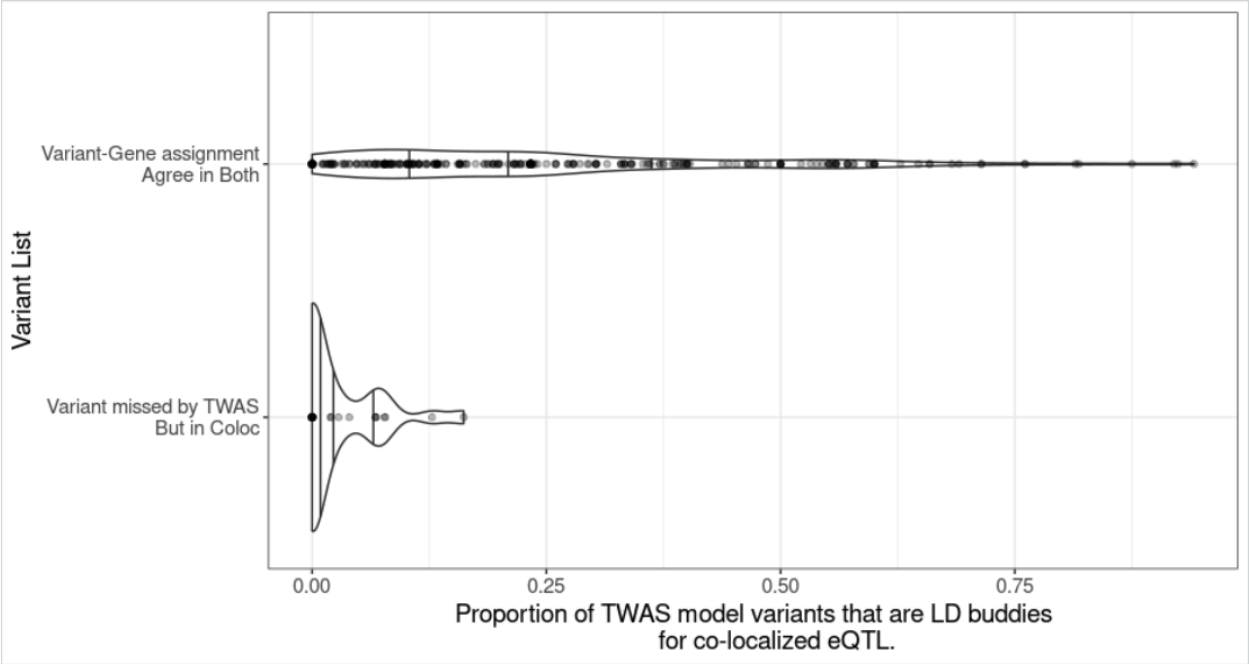

Figure S6 **- Variant assignments missed by TWAS but identified by *coloc* are driven by variants independent of co-localized eQTL.** We compared the 22 associations where the TWAS-based approach fails to assign target genes despite *coloc* identifying these variants as co-localized with an eQTL for a gene in the region to the variant-trait associations assigned by both methods. Supplemental Figure 6 shows that variants assigned to target genes by *coloc* but not by TWAS were more likely to co-localize to eQTLs which are not represented in the TWAS gene expression prediction model. The proportion of variants in LD (1000G EUR r2>0.5) with the eQTL which co-localized with the GWAS sentinel variant in the TWAS prediction model was remarkably lower than the proportions for variant-gene pairs identified by both methods. This suggests that

in these 22 prediction models, which were TWAS-significantly associated with the phenotype of interest, the TWAS predictions are not driven by the co-localized eQTLs, but other variants at the locus.

Supplemental Methods

ICD9/10 Exclusions

ICD9: 170, 1700, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 200, 2000, 2001, 2002, 2008, 201, 2010, 2011, 2012, 2014, 2015, 2016, 2017, 2019, 202, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2028, 2029, 203, 2030, 2031, 2038, 204, 2040, 2041, 2042, 2048, 2049, 205, 2050, 2051, 2052, 2053, 2058, 2059, 206, 2060, 2061, 2062, 2068, 2069, 207, 2070, 2071, 2072, 2078, 208, 2080, 2081, 2082, 2088, 2089, 2384, 2385, 2386, 2387, 282, 2820, 2821, 2822, 28220, 28221, 28222, 28229, 2823, 2824, 28240, 28241, 28242, 28243, 28244, 28245, 28246, 28247, 28248, 28249, 2825, 2826, 2827, 28270, 28271, 28272, 28273, 28274, 28275, 28279, 2828, 2829, 283, 2830, 2831, 28310, 28311, 28312, 28313, 28314, 28315, 28319, 2832, 28320, 28321, 28322, 28329, 2839, 28390, 28391, 28399, 284, 2840, 28400, 28401, 28402, 28409, 2848, 28480, 28481, 28482, 28483, 28484, 28485, 28489, 2849, 286, 2860, 2861, 2862, 2863, 28630, 28639, 2864, 2865, 2866, 2867, 28670, 28679, 2869, 287, 2870, 2871, 2872, 2873, 28730, 28731, 28732, 28739, 2874, 28740, 28741, 28742, 28749, 2875, 2878, 2879, 288, 2880, 28800, 28801, 28802, 28803, 28804, 28809, 2881, 2882, 2883, 2888, 28880, 28881, 28889, 2889, 289, 2890, 28900, 28908, 28909, 2891, 2892, 2893, 2894, 2895, 2896, 2897, 28970, 28971, 28979, 2898, 28980, 28981, 28989, 2899, 571, 5710, 5711, 5712, 5713, 5714, 5715, 57150, 57151, 57152, 57158, 57159, 5716, 5718, 5719, 790, 7900, 7901, 7902, 7903, 7904, 7905, 7906, 7907, 7908, 7909.

ICD10: B20, B21, B22, B23, B24, C40, C41, C81, C82, C83, C84, C85, C86, C87, C88, C89, C90, C91, C92, C93, C94, C95, C96, D45, D46, D47, D55, D56, D57, D58, D59, D60, D61, D63, D640, D641, D642, D643, D644, D65, D66, D67, D68, D69, D70, D71, D72, D73, D74, D75, D76, D77, D80, D81, D82, D83, D84, D85, D86, D87, D88, D89, K70, K71, K74, R70, R71, R72, R73, R74, R75, R76, R77, R78, R79