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Computational Analysis of the Coding Single Nucleotide Polymorphisms of Disrupted in Schizophrenia 1 (DISC 1) Gene

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Abstract: Bipolar disorder is one of the major psychiatric disorders that are still left unexplored on the genetic level. One of the major genes that play an important role in the onset of this illness is DISC1 (disrupted in schizophrenia 1) located on chromosome 1.42q. The focus of the study was Single Nucleotide Polymorphisms (SNPs) to understand the biological basis of complex traits and diseases as the Genetics of human phenotype variation could be understood by knowing the functions of SNPs. We applied an evolutionary perspective to screen the SNPs using a sequence homology-based SIFT tool, which suggested that 9 nsSNPs (38%) were found to be deleterious of 24 coding SNPs. The structure based approach PolyPhen server suggested that 13 nsSNPs (55%) may disrupt protein function and structure along with software Panther stating 4 nsSNPs (17%) above the damage threshold. The PupaSuite tool predicted the phenotypic effect of SNPs on the structure and function of the affected protein. Finally the mutational risk analysis of the deleterious SNPs was performed using FastSNP server. The further study can be done on the structural modeling of DISC1 and analyze the structural changes that these damaging mutations can probably cause.

Key words: Bipolar Disorder · DISC1 Gene · Snps · SIFT · Polyphen-2 · Damage Threshold · Risk Analysis

INTRODUCTION

Bipolar disorder (BD) is classified as a mood disorder characterized by alternating conditions of mania and depression [1]. BD is known to have a strong genetic component which causes almost 1-5% of the population to suffer from this disastrous psychiatric disorder. Various researchers have been exploring the underlying causes of this disease. Studies have shown that the abnormalities in the regulation of signaling and neural plasticity underline the neuropathology of the BD [2]. It has been shown that the Mood Stabilizing Drugs also play a significant role on the predisposition of the disease [1]. The cause of BD at the genetic level is also being studied. A number of the most probable genes involved in BD have been identified and are being studied for a better picture. Some of the genes identified to be involved include DISC1, BDNF, NRG1, SLC6A4, TPH2, DRD4, SLC6A3, DAOA and DTNBP1 and many others also [2]. Linkage and Genomic studies have been conducted to show the involvement of genes in this disease. However, the genes have to be further studied to have a better understanding of their role in BD. Here the study was focused on DISC1 gene for its critical importance in expression of many other proteins necessary for absolute brain functioning.

DISC1 protein localizes predominantly to perinuclear punctate structures which extend into neurites in many cells [3]. DISC1 is a scaffold protein essential for many critical brain processes, including regulation of neural precursor proliferation and differentiation [4], migration of newborn neurons within the developing cortex [5] and adult hippocampus. Also it is important for integration of newborn neurons into the existing neural circuitry [6], modulation of dendritic spines [7] and synapse formation [8]. A break point at chromosome 1q42 is found to co-segregate with a prominent presentation of mental illness, including major depression, bipolar disorder and schizophrenia. A gene is disrupted by this translocation named DISC1 and DISC2 that regulates its expression. The disruption in gene reduces gray matter density, reduced gray matter volume, abnormal hippocampal structure/ function and impaired memory [9].

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Full length DISC1 interacts by two-hybrid system with multiple proteins of the centrosome and cytoskeletal system, including MIPT3, MAP1A and NUDEL, a-actinin2 and b4-spectrin, ATF4 and ATF5. Jill A. Morris *et al*. [3] proposed that DISC1 is a multifunctional protein whose truncation contributes to schizophrenia and other mental illness by disrupting intracellular transport, neurite architecture and/or neuronal migration and many neuronal functions orchestrated by the centrosome-microtubule system, all of which have been hypothesized to be pathogenic in the schizophrenic brain.

Another protein DBZ a protein identical to human KIAA0844 interacts with DISC1, specifically with domains near the breakpoint of the (1;11) (q42.1;q14.3) translocation. This finding was put forward by Hattori *et al*. [10] by showing the possible involvement of DBZ in the formation of neurites and in the signaling pathway of PACAP, a neuropeptide regulating many neuropsychological functions.

In recent study by Eykelenboom *et al*. [11] in lymphoblastoid cell lines it was found that the translocation resulted in the production of abnormal transcripts due to the fusion of DISC1 with a disrupted gene on chromosome 11 (DISC1FP1/Boymaw). The chimeric transcripts encode abnormal proteins targeted to mitochondria, where they induce clustering and loss of membrane potential, indicative of severe mitochondrial dysfunction.

Over the past few years, a lot many studies have been performed to predict the functional consequences of an nsSNP, be it disease-related or neutral, based on sequential and structural attributes [12]. Due to the absence of crystallographic structure of many proteins the only way to predict the deleterious nsSNPs is theoretical [13-15]. Deleterious nsSNPs analyses for the DISC1 gene have not been estimated computationally until now, although they have been the focus for experimental researchers. So here we have studied DISC1 isoform Lv in brain tissue of patients with schizophrenia and bipolar by computationally analyzing the SNPs of the gene as the mechanism of the genetic association of DISC1 with bipolar disorder involves disruption of molecular pathways related to DISC1 function. Specifically, we tested the tolerance and damage of mutations at specific position in the respective non-synonymous coding SNPs of the DISC1 gene and the change of expression of DISC1 protein. The SNPs of DISC1 were obtained from NCBI dbSNP server which was initially subjected to SIFT for the detection of tolerance of mutation by homologous match. The coding SNPs obtained were further subjected to test by online PolyPhen-2 and Panther servers for the comparison and analysis of result obtained by SIFT. We have focused mainly on mutational damage risk on the DISC1 gene function. The risk estimation was performed using FastSNP server with the change in probable function predicted by PupaSuit3. The validation of the probable structural change of DISC1 protein due to the above predicted site specific mutations could not be performed due to the unavailability of the crystallographic structure of the DISC1 protein.

MATERIALS AND METHODS

The SNPs for the DISC1 Gene were obtained from National Center for Biotechnology Information (NCBI) database of SNPs, dbSNP (http:// www.ncbi.nlm.nih.gov/ projects/ SNP) for our computational analysis.

Tolerance Analysis of SNPs by SIFT: Sorting Intolerant from Tolerant (SIFT) is a sequence homology-based tool that sorts intolerant from tolerant amino acid substitutions and predicts whether an amino acid substitution in a protein will have a phenotypic effect. It predicts whether an amino acid substitution affects protein function. SIFT prediction is based on the degree of conservation of amino acid residues in sequence alignments derived from closely related sequences, collected through PSI-BLAST. SIFT presumes that important amino acids will be conserved in the protein family and so changes at well-conserved positions tend to be predicted as deleterious. SIFT can be applied to naturally occurring non-synonymous polymorphisms or laboratory-induced missense mutations. Here we submitted the coding non synonymous SNP ids as the input query to detect the deleterious SNPs substitutions without giving the homology details and also the other server parameters were kept as default. SIFT scores>0.05 are predicted by the algorithm to be intolerant or deleterious amino acid substitutions, whereas scores<0.05 are considered tolerant [16]. The higher a tolerance index, the less functional impact a particular amino acid substitution is likely to have.

Prediction by PolyPhen-2: Poly Phen-2 (Polymorphism Phenotyping v2) is a tool which predicts possible impact of amino acid substitution on the structure and function of a human protein using straightforward physical and

comparative. It is a new development of PolyPhen tool for annotating coding non-synonymous SNPs which has high quality MSA pipeline; machine learning based probabilistic classifier and is optimized for high-throughput analysis of next generation sequencing data [17]. PolyPhen-2 uses eight sequence-based and three structure-based predictive features which were selected automatically by an iterative greedy algorithm. Input options for PolyPhen server [18] is protein sequence or SWALL database ID or accession number together with sequence position with two amino acid variants. In our work the query was submitted in the form of protein sequence with mutational position and two amino acid variants keeping all the other parameters of scoring as default. For a mutation, PolyPhen-2 calculates Naïve Bayes posterior probability that this damaging mutations and estimates false positive (the chance that the mutation is predicted as damaging when non-damaging) and true positive (the chance that the mutation is predicted as damaging truly) rates. The mutation is also appraised qualitatively, as benign, possibly or probably damaging.

Functional significance of SNPs and mutation using PANTHER: PANTHER is a collection of protein families and sub – families and is used to predict the functional significance of the SNPs of a gene. The software requires an input of the list of SNPs of the gene and the output is given in the form of substitution position-specific evolutionary conservation (sub- PSEC) score, derived from the probabilities of observing the variant amino acids in a PANTHER hidden Markov model (HMM) [19]. Sub-PSEC score can be used to differentiate between the mutations in a gene and the coding SNPs and also the extent to which a SNP is deleterious in nature. The input that we submitted was a list of coding SNPs of the DISC1 gene. We obtained a table which gave the sub-PSEC score, probability score of deleterious SNP, substitution and the effect of substitution in the form of probability score.

Functional SNPs using PupaSuite: PupaSuite is software that combines the features of PupaSNP [20] and PupasView [21] with new algorithms to predict the functional haplotypes. It facilities the optimal set of SNPs for a large-scale genotyping study [23]. The input is in the form of list of genes that are involved in the disease, chromosomal regions associated with the disease or SNPs. The output of the software is in the form of putative functional effect of SNPs, haplotype blocks for chromosomal regions and Minor Allele Frequency (MAF) in different populations and Linkage Disequilibrium and haplotype blocks. Functional haplotypes: this option allows the user to test their own SNP data and to find haplotypes [23] with the functional SNPs [20, 21] and the tag SNPs [24] highlighted.After obtaining the coding SNPs from the SIFT and PolyPhen, those SNPs are submitted as input for Pupa Suite with all the parameters kept as default. For a SNP, Pupa Suite provides the data of change in the amino acid in the exon of the SNP, the conserved regions and the non-synonomous SNPs out of the SNPs given in the input data.

Risk identification with FastSNP: FASTSNP (function analysis and selection tool for single nucleotide polymorphisms) is a web server that allows users to efficiently identify the SNPs most likely to have functional effects. It prioritizes SNPs according to 13 phenotypic risks and putative functional effects, such as changes to the transcriptional level, pre-mRNA splicing, protein structure and so on Hsiang-Yu Yuan *et al*. [25]. A unique feature of FASTSNP is that the prediction of functional effects is always based on the most up-to-date information, which FASTSNP extracts from 11 external web servers at query time using a team of re-configurable web wrapper agents [25, 27]. The risk score is assigned as: Very high (5), Moderate to high (3-4), Low to moderate (2-3). For FastSNP we submitted the name of the gene DISC1 and the result obtained was the list of SNPs of DISC1 and their ranking from 0 to 5. The function type of the SNPs can be non-sense, missense, etc based on the type of SNP (coding or non-coding).

RESULT AND DISCUSSION

SNPs Dataset: The total data set of 230 SNPs was obtained from the NCBI server. There was total of 24 (11%) coding SNPs which are further used for the evaluation. Since only a small percentage of the SNPs were find to be coding, SNPs irrespective of the type were collectively tested computationally for their effect on the functioning of the DISC1 gene.

Deleterious nsSNP by SIFT Program: SIFT predicts the functional importance of amino acid substitutions based on the alignment of orthologous and/or paralogous protein sequences. The 24nsSNPs were submitted together to the SIFT program to check its tolerance index. Among the 24 nsSNPs, 9nsSNPs (38%) were identified to be deleterious with a tolerance index score of <0.05 as shown in Table 1. SIFT scores were classified as

Table 1: List of nsSNPs predicted deleterious by SIFT and olyPhen2

SNPs ID	AA Change	Protein ID	Allele	Tolerance index	Naïve Bayes Score	
rs3738400	G5V	NP_001012975	G/T	0	0.717	Possibly Damaging
rs79978593	A13G	NP_001012975	G/C	0.05	0	Benign
rs77062350	S76F	NP_001012975	C/T	0.11	0.792	Possibly Damaging
rs76175896	A83V	NP_001012975	C/T	0.01	0.835	Possibly Damaging
rs34574703	P106T	NP_001012975	C/A	0.09	0.775	Possibly Damaging
rs56020408	A116V	NP_001012975	C/T	0.18	0.093	Benign
rs112577310	P193S	NP_001012975	C/T	0.04	0.081	Benign
rs55795950	T328N	NP_001012975	C/A	0.29	0.135	Benign
rs34622148	L330F	NP_001012975	C/T	0.01	0.999	Probably Damaging
rs77080351	R345Q	NP_001012975	G/A	0.2	0.905	Probably Damaging
rs76372333	Q347R	NP_001012975	A/G	0.25	0.049	Benign
rs78640112	V350L	NP_001012975	G/C	0.3	0.982	Probably Damaging
rs78792190	P432L	NP_001012975	C/T	0.21	0	Benign
rs28930675	T453M	NP_001012975	C/T	0.01	0.979	Probably Damaging
rs78852015	R455Q	NP_001012975	G/A	0.08	0.994	Probably Damaging
rs56229136	G531R	NP_001012975	G/C	0.16	0.047	Benign
rs76230451	T561A	NP_001012975	A/G	0.03	0.208	Benign
rs821616	S704C	NP_001012975	A/T	0.01	0.924	Probably Damaging
rs117884450	R569Q	NP_001158017	G/A	0.18	0.921	Probably Damaging
rs117884450	G551S	NP_001158020	G/T	not scored	0	Benign
rs2806455	S682Y	NP_001158013	C/A	0.03	0.013	Benign
rs821616	R683S	NP_001158013	C/A	0.72	0.998	Probably Damaging
rs115112816	E783Q	NP_001158009	C/G	0.45	0.971	Probably Damaging
rs61737326	H787Y	NP_001158009	C/T	0.04	0.002	Benign

intolerant (0.00–0.05), potentially intolerant (0.051–0.10), borderline (0.101–0.20), or tolerant (0.201–1.00) according to the proposed classification of Xi *et al*. in 2004 [28]. The higher the tolerance index, the less functional impact a particular amino acid substitution is likely to have and vice versa. SNP rs3738400 showed the highest intolerant score of 0 while that of rs117884450 was not scored by the server.

Damaged nsSNP by PolyPhen-2 Server: The structural levels of alteration were determined by applying the PolyPhen program. It predicts the functional effect of amino acid changes by considering evolutionary conservation, the physiochemical differences and the proximity of the substitution to predicted functional domains and/or structural features. All the 24 protein sequences of nsSNPs submitted to SIFT were also submitted as input to the PolyPhen-2 server. 13 nsSNPs (55%) listed in Table 1were considered to be damaging based on Naïve Bayes posterior probability score. PolyPhen-2 scores were classified as probably damaging, possibly damaging and benign.SNPrs79978593 was scored as benign by this server but predicted as intolerant by SIFT. 5nsSNPs (21%) that were observed to be deleterious by the SIFT program also were detected as damaging according to PolyPhen. But a many contradictory results were shown by both servers. SNPsrs77080351, rs78640112, rs117884450, rs821616 and rs115112816 were predicted damaging by Polyphen-2 but tolerant as per SIFT. Also SNPsrs79978593, rs112577310, rs76230451, rs2806455 and rs61737326 were intolerant mutations as per SIFT but predicted benign by Polyphen-2. The further comparison of the effect of mutation on SNPs is done using Panther.

Validation by Panther: The output of PANTHER is presented in Table 2, the subPSEC score, is the negative logarithm of the probability ratio of the wild-type and mutant amino acids at a particular position. PANTHER subPSEC scores are continuous values from 0 (neutral) to about -10 (most likely to be deleterious) [19]. Those variants with a greater $P_{deleterious}$ tend to have more severe impairments in function. It was seen that only 4 out of 24 (17%) SNPs scored greater than score of -3 and rest 62% were below than that the damage threshold. The remaining 21% of the SNPs were not scored as the result showed the difference in amino acid in the wild gene sequence. The SNPs rs117884450, rs2806455, rs821616 has wild type amino acid Lys and rs61737326 has Gln as wild type amino acid. Comparing the results from all three SIFT, PolyPhen-2 and Panther is can be concluded that the SNPs with id rs821616 (protein id NP_001012975), rs28930675 and rs34622148 were found to be the most sensitive spot of gene and alteration of amino acids at

Table 2: List of amino acid substitutions with propability score as predicted by Panther

subPSEC	$P_{deleterious}$	substitution	$P_{substituted}$	NIC
-0.46851	0.07368	G5V	0.06433	1.524
-0.9579	0.11485	A13G	0.11701	1.599
-1.26386	0.1498	S76F	0.08181	1.752
-2.49608	0.37662	A83V	0.03731	2.189
-1.28213	0.15215	P106T	0.13907	2.189
-0.83289	0.10274	A116V	0.15982	2.189
-1.1024	0.13038	P193S	0.11931	2.261
-1.46068	0.17663	T328N	0.1202	2.261
-3.05409	0.51352	L330F	0.03157	2.261
-2.58795	0.39842	R345Q	0.07453	2.261
-2.12266	0.29373	Q347R	0.04668	2.261
-2.31534	0.33522	V350L	0.07293	2.261
-2.16116	0.30178	P432L	0.02743	1.018
-3.38145	0.59422	T453M	0.01176	1.961
-3.8443	0.69937	R455Q	0.02061	1.961
-0.68933	0.09024	G531R	0.08874	1.961
-2.40571	0.35565	T561A	0.04914	1.961
-3.80617	0.69129	S704C	0.01027	1.961
		R569Q	wild type amino acid is K	
		G551S	wild type amino acid is K	
		S682Y	wild type amino acid is C	
		R683S	wild type amino acid is K	
-2.05826	0.28055	E783Q	0.05135	1.961
		H787Y	wild type amino acid is Q	

Table 3: List of nsSNPs that were predicted to be functionally significant by PupaSuite

SNP ID	Allele	Transcript Consequence Type	Functionality
rs3738400	G/T	Non Synonymous Coding	Interaction with MAP1A
rs34574703	C/A	Non Synonymous Coding	Interaction with MAP1A
rs56020408	C/T	Non Synonymous Coding	Interaction with MAP1A
rs55795950	C/A	Non Synonymous Coding	Interaction with TRAF3IP1
rs34622148	C/T	Non Synonymous Coding	Interaction with TRAF3IP2
rs28930675	C/T	Non Synonymous Coding	Interaction with TRAF3IP3, Reqired for localization to puctate ctoplasmic foci
rs56229136	G/C	Non Synonymous Coding	Reqired for localization to puctate ctoplasmic foci, Necessary and sufficient for inteation with PCNT and localization at centromere
rs2806455	C/A	Non Synonymous Coding	Necessary and sufficient for inteation with PCNT and localization at centromere
rs821616	A/T	Non Synonymous Coding	Interaction with ATF4 and ATF5
rs61737326	C/T	Non Synonymous Coding	Interaction with PAFAH1B1

these can play a major role in gene disruption. The next favorable damaging spot can be rs78852015 which was identified damaging by both Panther and PolyPhen-2.

Phenotypic Effect by PupaSuite: The server was tested for all the parameters of the software including Non-synonomous SNPs, omega result, Transcription factor binding site, micro RNA, conserved regions and exonic splicing enhancers. The result was obtained only for omega, conserved regions and non – synonomous SNPs. The omega result for 3 SNPs (6%), Conserved regions for 10 SNPs (21%) and non-synonomous SNPs for 50 SNPs (100%) was obtained by PupaSuite. The SNPs given as input did not include any exonic splicing enhancers (ESEs). The 24 SNPs were negative for all the others parameters also as shown in Table 3.

Risk Analysis by FastSNP: Polymorphism in the 3’ UTR region affects the gene expression by affecting the ribosomal translation of mRNA or by influencing the RNA half-life [29]. The 5’ and 3' UTRs are involved in various biological processes such as posttranscriptional regulatory pathways, stability and translational efficiency [30,31]. We found that out of 3 UTR SNPs, all in 3’ UTR region with ids rs821616, rs2806455 and rs61737326 respectively were predicted to be damaging by FAST SNP server as depicted in Table 4.

Table 4: List of SNPs (UTR mRNA) predicted to be functionally significant by FastSNP UTR position

SNP ID(rs)	Allele	UTR position	Level of risk	Possible Functional Effects
rs821616	A/T	3' UTR	Medium-High	Splicing regulation
rs2806455	C/A	3' UTR	Low-Medium	Splicing regulation
rs61737326	C/T	3' UTR	Low-Medium	Splicing regulation

CONCLUSION

DISC1 is a potential target for the analysis and detection of the psychiatric illness as in bipolar disorder. The 24 functional SNPs found were all with their specific function and role in illness. The in depth study of the protein is important to understand the molecular biology of the illness and to find an appropriate diagnosis with treatment. The study can be done by structure analysis and evolutionary study. But for DISC1 the evolutionary origin is obscure with rapid evolution and unusual amino acids in helix. DISC1 is found to be orthologous in diverse eukaryotic organisms, including early in invertebrates though absent in *Drosophila* [32]. Even with the structural information about DISC1 no crystallographic structure of the protein is available. The future scope of study is to obtain the 3D structure of the protein in order to investigate the effects of defective DISC1 gene on the mental disorders and develop diagnostic tools.

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