Journal of Pharmacology Research, ISSN: 0976–7134 & E-ISSN: 0976–7142 , Vol. 1, Issue 1, 2010, PP-09-16

Computational intelligence towards the Schizophrenia- A neuropsychiatric abnormality in humans

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Abstract- Schizophrenia is psychiatric diagnosis that describes a neuropsychiatric abnormality and mental disorder. As per the current research status of this hazardous disorder, we built a model of a target sequence that is our interested sequence is a protein sequence of schizophrenia which is not yet predicted. There are no unambiguously homologous structure in PDB though there are clues that can be brought together to align ate target with a possible template and build model. We may no claims that the model is correct; its purpose is to illustrate the kind of processes to build a partial 3D model of a protein based on a distant similarity. The process for building an initial homology model starts with searching homology model from PDB by both FASTA and BLAST. Then we put the sequence for secondary structure prediction into HNN. We also calculated physical properties of that sequence with the help of ProtParam then after that we used three well known methods to calculate 3D structure of our sequence of interest. First of all we find the homologous sequence from PDB search then we put that sequence in Swiss model to find the template sequence and after that put query sequence for modeling structure using template. Second method we used is Geno3D, by that we find template according to the sequence similarity. We got sequence list from that we selected three templates and the result is in the form of Ramachandran plots and also with PDB file. The third method is offline method using MODELLER software. The template found from sequence similarity and our target protein sequence we put together into alignment files written in Python and got PDB file of our query. We also calculated the structural alignment of query and target (structure from modeller) with the help of Combinatorial Extension (CE). At the last we verified the modeled 3D structure with help of verify 3D from NCBI.

Introduction

Schizophrenia is defined as a *psychiatric diagnosis* that describes a neuropsychiatric abnormality and mental disorder characterized by abnormalities in the perception or expression of reality. It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking with significant social or occupational dysfunction. Onset of symptoms typically occurs in young adulthood, with around 0.4–0.6% of the population affected. Diagnosis is based on the patient's self-reported experiences and observed behavior. No *laboratory test for schizophrenia currently exists*. Studies suggest that genetics, early environment, neurobiology, psychological and social processes are important contributory factors; Current psychiatric research is focused on the role of neurobiology, but no single organic cause has been found. As a result of the many possible combinations of symptoms, there is debate about whether the diagnosis represents a single disorder or a number of discrete syndromes.[1] Despite its etymology, schizophrenia is not the same as dissociative identity disorder, previously known as *multiple personality disorder or split personality*, with which it has been erroneously confused. *Increased dopamine activity in the mesolimbic pathway of the brain is consistently found in schizophrenic individuals.* The mainstay of treatment is antipsychotic medication; this type of drug primarily works by suppressing dopamine activity. Psychotherapy, and vocational and social rehabilitation are also important. People with schizophrenia are likely to have additional (comorbid) conditions, including major depression and anxiety disorders, the lifetime occurrence of substance abuse is around 40%. Social problems, such as long-term unemployment, poverty and homelessness, are common. Furthermore, the average life expectancy of people with the disorder is 10 to 12 years less than those without, due to increased physical health problems and a higher suicide rate.[2]

Diagnosis

Schizophrenia is diagnosed on the basis of symptom profiles. Neural correlates do not provide sufficiently useful criteria. Diagnosis is based on the self-reported experiences of the person, and abnormalities in behavior reported by family members, friends or co-workers, followed by a clinical assessment by a psychiatrist, social worker, clinical psychologist or other mental health professional. Psychiatric assessment includes a psychiatric history and some form of mental status examination [3]. Characteristic symptoms: Two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).

a. Delusions

b. Hallucinations

c. Disorganized speech, which is a manifestation of formal thought disorder

d. Grossly disorganized behavior (e.g. dressing inappropriately, crying frequently) or catatonic behavior

e. Negative symptoms: Blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

Status of schizophrenia in INDIA

March 2004 - On the 6th of February, 2004, the President of India, APJ Abdul Kalam, launched a nationwide campaign in Chennai to remove the stigma and discrimination associated with mental illness. He was addressing the 20th Anniversary of the Schizophrenia Research Foundation (SCARF), the country's leading NGO research facility in the field. Schizophrenia is among the ten most disabling conditions that affect mankind. Of the 30 million mentally ill Indians, over seven million suffer from schizophrenia, the most disabling of all psychiatric disorder [5].

Dr. Kalam emphasized the need for a greater understanding of the disease. Activists and mental health professionals welcomed this campaign, stressing that even the media failed to distinguish between different mental health conditions. In his newly released book "The Splintered Mind" (Penguin India Books), author and counselor Dr.Vijay Nagaswamy comments on the tendency to generalize and label mental health under the umbrella of 'lunacy' or 'madness'.[6] The media uses the term 'schizo' or 'schizophrenic' to label dichotomous descriptions adding to the prevailing confusion/misunderstanding. A wider understanding of schizophrenia is needed [7].

MATERIALS AND METHODS

We are implementing the bioinformatics approach in the case study of Schizophrenia. With the help of online as well as offline resources, some noticeable outputs have been observed which are mentioned and given below:

Ab- initio structure prediction

Comparative protein modeling

Conformational Analysis and best template searching

Model generation via Modeller 9v7.

Structure prediction and model generation:

The given query sequence belongs to the case study of Schizophrenia disrupted in schizophrenia 1 isoform 49 [Homo sapiens]

Disrupted in schizophrenia 1 isoform 49 [Homo sapiens]

MSNKEGSGGFRKRKHDNFPHNQRREGKDVNSSSPVMLAFKSFQQELDARHDKYERLVKLSRDITVESK
RTIFLLHRITSAPDMEDILTESEIKLDGVRQKIFQVAQELSGEDMHQFHRAITTGLQEYVEAVSFQHFIKTRS
LISMDEINKQLIFTTEDNGKENKTKFTGKILLTEALGIKADRSSI

186 aa protein

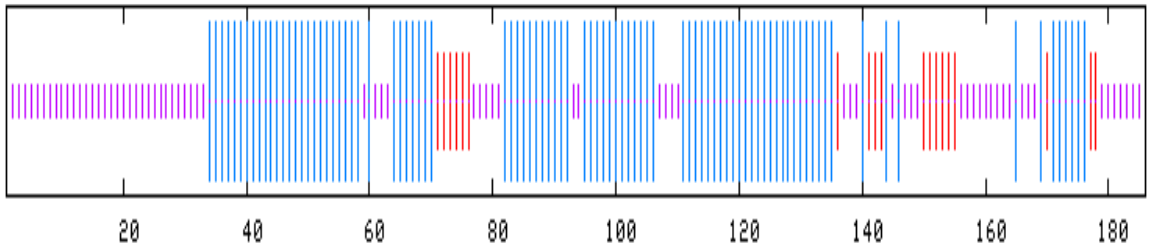


Fig. 1- From the linear sequence, secondary structure is predicted with percentage composition of secondary structure elements.

Query sequence to template searching via Swissmodel workspace

Interpro scan detects the location of 2 motifs corresponds the functional regulation:

IPR002848: Translin, Family

PF01997: 50 - 185

noIPR , unintegrated

SSF74784: 33 - 159 Translin

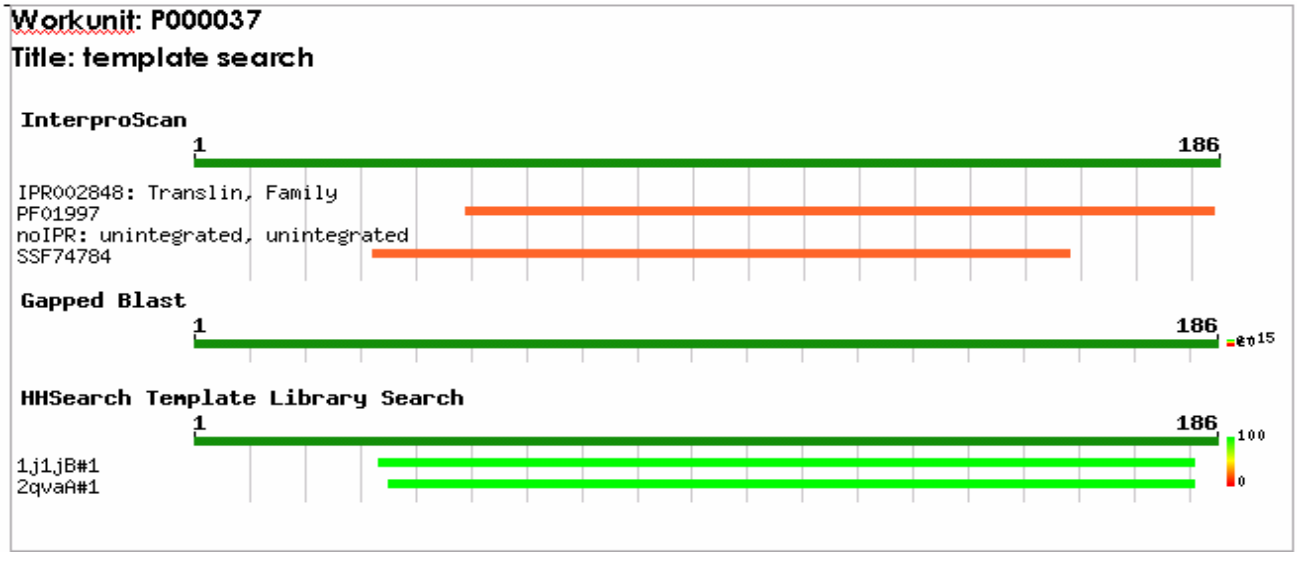


Fig. 2- Similarity searching via gapped blast showing the consensus sites in between the query sequence

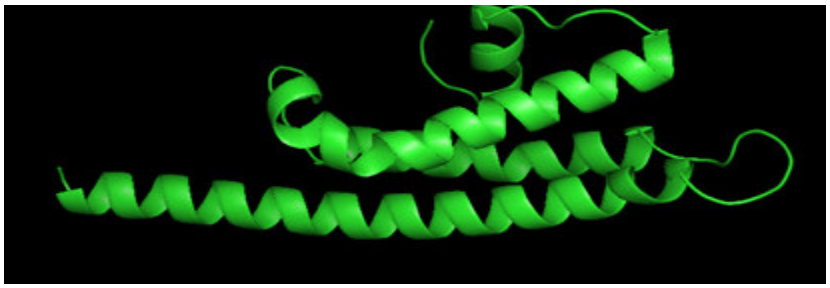


Fig. 3- Model Structure generation via swiss model workspace

Full template model analysis

Models energy evaluation in (kcal/mol):

. Model 1: +4875.36

. Model 2: -2546.60

. Model 3: -2341.17

Stereochemical quality of models with PROCHECK

	Core	allowed	generously	disallowed
Model 1	50.0%	37.5%	7.1%	5.4%

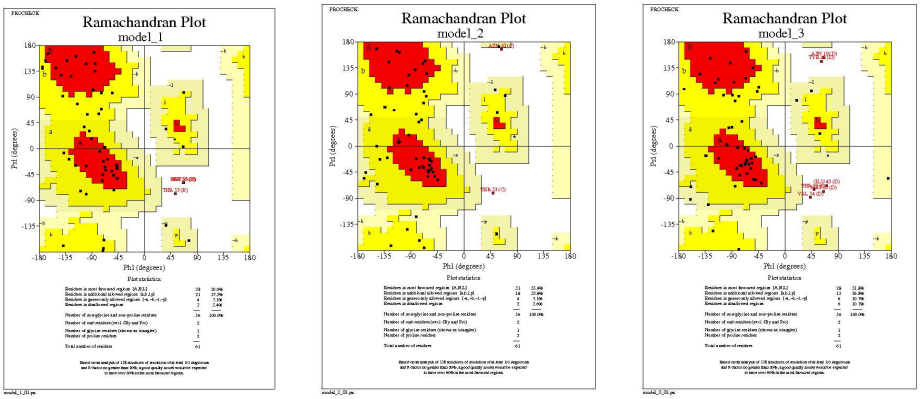
. Ramachandran plot analysis via procheck

Model 2	55.4%	33.9%	7.1%	3.6%

. Ramachandran plot analysis via procheck

Model 3	51.8%	26.8%	10.7%	10.7%

. Ramachandran plot analysis via procheck



Model1 Model 2 Model 3

Fig. 4- Conformational plots of 3 models in which 3rd is best due to maximum core

Region and minimum residues in the disallowed region

With respect to our query sequence of schizophrenia, templates models are observed in which percentage identity is existing. Thus, with the help of conformational analysis of template models, we are assuming the best model against the query sequence of schizophrenia. In this manner, the second model is supposed to be best in terms of maximum confirmation in the core area, minimum residues in the disallowed region and minimum energy in kcal/mol.

Structural alignment analysis via Combinatorial extension

Model generation via combinatorial extension (CE)

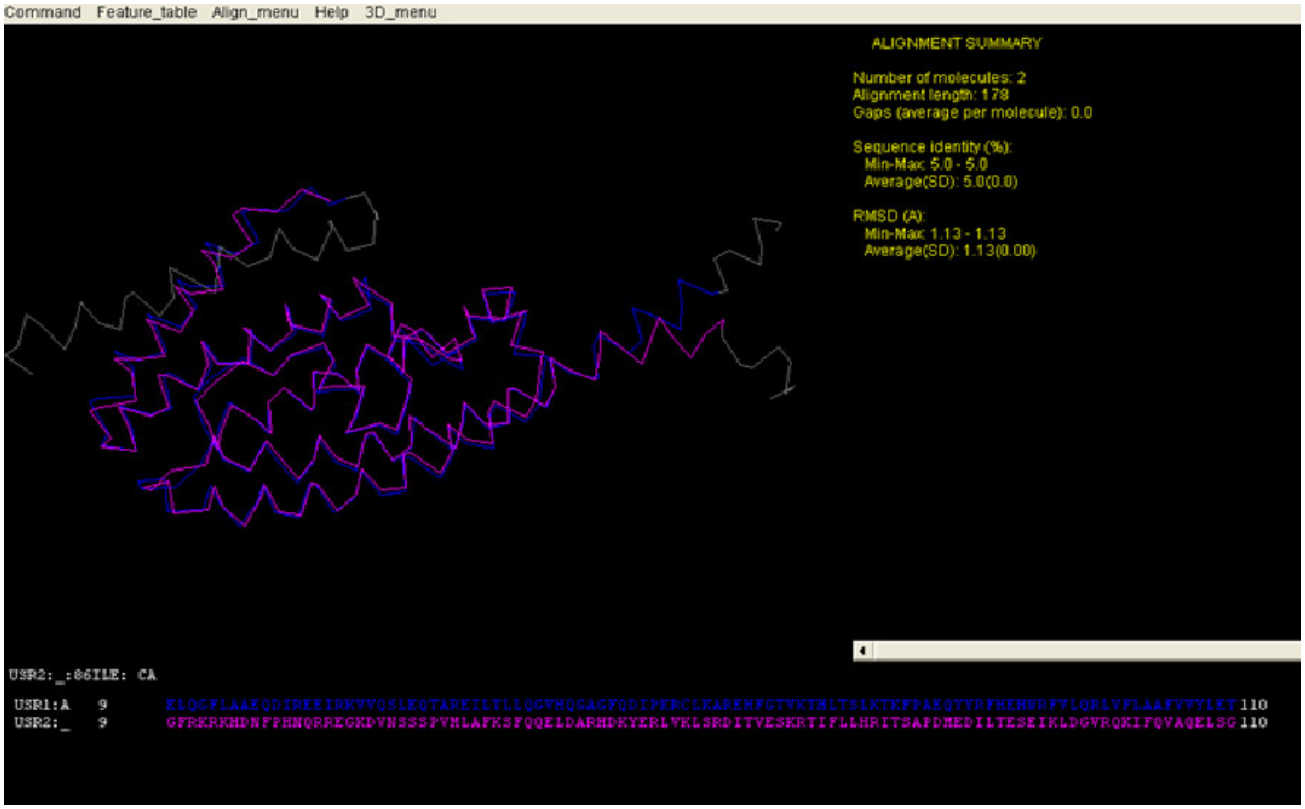


Fig. 5- Prepared model in between query and subject

Model preparation via Modeller 9v7.

MODELLER is used for homology or comparative modeling of protein three-dimensional structures. We are providing an alignment file of a sequence to be modeled with known related structures and then MODELLER automatically calculates a model containing all non-hydrogen atoms.

Input of Python file for modeller

```
# Homology modeling with multiple templates
from modeller import *              # Load standard Modeller classes
from modeller.automodel import *    # Load the automodel class

log.verbose()    # request verbose output
env = environ()  # create a new MODELLER environment to build this model in

# directories for input atom files
env.io.atom_files_directory = ['.', '../atom_files']

a = automodel(env,
              alnfile  = 'align-multiple.ali', # alignment filename
              knowns   = ('1J1J'),     # codes of the templates
              sequence = '1fdx')               # code of the target
a.starting_model= 1                 # index of the first model
a.ending_model  = 1                 # index of the last model
                                    # (determines how many models to calculat
a.make()                            # do the actual homology modeling
```

Fig. 6- Alignment file for supporting python file

```
C; A multiple alignment in the PIR format; used in tutorial

>P1;1J1J
structureX:1J1J:    1 :A:+868 :D:MOL_ID  1; MOLECULE  TRANSLIN; CHAIN  A, B, C,
MSVSEIFVELQGFLAAEQDIREEIRKVVQSLEQTAREILTLLQGVHQGAGFQDIPKRCLKAREHFGTVKTHLTSL
KTKFPAEQYYRFHEHWRFVLQRLVFLAAFVVYLETETLVTREAVTEILGIEPDREKGFHLDVEDYLSGVLILASE
LSRLSVNSVTAGDYSRPLHISTFINELDSGFRLLNLKNDSLRKRYDGLKYDVKKVEEVVYDLSIRGF/MSVSEIF
VELQGFLAAEQDIREEIRKVVQSLEQTAREILTLLQGVHQGAGFQDIPKRCLKAREHFGTVKTHLTSLKTKFPAE
QYYRFHEHWRFVLQRLVFLAAFVVYLETETLVTREAVTEILGIEPDREKGFHLDVEDYLSGVLILASELSRLSVN
SVTAGDYSRPLHISTFINELDSGFRLLNLKNDSLRKRYDGLKYDVKKVEEVVYDLSIRGF/MSVSEIFVELQGFL
AAEQDIREEIRKVVQSLEQTAREILTLLQGVHQGAGFQDIPKRCLKAREHFGTVKTHLTSLKTKFPAEQYYRFHE
HWRFVLQRLVFLAAFVVYLETETLVTREAVTEILGIEPDREKGFHLDVEDYLSGVLILASELSRLSVNSVTAGDY
SRPLHISTFINELDSGFRLLNLKNDSLRKRYDGLKYDVKKVEEVVYDLSIRGF/MSVSEIFVELQGFLAAEQDIR
EEIRKVVQSLEQTAREILTLLQGVHQGAGFQDIPKRCLKAREHFGTVKTHLTSLKTKFPAEQYYRFHEHWRFVLQ
RLVFLAAFVVYLETETLVTREAVTEILGIEPDREKGFHLDVEDYLSGVLILASELSRLSVNSVTAGDYSRPLHIS
TFINELDSGFRLLNLKNDSLRKRYDGLKYDVKKVEEVVYDLSIRGF*


>P1;1fdx
sequence:1fdx:1     : :54    : :ferredoxin:Peptococcus aerogenes: 2.00:-1.00
MSNKEGSGGFRKRKHDNFPHNQRREGKDVNSSSPVMLAFKSFQQELDARHDKYERLVKLSRDITVESKRT
IFLLHRITSAPDMEDILTESEIKLDGVRQKIFQVAQELSGEDMHQFHRAITTGLQEYVEAVSFQHFIKTR
SLISMDEINKQLIFTTEDNGKENKTKFTGKILLTEALGIKADRSSI*
```

Fig. 7- Files created by MODELLER when run from command prompt

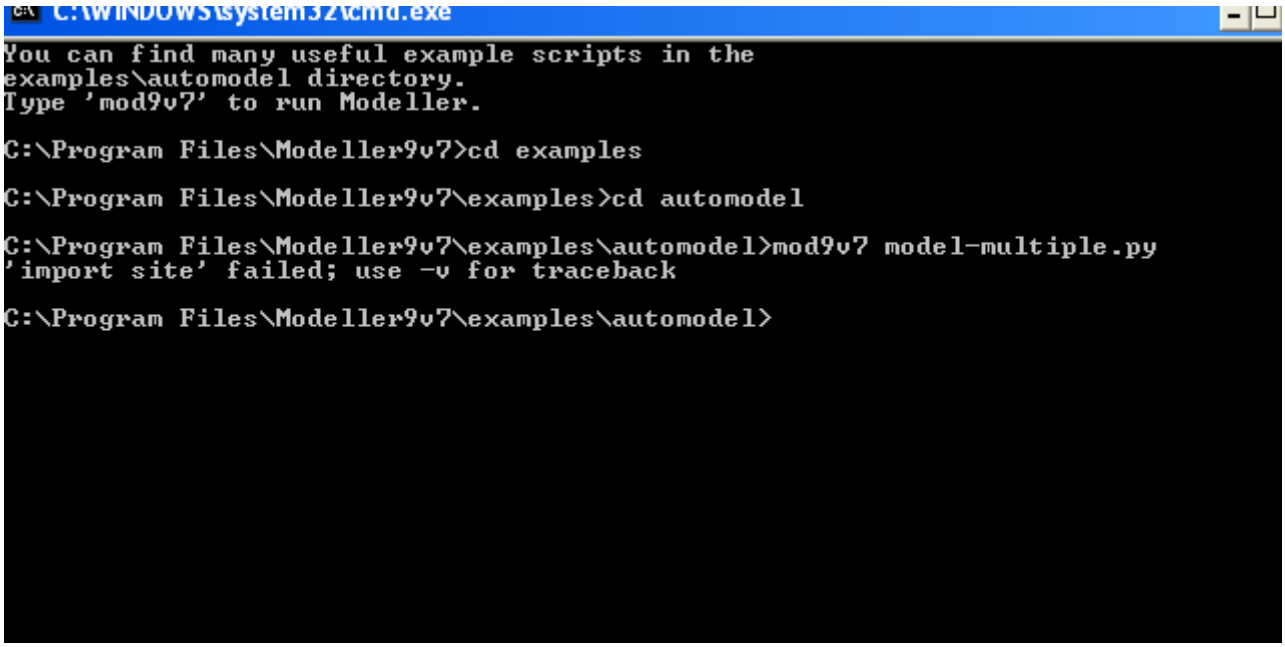


Fig.8- Result from modeller by taking template 1J1J

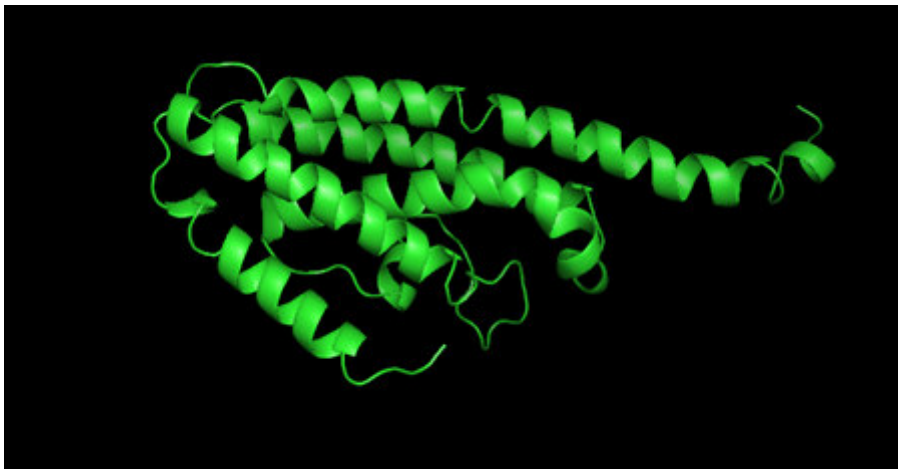


Fig.9- Target Model prepared by Modeller.

Conclusion

With the implementations of Bioinformatics approach, we have prepared a predicted protein model corresponds to Schizophrenia, because right now- a very least and limited information is known regarding this topic. Till now not any type of structural information is known thus with the help of homology modeling and comparative modeling concept, we find outs the possible and related templates in which percentage similarity occurs. For future proceedings we are trying to design chemical fragment to block the binding pocket site of this predictive protein, and provide the novel lead compound to designing of novel drug for schizophrenia.

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