Dopamine beta hydroxylase (DBH) synthesizes norepinephrine, a critical neurotransmitter both centrally and peripherally. Previous studies have associated DBH variants with a spectrum of clinical phenotypes, demonstrating substantially lower serum DBH levels in carriers of the promoter variant rs1611115, by uncertain mechanisms. In the present study, analysis of mRNA in human tissues confirmed high levels in the brain (locus coeruleus) and adrenals, but also unexpectedly in sympathetically innervated organs (liver>lung>heart), suggesting DBH mRNA may be transported to local nerve terminals. Allele-specific expression of mRNA revealed small (<twofold) effects in LC and adrenals, but pronounced allelic differences in the liver (2-11 fold), indicating the presence of multiple regulatory variants. Scanning of the DBH locus identified two variants, promoter rs1611115 (MAF 21%) and splice site rs1108580 (MAF 46%, in partial LD with rs161115), associated with significantly reduced DBH mRNA expression in liver and lung, but not brain and adrenals. In the Jackson Laboratories’ database of in-bred mouse strains, DBH mRNA levels in the liver correlated positively with increased BMI and other cardiovascular risk phenotypes, expected from increased DBH and hence norepinephrine activity. As the molecular genetic effects were observed in unexpected tissue types, a PheWAS analysis was performed by the P-STAR group to determine other phenotypes affected by these SNPs. Testing the combined effect of the minor alleles of rs161115 and rs1108580 suggested protection against angina pectoris and myocardial infarction, and increased risk of asthma and type II diabetes. Applying molecular genetics in human tissue, use of mouse databases, and clinical association studies, we find evidence for frequent DBH variants modulating risk for cardiovascular disease and affecting sympathetic activity. Supported by NIGMS U01092655.