Pharmacogenomic Studies of Asthma from the ALA ACRC Network

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The American Lung Association Asthma Clinical Research Center (ALA ACRC) Network was formed in 1999 and currently consists of 18 ACRCs nationwide and one Data Coordinating Center at Johns Hopkins University. The primary mission of the ALA ACRC is to conduct large clinical trials in diverse populations of people with asthma that will have a direct impact on patient care and asthma treatment. It is well known that on average, only about 60% of patients with asthma will respond to any prescribed asthma drug, and that the major reason for variable drug responsiveness is related to genomic variation. The study of the influence of genomic polymorphisms on drug response defines pharmacogenomics. The consequences associated with pharmacogenomic variants can be classified and pharmacokinetic (PK) or pharmacodynamic (PD). Variations in genes the pharmacokinetics (tend to have big effect sizes) and pharmacodynamics (tend to have small effect sizes). Since its beginning in 1999, the ALA ACRC has completed 9 clinical trials and have 3 on-going. DNA has been collected from individuals participating in most ACRC trials. Our pharmacogenomic trials can be classified as ancillary, which study association between response and single or multiple polymorphisms in candidate genes; and replication studies; which usually candidate gene or whole genome association studies. The goals of pharmacogenomic studies are to indentify genetic variants that associate with inter-patient variability in response to asthma drugs; to explore mechanisms that underlie genotype/phenotype associations; and to personalize asthma treatment based on pharmacogenetic biomarkers. The results of three clinical trials have been published (LODO, LOCCS and SARCA)[1-3] for which ancillary pharmacogenomic studies have been completed[4-7]. SNPs in novel genes that associate with response variability to either inhaled corticosteroid or montelukast treatments include ALOX5; ABCC1; LTA4H; GLCCI1; ARG1; SLCO2B1; CHRM2; COL2A1; CYP2C19. The fraction of total PGX variability in patient response to asthma drugs that we can account for so far is small, which limits personalizing asthma treatment. Future ACRC pharmacogenomic studies should include genotyping rare variants; determining genetic basis of asthma phenotypes; employing ‘omic’ approaches; and seeking collaborations with national and international asthma networks.