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Research Article

POSSIBLE ROLE OF T102C POLYMORPHISM IN RNA FOLDING DURING TRANSCRIPTION OF 5HT2A GENE

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ABSTRACT

Human biodiversity or individual traits are not well explained by exonic mutations of all 20,000 known human genes. Accumulating evidence has demonstrated that not all non-coding regions are junk DNA sequences, and that some functionally important non-coding variants contribute significantly to altered gene expression, qualitatively or quantitatively. Thus, functional profiling or clinical relevance of non-coding variations should not be underestimated or ignored. Variations in the gene encoding for the 5-hydroxytryptamine (serotonin) receptor 2A (5-HTR2A) have shown to be associated with Schizophrenia(Scz). Further, there is no involvement and not replicated role for HTR2A variants. In this study the role of T102C polymorphism in the promoter of 5HT2A receptor gene was analysed for its possible role in mRNA folding. Difference in the mRNA folding structure was observed as observed as revealed by mfold bioinformatics analysis.

INTRODUCTION

Schizophrenia(Scz) is one of the most important mental disorders of brain (http://www.who.int/topics/mental_disorders/en/). Advances in genetics of scz research have established the significance of genes in aetiology, but have not identified the main relationship between observed genetic risks and specific DNA variants, protein alterations or biological processes (Chen *et al*., 2015).

A meta-analysis of whole-genome linkage scans confirmed linkage between scz and markers on the long arm of chromosome 13 where the *5-HTR2A*, which codes for the 5HT2a receptor, is located (Linda *et al*., 1999). Several lines of evidence indicate that dysfunction of serotonin signaling and HTR2A receptor are involved in the pathogenesis of scz. Two common polymorphisms, T102C (rs6313) and -1438AG, of the serotonin 2A gene (5HT2A) have been studied for association with scz, although equivocally (Sáiz *et al*., 2011; Yildiz *et al* 2013).Of the several variants in the 5HT2A gene the SNPT102C has been the subject of research. The productionof the C-allele form of 5-HTR2A is significantly lessthan that of the T-allele form in normal controls and scz patients. The polymorphism is asscoiated with drug response (Dmitrzak-Weglarz *et al* 2005; Olajossy-Hilkesberger *et al* 2011). Hypomethylation of the serotonin receptor type-2A Gene (HTR2A) at T102C polymorphic site in DNA derived from the saliva of patients with scz is reported (Ghadirivasfi *et al* 2011).

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Approximately 10 million common single nucleotide polymorphisms (or SNPs; with >1% allele frequency) populate the human genome, the vast majority of which reside in noncoding regions (The International HapMap Consortium, 2013). Furthermore, incredibly large number of non-coding SNPs (ncSNPs), which may potentially be involved in disease by altering gene expression. Identification of the specific polymorphisms altering gene expression is not feasible using current laboratory assays and technologies.

It remains largely unknown if and how these non-coding DNA variants influence phenotypic traits at the molecular level. Computational strategies focused on the identification and prediction of the functional effects of nucleic acid substitutions within transcription factor binding sites have also been developed, but many are restricted to either solely elucidating relevant binding site motifs and determining whether a SNP falls within these motifs (Andersen *et al*., 2008). Difference in the mRNA folding structure by the synonymous polymorphism could be studied using mfold (Zuker 2003) http://www.bioinfo.rpi.edu/applications/mfold. Mfold algorithm predicts a minimum free energy (dG), for foldings that must contain any particular base pair.

In the present study MFOLD prediction of foldig of the T102C polymorphism was conducted.

MATERIALS AND METHODS

MFold is an adaptation of the *mfold* package (version 2.3) by Zuker and Jaeger that has been modified to work with the Wisconsin Package(TM). Their method uses the energy rules

developed by Turner and colleagues to determine optimal and suboptimal secondary structures for an RNA molecule and the energy to determine optimal and suboptimal secondary structures for a single-stranded DNA molecule.

Nucleotide sequence (NT_033777) approximately 800 neucleotide sequences flanking the SNP rs6313 was downloaded from the ncbi web server http://www.ncbi.nlm.nih.gov/build.The sequence was pasted on the Window of the mfold server at (http://unafold.rna.albany.edu/?q=mfold/RNA-Folding-Form) in fasta format with the two variants T102 and C102 respectively. Energy maps were generated using default parameters. An RNA secondary structure is composed of smaller structural motifs. The total free-energy of these structural motifs are summed to determine the free-energy of the entire RNA secondary structure. The general classes of these motifs are helices, hairpin loops, internal loops and multi-stem loops. As a general rule, mfold considers helices to be stabilizing while the loops (unpaired) segments are destabilizing

RESULTS

In the area of Disease genomics most Genome-wide association studies (GWAS) have successfully identified numerous genetic variants in the non-coding DNA and non-synonnymous variants that are significantly associated with complex diseases such as autoimmune disease, asthma and schizophrenia. Mfold a predicting the secondary structure of RNA and DNA, mainly by using thermodynamic methods. RNA secondary structures with pseudoknots are often predicted by minimizing free energy, which is NP-hard. Most RNAs fold during transcription from DNA into RNA through a hierarchical pathway wherein secondary structures form prior to tertiary structures.

Energy maps are depicted in figure 1a,b and 2 a,b. As evident from the figures a difference in the stem folding at the sequences flanking the SNP rs6313 was observed. The T and C alleles differ considerably in their predicted most favorable secondary mRNA structure.

DISCUSSION

Single-nucleotide polymorphisms (SNPs) comprise a large part of human diversity, and their inheritance may alter susceptibility to disease (David Altshuler *et al*., 2009). For SNPs in coding regions, it is often possible to predict consequences for protein structure and function, but mostSNPs are found in non-coding DNA. These SNPs may affect gene regulation or they may have no biological consequence. Screening for SNPs that affect transcriptional regulation is commonly done by *in vitro* assays of protein–DNA interaction and plasmid reporter-gene expression. Mfold predicts the secondary structure of RNA and DNA, mainly by using thermodynamic methods. The biological functions of RNAs are dictated by their three-dimensional structures. RNA's correct secondary and tertiary structure is crucial to understanding its function and mechanism in the cell (Yue *et al* 2013).

Mfold results strongly suggest that rs6313 has a marked effect on 5HT2A mRNA structure. Furthermore, alterations of the secondary structure itself can interfere with RNA-binding proteins, which can lead to altered mRNA stability.

In summary the role of SNP rs6313 in the promoter of 5HT2A receptor gene was analysed for its possible role in mRNA folding. Difference in the mRNA folding structure was observed. Further analysis of the SNP for Micro RNA association, and perhaps reporter assays using firefly can shed further light on the role of the SNP in gene expression and regulation.

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