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A Novel Approach to Investigate Functional Exonic SNPs Associated with Lung Diseases at Post-Transcriptional Stage

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Genome wide association studies (GWAS) have resulted in the identification of novel genetic loci associated with a variety of diseases and clinical phenotypes, including complex lung disease such as asthma and COPD. However, the translational utilization of these expensive datasets has been restricted by multiple reasons including limited methodology to understand the exact molecular function of these single nucleotide polymorphisms (SNPs).

mRNA encodes amino acid information with linear nucleotide sequences. In addition to mRNA primary sequence, base pairing of nucleotides in mRNAs creates specific secondary structures, such as hairpins and stem-loops. A growing body of studies indicate that mRNA secondary structure contains key regulatory information in different biological processes [1-3], including pre-mRNA splicing [4], microRNA (miRNA) mediated gene regulation [5-7], and protein synthesis [8-11]. Experimental profiling of mRNA structure at genome-scale both *in vitro* [10,12-14] and *in vivo* [15] has confirmed the post-transcriptional regulatory role of mRNA secondary structure in various organisms.

SNPs are single base-pair substitutions which occur within genome. SNPs within mRNA can be categorized into three groups by location and function: non-coding SNPs located in 5' untranslated region (5' UTR) and 3' untranslated region (3' UTR), non-synonymous coding SNPs which change protein primary sequences, and synonymous coding SNPs which don't modify the encoded amino acid. The non-synonymous SNPs within mRNAs have been heavily documented and investigated in the past thirty years because this kind of nucleotide substitution potentially alters protein structure and function due to the different chemical/physical properties of the altered amino acid. Nevertheless, at mRNA level, it should be noted that SNPs may also give rise to different allelic forms of mRNA secondary structure, no matter the SNPs are non-synonymous or not, which may consequently affect final protein expression [16-19]. Several SNPs within mRNA are already known to contribute to human diseases by altering mRNA secondary structure [16,19-20]. Comparison of mRNA structure against published GWAS results indicates that some strong genetic signals from GWAS may exhibit their functional effects through modified mRNA structures

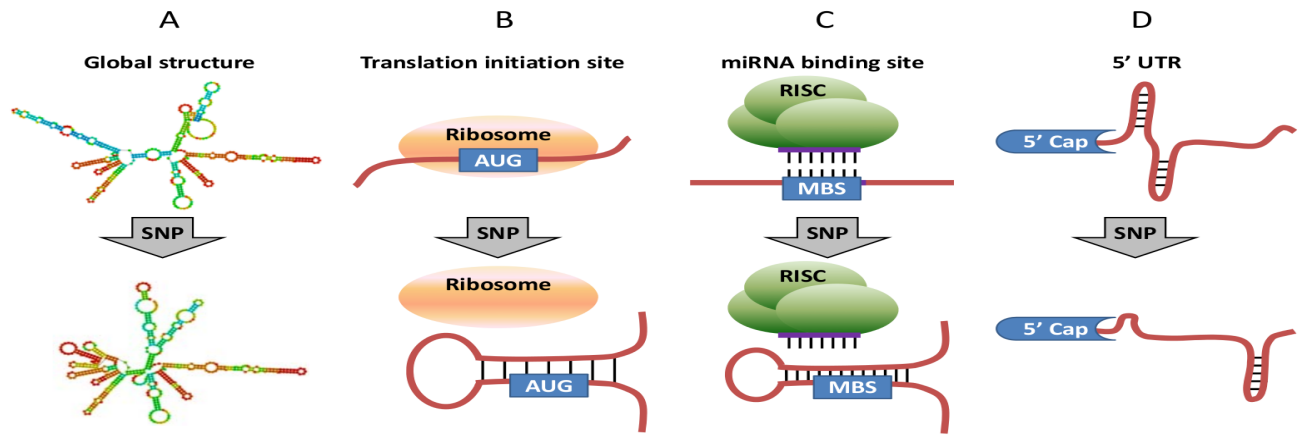

Figure 1: Structural effect caused by exonic SNPs. (A) Exonic SNPs that cause substantial change in mRNA global structure and stability. (B) Exonic SNPs that change the mRNA local structure around translation initiation sites. (C) Exonic SNPs that change the structural accessibility of miRNA binding sites (MBSs). (D) Exonic SNPs in 5' UTR that may change mRNA local structure near 5' cap and thus affect miRNA-mediated translation inhibition.

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[18]. However, as of now, the structural effects on mRNA by SNPs have not been systematically analyzed. Especially, the influence of SNPs on protein expression via mRNA structural alteration is largely unknown. Thereby we hypothesize here that a considerable proportion of lung diseaseassociated exonic SNPs may change mRNA secondary structure and in turn affect protein expression (Figure 1).

Recently, we investigated a coding non-synonymous SNP in the gene of myosin light chain kinase (*MYLK*), which is associated with severe asthma in African Americans. We have found that this single SNP mediates significant *MYLK* mRNA structure disruption (not only local effects), thereby inducing mRNA stability alteration and decay rate change. More importantly, the change of global structure of *MYLK* mRNA by this SNP alters the local accessibility of mRNA translation initiation site, which mediates the change of translational efficiency of the gene. As a first time, it proved that this asthma susceptible non-synonymous SNP changes protein expression levels, while not in the traditional concept of protein activity/structure modification. These novel theories has been further validated , *in vitro* and *in vivo*, that, this SNP alters the expression levels of *MYLK* coded proteins, due to mRNA stability and translation initiation efficiency, and thereby mediate higher susceptibility of severe asthma. This study provides a example of this novel translational approach.

In conclusion, novel methods are needed for these fast-growing GWAS and expression array datasets for lung diseases, especially for the complex diseases in need of more effective and selective therapies. The investigation of the impact of mRNA structural by disease associated SNPs will reveal novel mechanisms of genetic function of SNPs on gene expression and disease susceptibility, therefore identify novel therapeutic targets.

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