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RNA binding protein HuR regulates CCL2 allelic expression imbalance

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CC-chemokine ligand 2 (CCL2) is involved in the pathogenesis of several diseases that are associated with monocyte/macrophage recruitment such as HIV-associated Neurocognitive Disorder (HAND). CCL2 is also implicated in addictive drug induced activation of reward system. The rs1024611G-rs13900T haplotype is associated with increased CCL2 expression *in vitro* and *ex vivo*, leukocyte recruitment *in vivo*, and deleterious disease outcomes. Notably, it is also in linkage disequilibrium with a GWAS signal for Crohn's disease. We previously showed that this allele is associated with allelic expression imbalance (AEI) in lipopolysaccharide treated primary monocytes/macrophages. Here, we tested the hypothesis that the rs13900 in CCL2 3'-UTR could lead to altered mRNA stability and AEI. Bioinformatic analysis showed that rs13900 altered a predicted HuR binding site in CCL2 3'-UTR and its secondary structure. Supporting this prediction, we determined that the rs13900 T allele bound with a higher affinity to HuR both *in vitro* and *ex vivo* using RNA electrophoretic mobility shift assay and RNA immunoprecipitation, respectively. Furthermore, rs13900T conferred greater stability to CCL2 transcript in transcriptional inhibition studies. The rs13900T showed increased luciferase activity relative to rs13900C in reporter assays and conferred increased transcript stability. Finally, a direct role for HuR in mediating this increased stability is demonstrated in overexpression and silencing studies in cell line and primary cell models and in reporter assays. In summary, our studies showed that HuR modulates CCL2 expression by differential interactions with rs13900 by altering its stability and a novel mechanism might underlie the interindividual differences in CCL2-mediated disease susceptibility.