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Research Article

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RPIA (ribose 5-phosphate isomerase A) - [Homo sapiens (human)]-Genomic analysis and structure prediction

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Abstract

RPI deficiency. Ribose-5-phosphate isomerase deficiency is a human disorder caused by mutations in the pentose phosphate pathway enzyme ribose-5-phosphate isomerase Developmental delay, insidious psychomotor regression, epilepsy, leukoencephalopathy and abnormal polyol metabolism.seizures, psychomotor regression and diffuse white matter abnormality Neonatal onset leukoencephalopathy and psychomotor delays. Cause of Ribose-5-Phosphate Isomerase Deficiency. Ribose-5-Phosphate Isomerase Deficiency: New Inborn Error in the Pentose Phosphate Pathway Associated with a Slowly Progressive Leukoencephalopathy.The molecular cause of the pathology is not fully understood. One hypothesis is that ribose-5-phosphate may lack for RNA The main objective is to find out the treatment for the rpi deficiency which inhibits in the pathway and find a cure by genomic and structural analysis by the protein sequence.

Keywords: RPIA ribose 5-phosphate isomerase A [Homo sapiens (human)], Pentose Phosphate shunt pathway,epilepsy, leukoencephalopathy, abnormal polyol metabolism.

1. Introduction

Ribose-5-phosphate isomerase deficiency, a disorder of the pentose phosphate shunt, was described in 1999. There are 2 previously reported cases of ribose-5-phosphate isomerase deficiency. Here, we describe the clinical course, diagnostic odyssey, and molecular findings in the third case of ribose-5-phosphate isomerase deficiency to further delineate the syndrome. Whole-exome sequencing demonstrated 2 mutations in the ribose-5-phosphate isomerase gene, RPIA, in a child with neonatal onset leukoencephalopathy and psychomotor delays. Urine polyols were elevated confirming deficiency of ribose-5-phosphate isomerase (RPI, EC. 5.3.1.6) and pathogenicity of the variants. Measurement of urine polyols should be considered in cases of early-onset white-matter disease[1]

We report on a subject with RPIA associated progressive leukoencephalopathy with elevated urine arabitol and ribitol levels and a novel missense variant c.770T > C p.(Ile257Thr) in exon 8 of RPIA. We also compare the phenotypes of all the four subjects. Our report confirms the phenotype and the genetic cause of this condition[2]

Genetic information :

RPIA ribose 5-phosphate isomerase A [Homo sapiens (human)]				
Gene ID: 22934, updated on 2-Mar-2021 Official Full Name ribose 5-phosphate isomerase. A Gene type				
protein coding. Organism :Homo sapiens.				
Lineage : Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo				
Location:2p11.2				
Exon count: 9				
Annotation release	Status	Assembly	Chr	Location
109.20210226	current	GRCh38.p13 (GCF_000001405.39)	2	NC_000002.12 (88691673..88750929)
105.20201022	previous assembly	GRCh37.p13 (GCF_000001405.25)	2	NC_000002.11 (88991191..89050446)
NC_000002.12		Chromosome 2 - [88627629 [88825207 EIF2AK3-DT RPIA MIR4436A LOC102724805 ANKRD36BP2 LOC105374853 MALLP2		

Fig.1

Target Sequence:

Homo sapiens chromosome 2, GRCh38.p13 Primary Assembly
>NC_000002.12:88691673-88750929 Homo sapiens chromosome 2, GRCh38.p13 Primary Assembly
AGCGGAGGCCGGAGCGAGGCGTCGGGATGCAGCGCCCCGGGCCCTTCAGCACCCTC TACGGGCGGGTCTT
GGCCCCGCTGCCCGGGAGGGCCGGGGGCGCGGCCTCCGGCGGAGGAGGGAACAGC TGGGACCTCCCGGGT
TCCCACGTGCGGCTGCCGGGGCGTGCACAGTCTGGGACCCGTGGCGGTGCTGGCAA CACAAGCACCAGCT
GCGGGGACTCCAACAGCATCTGCCCGGCCCCCTCCACGATGTCCAAGGCCGAGGAG GCCAAGAAGCTGGC
GGGCCGCGCGGCTGTGGAGAACCACGTGAGGGTGAGCACTTCGAAACGTGGGGCGC GGGGCGCATGTCCT
TGGCGTGATGGGCTACTGTTGCGCGTTGTGGGTGCTGCCGGGGCGCGCCTAGCTCCT GGCAGGGCGGGAG
CTGAGTGAGAGGGTAGAGGGTGTGCACTTTACCCGAGTTTAGACCCCTCTTCCCTGC TCCTTAAAGACCT
TTTAGATGTGGAATCGGTTGGGGGCGAATCTTCTAATACTTGAGCTTTCTAAAGACT CCTTGTCCAGCTG
GAACAGTTTGCAAAGTGGAGCCTGGTGCTGTCTGATGTTTGGAATGGGGGCTAGAG GCACTTGCCTTGTG
GCCTCCTTATCAATAAATGGAAAATGGTGGGCTTTGGGGCTGCGGAGAGGTTTTCAT TTCTCTTTACTGA
CCCGGAAGCCGGCGGAGAGTTGGTTTGCTAGTGCTTTGAAATTTCAGTCGAAGGAG GTTCTGGGCTTGGT
GCGCGCCGGCCCCTGAGTGTACTCTTGGAGGGAAGGGAAGACCCGGGGCTTCAAAC TTCCTTCTTTCCAT
AGGGCTGGGTGGACTAAGTCTGGAGGATGCTGGTTTATTTTTTAAGGCGGGTCTGCA GAGATGTTTAGCT
GTTATTCAGTCAGGTCGTGGTCCCTACTTGTTTGTTAAGTGGCAGGTGTGGTGCTGTT AGTGGAGTTTTT
TTAATCCAAGTGGTTTTGCTGTCACCAATCAAGTATCTTAATTATAATAAGGAAGCC AAGTGGAGTATGT
CTGCCCTGTGGTGTAGTTTCCTTGGTCTTATTGGCTTTTTATCTCTCGTTTCTACTTAT TAGAAAGTGGT
ATTAGAGTCTCTTTTCTTCTCCGATAATAGTTCTTTACATTTGTTAATGCTTTACAAA ATTATTTTGCTT
AGATGATGTTGGATGAGCTTCACCACAGCCTGTTTGAGTGGGAGTGGACAATGTGGT AACCTGTGGCTCA
Approved symbol- RPIA
Approved name -ribose 5-phosphate isomerase A
Chromosomal location 2p11.2

Fig.2

Protein Sequence:

>sp|P49247|RPIA_HUMAN Ribose-5-phosphate isomerase OS=Homo sapiens OX=9606 GN=RPIA PE=1 SV=3
MQRPGPFSTLYGRVLAPLPGRAGGAASGGGGNSWDLPGSHVRLPGRAQSGTRGGAGNTST
SCGDSNSICPAPSTMSKAEEAKKLAGRAAVENHVRNNQVLGIGSGSTIVHAVQRIAERVK
QENLNLVCIPTSFQARQLILQYGLTLSDLDRHPEIDLAIDGADEVDADLNLIKGGGGCLT
QEKIVAGYASRFIVIADFRKDSKNLGDQWHKGIPIEVIPMAYVPVSRAVSQKFGGVVELR
MAVNKAGPVVTDNGNFILDWKFDRVHKWSEVNTAIKMIPGVVDTGLFINMAERVYFGMQD
GSVNMREKPFC

2. Materials and Methods

MATERIALS:

NCBI:

NCBI is database which is used to charged with creating automated systems for storing and analyzing knowledge about molecular biology, biochemistry, and genetics.NCBI is now a leading source for public biomedical databases, software tools for analyzing molecular and genomic data, and research in computational biology.

PUBCHEM:

PUBCHEM is the database which is used to drug discovery and many aspects such as lead identification and optimization, compound-target profiling, polypharmacology studies and unknown chemical identity elucidation. **PubChem** has also become a valuable resource for developing secondary databases, informatics tools and web services.

UNIPROT

UNIPROT also called as SWISSPROTIt provides an up-to-date, comprehensive body of **protein** information at a single site.It aids scientific discovery by collecting, interpreting and organising this information so that it is easy to access and use.

SWISSMODEL

SWISSMODEL is the online web server dedicated to homology modeling of 3D protein structures. Homology modeling is currently the most accurate method to generate reliable three-dimensional protein structure models and is routinely used in many practical applications.

CASTp

CASTp can be used to study surface features and functional regions of proteins. CASTp includes a graphical user interface, flexible interactive visualization, as well as on-the-fly calculation for user uploaded structures

ProtParam

ProtParam is a tool which allows the computation of various physical and chemical parameters for a given protein stored in Swiss-Prot or TrEMBL or for a user entered protein sequence. The computed parameters include the molecular weight, theoretical pI, amino acid composition, atomic composition, extinction coefficient, estimated half-life, instability index, aliphatic index and grand average of hydropathicity

GORIV

Goriv is used for secondary structure prediction of protein sequence

COILS

Coils is a program that compares a sequence to a database of known parallel two-stranded coiled-coils and derives a similarity score. By comparing this score to the distribution of scores in globular and coiled-coil proteins, the program then calculates the probability that the sequence will adopt a coiled-coil conformation.

PROCHECK

checks the stereochemical quality of a protein structure, producing a number of PostScript plots analysing its overall and residue-by-residue geometry.

Results and Discussion

1. Primary sequence alignment:

PROTPARAM:

Expasy

ProtParam

User-provided sequence:

```
        10         20         30         40         50         60
MQRPGPFSTL YGRVLAPLPG RAGGAASGGG GNSWDLPGSH VRLPGRAQSG TRGGAGNTST

        70         80         90        100        110        120
SCGDSNSICP APSTMSKAEE AKKLAGRAAV ENHVRNNQVL GIGSGSTIVH AVQRIAERVK

       130        140        150        160        170        180
QENLNLVCIP TSFQARQLIL QYGLTLSDLD RHPEIDLAID GADEVDADLN LIKGGGGCLT

       190        200        210        220        230        240
QEKIVAGYAS RFIVIADFRK DSKNLGDQWH KGIPIEVIPM AYVPVSRAVS QKFGGVVELR

       250        260        270        280        290        300
MAVNKAGPVV TDNGNFILDW KFDRVHKWSE VNTAIKMIPG VVDTGLFINM AERVYFGMQD

       310
GSVNMREKPF C
```

Fig.3

Number of amino acids: 311	
Molecular weight: 33268.94	
Theoretical pI: 8.78	
Amino acid composition: CSV format	
Ala (A)	27 8.7%
Arg (R)	19 6.1%
Asn (N)	16 5.1%
Asp (D)	17 5.5%
Cys (C)	5 1.6%
Gln (Q)	12 3.9%
Glu (E)	13 4.2%
Gly (G)	37 11.9%
His (H)	6 1.9%
Ile (I)	19 6.1%
Leu (L)	22 7.1%
Lys (K)	15 4.8%
Met (M)	8 2.6%
Phe (F)	10 3.2%
Pro (P)	16 5.1%
Ser (S)	21 6.8%
Thr (T)	12 3.9%
Trp (W)	4 1.3%
Tyr (Y)	5 1.6%
Val (V)	27 8.7%
Pyl (O)	0 0.0%
Sec (U)	0 0.0%
(B)	0 0.0%
(Z)	0 0.0%
(X)	0 0.0%

Total number of negatively charged residues (Asp + Glu): 30
Total number of positively charged residues (Arg + Lys): 34

Atomic composition:	
Carbon	C 1458
Hydrogen	H 2333
Nitrogen	N 427
Oxygen	O 438
Sulfur	S 13
Formula: $C_{1458}H_{2333}N_{427}O_{438}S_{13}$	
Total number of atoms: 4669	

Extinction coefficients:

Extinction coefficients are in units of M^{-1} cm^{-1}, at 280 nm measured in water.

Ext. coefficient 29700
Abs 0.1% (=1 g/l) 0.893, assuming all pairs of Cys residues form cystines

Ext. coefficient 29450
Abs 0.1% (=1 g/l) 0.885, assuming all Cys residues are reduced

Estimated half-life:

The N-terminal of the sequence considered is M (Met).

The estimated half-life is: 30 hours (mammalian reticulocytes, in vitro).
>20 hours (yeast, in vivo).
>10 hours (Escherichia coli, in vivo).

Instability index:

The instability index (II) is computed to be 33.62
This classifies the protein as stable.

Aliphatic index: 85.27

Grand average of hydropathicity (GRAVY): -0.177

2. Secondary Sequence alignment

GORIV:

Fig.4

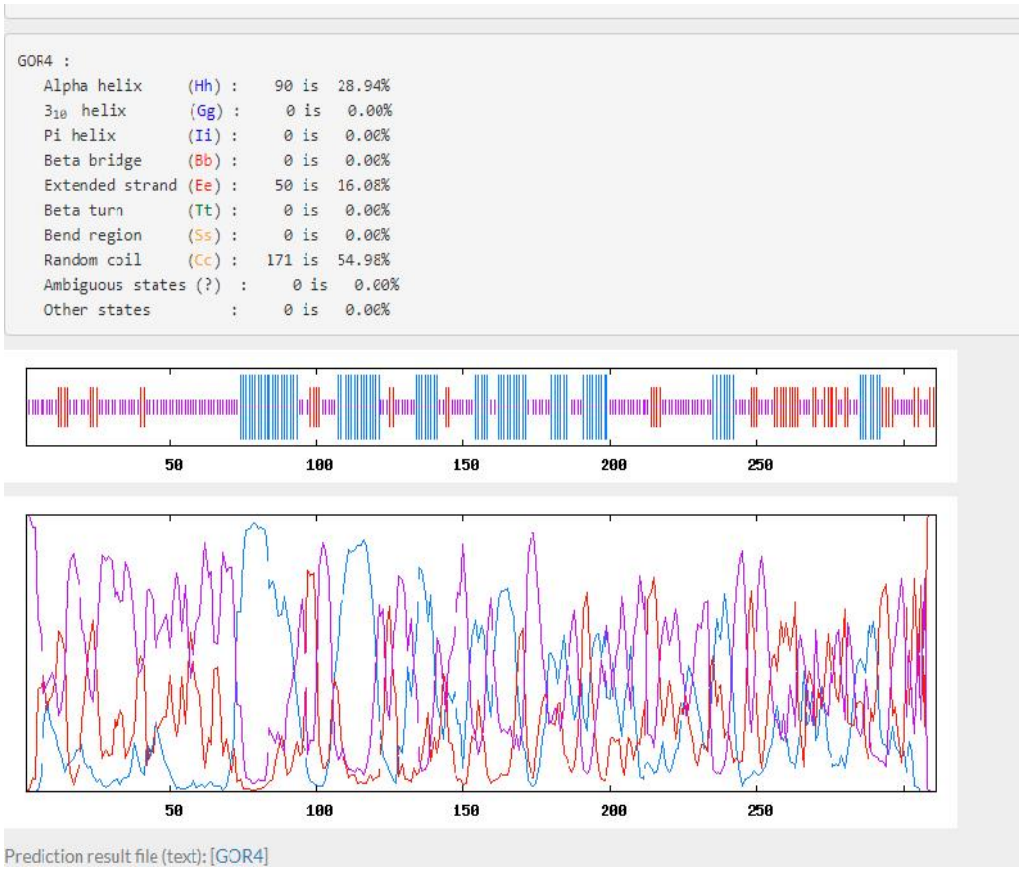


Fig.5

COILS:

NCOILS version 1.0
using MTIDK matrix
No weights
Input file is COILS.18814.6245.seq

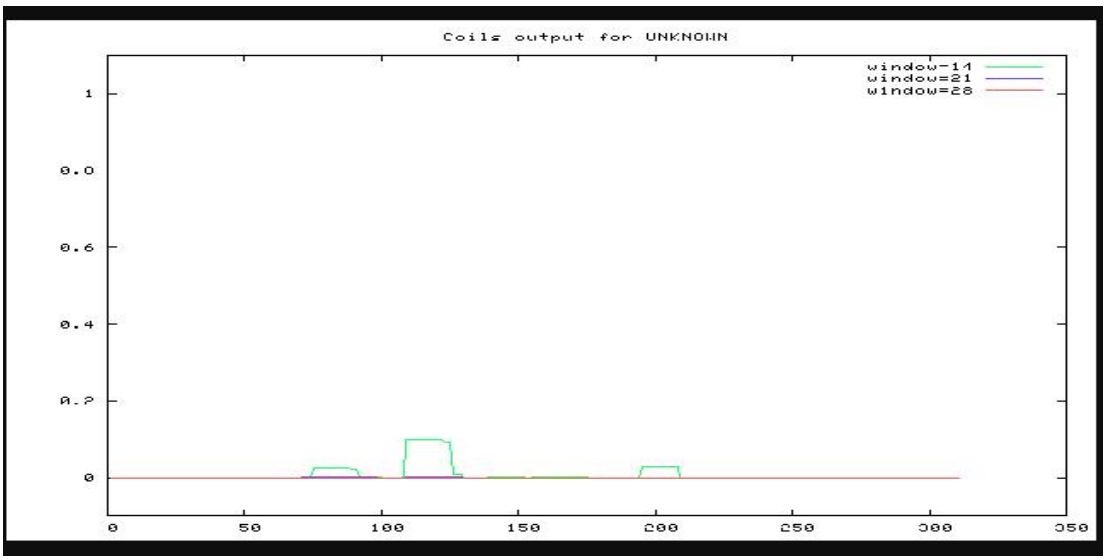


Fig.6

3. Tertiary Sequence Alignment

Model Evaluation :

SWISSMODEL :

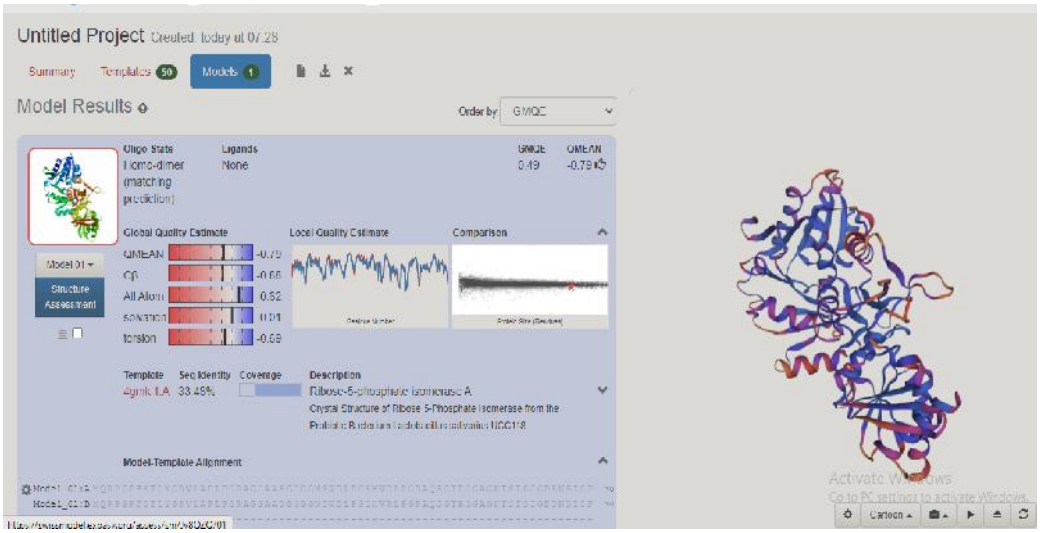


Fig.7

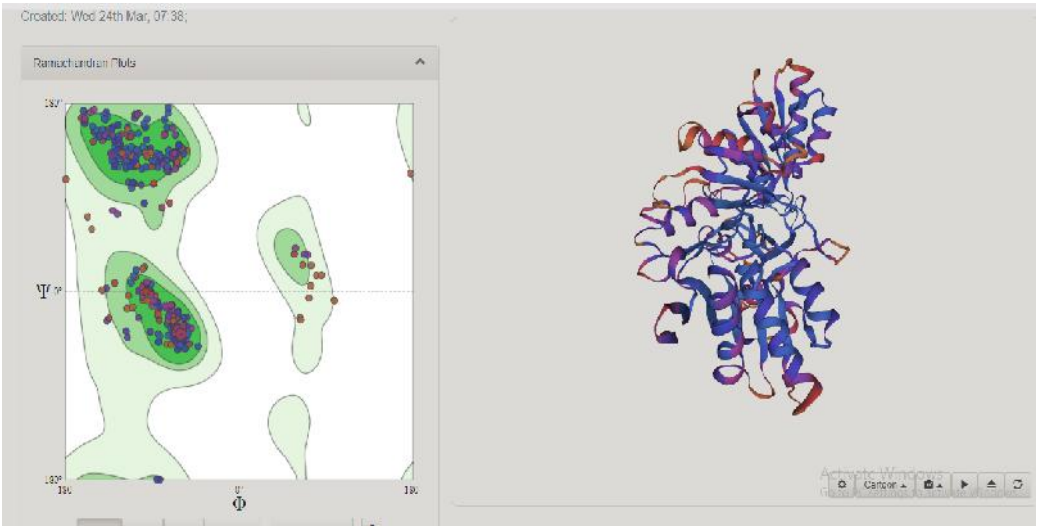


Fig.8

VERIFY 3D:

VERIFY3D

94.10% of the residues have
averaged 3D-1D score >= 0.2

Pass

At least 80% of the amino acids have scored >= 0.2 in the 3D/1D profile.

Fig.9

PROCHECK RESULTS:

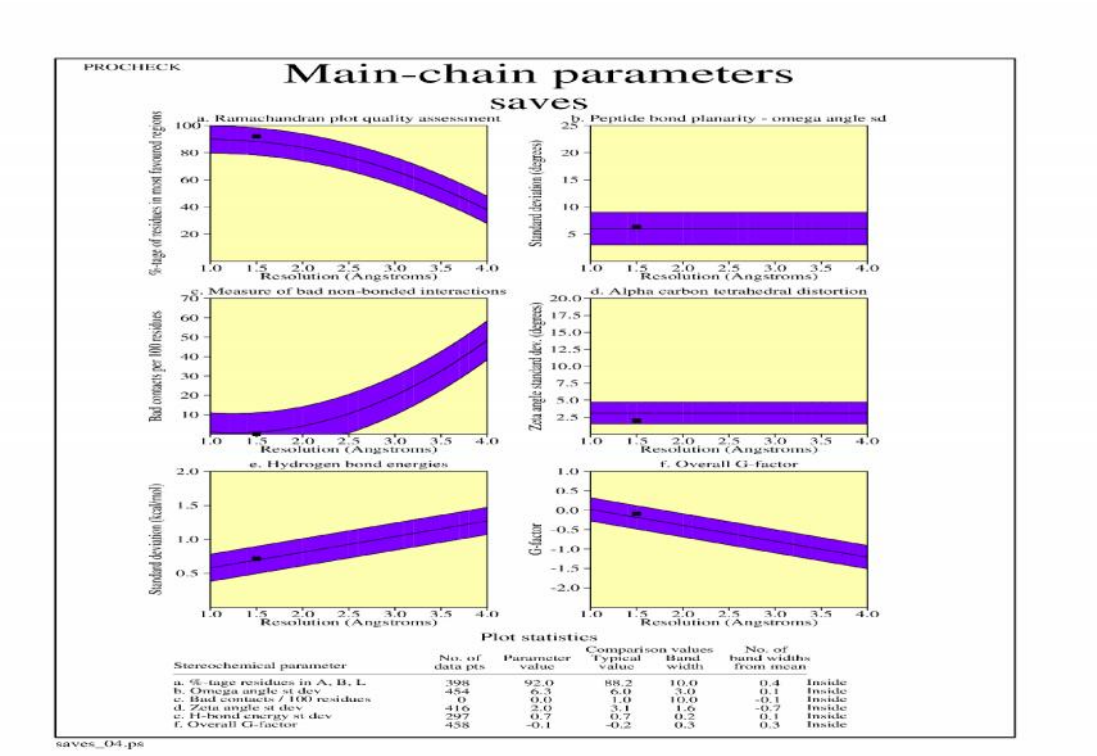


Fig.10

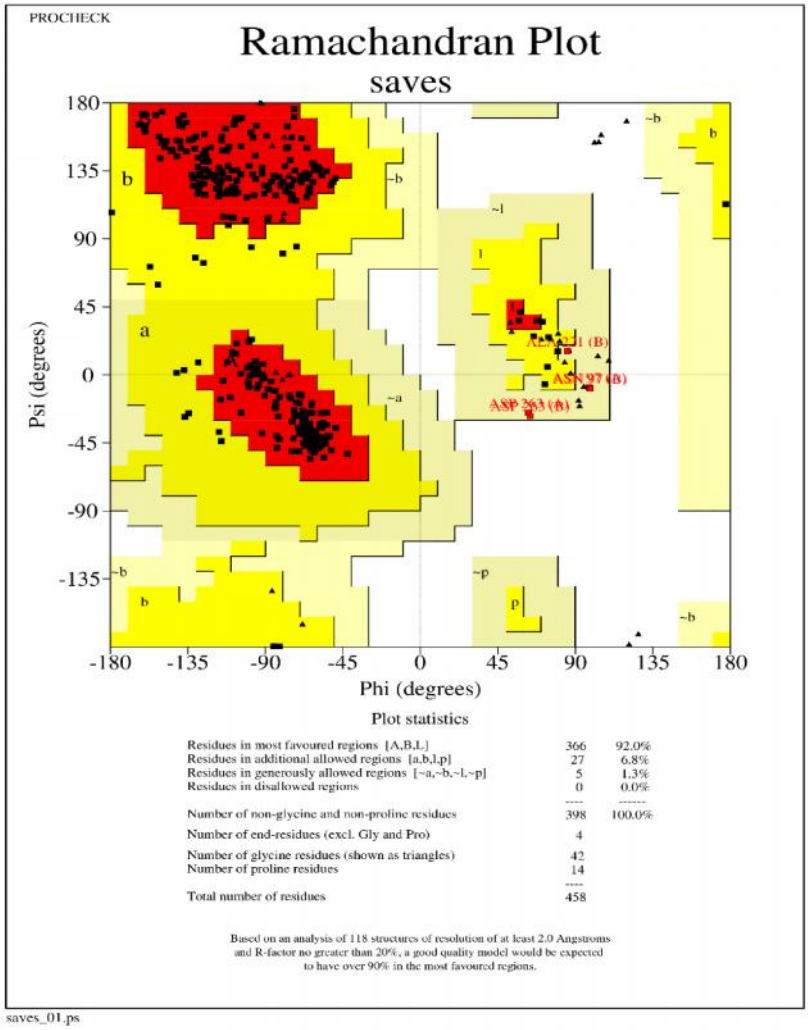


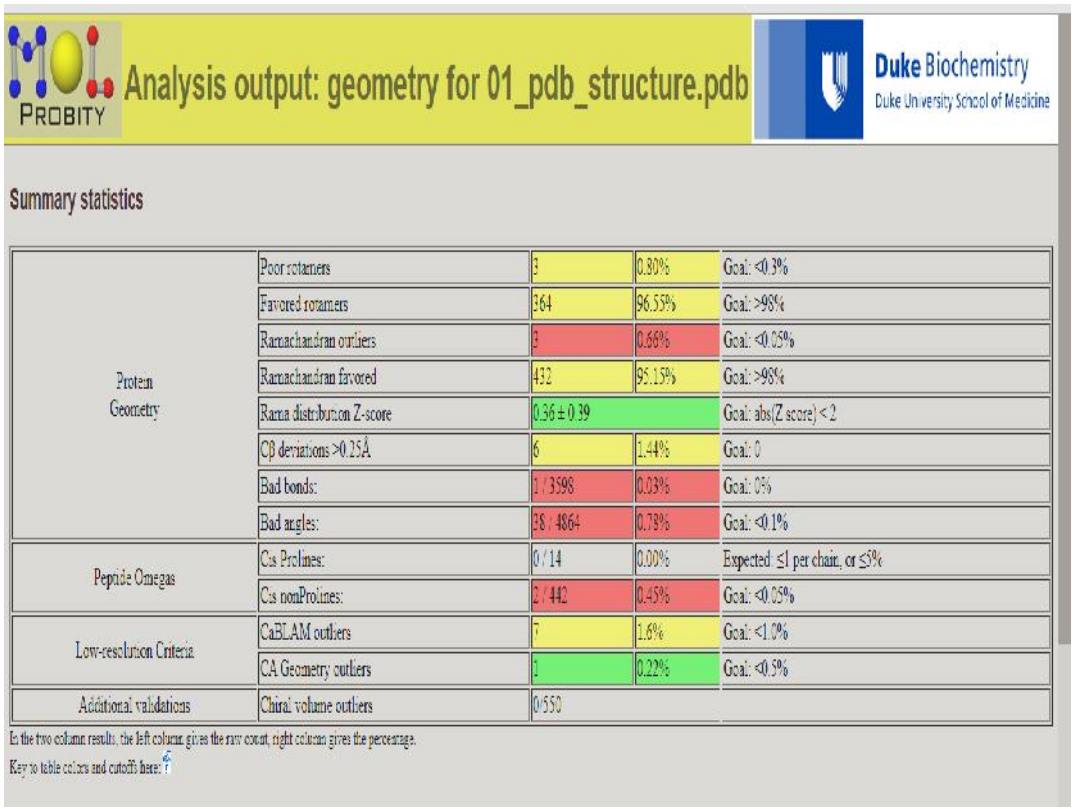
Fig.11

MOL PROBITY: (MODEL VALIDATION)

MolProbity:

MolProbity is a structure-validation web service that provides broad-spectrum solidly based evaluation of model quality at both the global and local levels for both proteins and nucleic acids. It relies heavily on the power and sensitivity provided by optimized hydrogen placement and all-atom contact analysis, complemented by updated versions of covalent-geometry and torsion-angle criteria. Some of the local corrections can be performed automatically in MolProbity and all of the diagnostics are presented in chart and graphical forms that help guide manual rebuilding. X-ray crystallography provides a wealth of biologically important molecular data in the form of atomic three-dimensional structures of proteins, nucleic acids and increasingly large complexes in multiple forms and states. Advances in automation, in everything from crystallization to data collection to phasing to model building to refinement, have made solving a structure using crystallo-graphy easier than ever. However, despite these improvements, local errors that can affect biological interpretation are widespread at low resolution and even high-resolution structures nearly all contain at least a few local errors such as Ramachandran outliers, flipped branched protein side chains and incorrect sugar puckers.

It is critical both for the crystallographer and for the end user that there are easy and reliable methods to diagnose and correct these sorts of errors in structures. MolProbity is the authors' contribution to helping solve this problem and this article reviews its general capabilities, reports on recent enhancements and usage, and presents evidence



Analysis output: geometry for 01_pdb_structure.pdb

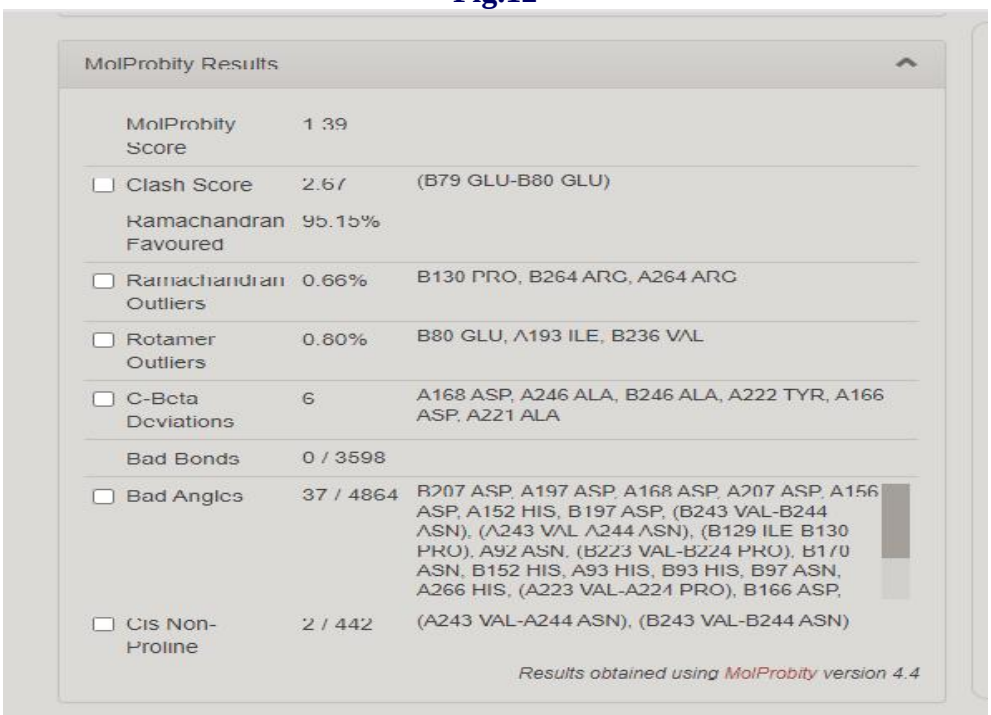
Duke Biochemistry
Duke University School of Medicine

Summary statistics

Protein Geometry	Poor rotamers	3	0.80%	Goal: <0.3%
	Favored rotamers	364	96.55%	Goal: >98%
	Ramachandran outliers	3	0.66%	Goal: <0.05%
	Ramachandran favored	432	95.15%	Goal: >98%
	Rama distribution Z-score	0.36 ± 0.39		Goal: abs(Z score) < 2
	Cβ deviations >0.25Å	6	1.44%	Goal: 0
	Bad bonds:	1 / 3598	0.03%	Goal: 0%
	Bad angles:	28 / 4864	0.78%	Goal: <0.1%
Peptide Omegas	Cis Prolines:	0 / 14	0.00%	Expected: ≤1 per chain, or ≤5%
	Cis nonProlines:	2 / 442	0.45%	Goal: <0.05%
Low-resolution Criteria	CaBLAM outliers	7	1.6%	Goal: <1.0%
	CA Geometry outliers	1	0.22%	Goal: <0.5%
Additional validations	Chiral volume outliers	0/550		

In the two column results, the left column gives the raw count, right column gives the percentage.
Key to table colors and cutoffs here:

Fig.12



MolProbity Results

MolProbity Score	1.39	
Clash Score	2.67	(B79 GLU-B80 GLU)
Ramachandran Favoured	95.15%	
Ramachandran Outliers	0.66%	B130 PRO, B264 ARG, A264 ARG
Rotamer Outliers	0.80%	B80 GLU, A193 ILE, B236 VAL
C-Beta Deviations	6	A168 ASP, A246 ALA, B246 ALA, A222 TYR, A166 ASP, A221 ALA
Bad Bonds	0 / 3598	
Bad Angles	37 / 4864	B207 ASP, A197 ASP, A168 ASP, A207 ASP, A156 ASP, A152 HIS, B197 ASP, (B243 VAL-B244 ASN), (A243 VAL-A244 ASN), (B129 ILE-B130 PRO), A92 ASN, (B223 VAL-B224 PRO), B170 ASN, B152 HIS, A93 HIS, B93 HIS, B97 ASN, A266 HIS, (A223 VAL-A224 PRO), B166 ASP,
Cis Non-Proline	2 / 442	(A243 VAL-A244 ASN), (B243 VAL-B244 ASN)

Results obtained using MolProbity version 4.4

Fig.13

Ramachandran plot PDF

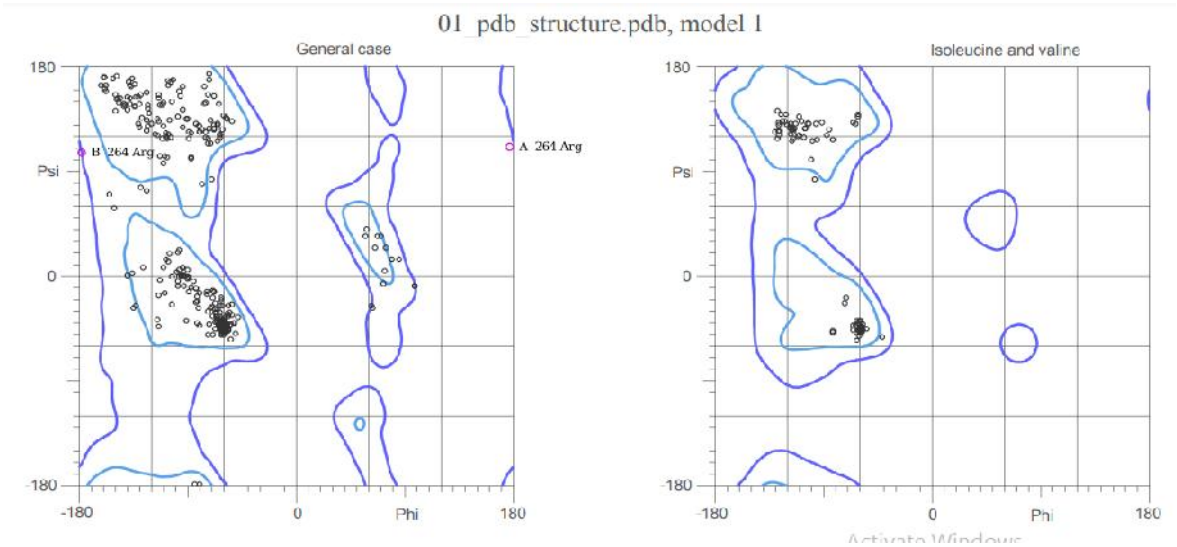


Fig.14

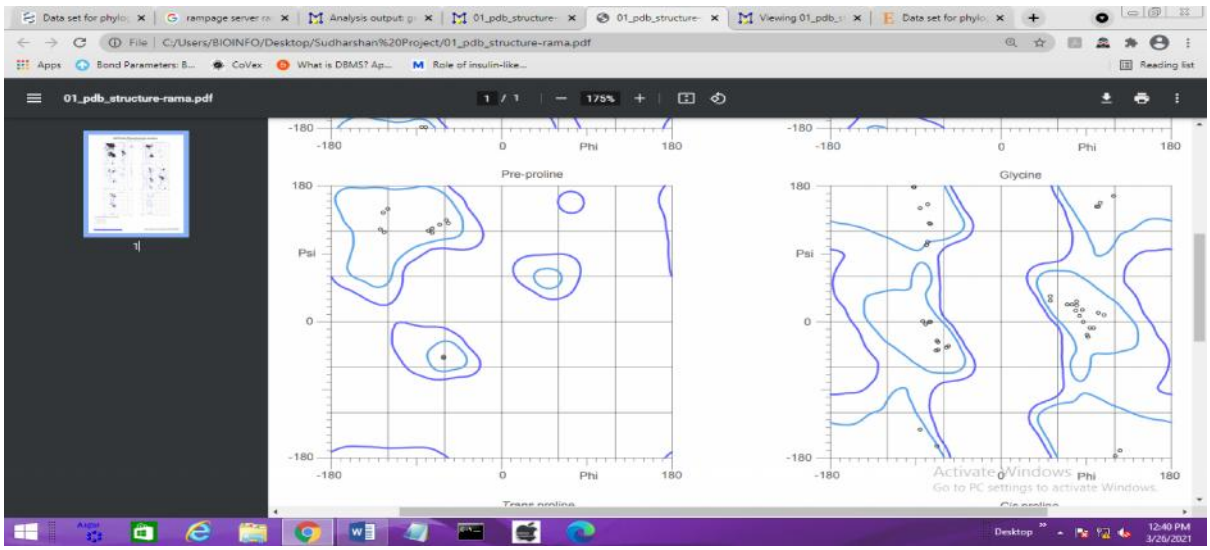


Fig.15

Ramachandran distribution Z-score analysis

Rama-Z (Ramachandran plot Z-score):
Interpretation: bad |Rama-Z| > 3; suspicious 2 < |Rama-Z| < 3; good |Rama-Z| < 2.
Scores for whole/helix/sheet/loop are scaled independently; therefore, the values are not related in a simple manner.
whole: 0.36 (0.39), residues: 454
helix: 1.23 (0.39), residues: 152
sheet: -0.43 (0.52), residues: 111
loop : 0.02 (0.44), residues: 191

Conclusion

RPI deficiency is a novel inborn error in the PPP. The most likely explanation for the biochemical abnormalities in our patient is that deficient conversion of ribulose 5-phosphate into ribose-5-phosphate leads to accumulation of pentoses and pentose phosphates, which in turn lead to accumulation of ribitol and D-

arabitol as metabolic end products. Ribose-5-phosphate isomerase deficiency (RPI deficiency) is a human disorder caused by mutations in the pentose phosphate pathway enzyme ribose-5-phosphate isomerase.

- One allele is a non-functional null allele, while the other encodes for a partially active enzyme. Furthermore, the partially functional allele has expression deficits that depend on the cell type in which it is expressed. Therefore, some of the patient's cells have a considerable amount of RPI activity, whereas others do not.
- The molecular cause of the pathology is not fully understood. One hypothesis is that ribose-5-phosphate may be insufficient for RNA synthesis. Another possibility is that the accumulation of D-ribitol and D-arabitol may be toxic.

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