Research Article

The Association between *SLC25A15* Gene Polymorphisms and Hyperornithinemia-hyperammonemia-homocitrullinuria Syndrome: Using In Silico Analysis

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Background: Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is an autosomal recessive inborn error of the urea cycle. It is caused by mutations in the *SLC25A15* gene that codes the mitochondrial ornithine transporter. The aim of this study is to detect and identify the pathogenic SNPs in *SLC25A15* gene through a combination set of bioinformatics tools and their effect on the structure and function of the protein.

Methods: The deleterious SNPs in *SLC25A15* are detected by various bioinformatics tools, with addition to identifying their effects on the structure and function of this gene.

Results: 20 deleterious SNPs out 287of were found to have their own damaging effects on the structure and function of the *SLC25A15* gene.

Conclusion: This study is the first in silico analysis of *SLC25A15* using a selection of bioinformatics tools to detect functional and structural effects of deleterious SNPs. Finding the pathogenic SNPs is a promising start to innovate new, useful SNP diagnostic markers for medical testing and for safer novel therapies specifically targeting mutant *SLC25A15*.

Keywords:

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH), *SLC25A15*, SNPs, urea cycle, in silico analysis.

1. Introduction:

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is an autosomal recessive inborn error of the urea cycle (1-5), (OMIM#238970) (6-8), it is located on chromosome 13q14(7, 9). This syndrome occurs in the early infancy or childhood period, although, few cases of adult onset have also been reported (7, 10-14). HHH syndrome is caused by mutations in the *SLC25A15* gene that codes the mitochondrial ornithine transporter, which transports ornithine across the inner mitochondrial membrane from the cytosol to the mitochondrial matrix (15). This is a vital step in the urea cycle, which serves to eliminate toxic ammonium ions from the breakdown of nitrogen (6, 16-21). The HHH clinical symptoms are highly variable, which include spastic paraplegia, extrapyramidal signs, stroke-like episodes, hypotonia, seizures, ataxia, protein intolerance, failure to thrive, pyramidal dysfunction developmental delay/intellectual disability, hepatic failure (13, 16, 20, 22-24), and even death can arise if the condition is not diagnosed early and treated quickly (25).

Even though, this disease targets a wide variation of different ethnicities, Canada (23%), Italy (17%) and Japan (13%) were reported with the highest prevalence rates (15, 26-28)

Albeit HHH treatment includes a strict treatment protocol consisting control of dietary protein, nitrogen forager medications, as well as, amino acid and vitamins supplementations, still there is no effective therapy for this type of inborn disease (4, 22-25), thus identifying the *SLC25A15* gene holds a promising future tool to improve both survival rates as well as the quality of life in surviving of HHH patients(29, 30).

Detection and identification of pathogenic SNPs of *SLC25A15* through different in silico prediction software are the main aims of this study. As well as, to determine the structure, bio functions and the regulatory mechanism of their respective proteins. This study is the first in silico analysis of the *SLC25A15* coding region. Using this approach to identify the pathogenic SNPs with no cost; novel therapies specifically targeting mutant *SLC25A15* will open new methods of treatment for HHH patients(31).

2. Methods:

2.1 Data Mining:

The *SLC25A15* human gene data was obtained from the National Center for Biotechnology Information (NCBI) (<http://www.ncbi.nlm.nih.gov/>). The variant's information of the gene was collected from the NCBI dbSNP database (<http://www.ncbi.nlm.nih.gov/snp/>) and the *SLC25A15* protein sequence was obtained from UniProt database (<https://www.uniprot.org/>).

2.2 SIFT:

The Sorting Intolerant from Tolerant (SIFT) algorithm is a standardized tool for detecting all missense SNPs in the protein sequence by searching for homologous sequences and carry out multiple sequence alignment. The score of each variant ranges from 0 to 1, deleterious SNP is considered when the score is ≤ 0.05 , while tolerated SNP's score is >0.05 (32, 33) SIFT is an available online tool (34) (<http://sift-dna.org>).

2.3 PolyPhen-2:

PolyPhen-2 (polymorphism phenotyping v2) is a tool that predicts the impact of substitution of the amino acid on the structure and function of the protein. The input data needs accession number, position of variants, original and mutant amino acids. The PolyPhen figures the PSIC (position-specific independent count) and counts the score difference between the two variants. When resulted with a score of (0.96–1) it's considered 'Probably damaging', while (0.71–0.95) scores considered as 'Possibly damaging and Benign' (0.31–0.7) (32, 35, 36). PolyPhen-2 is available at (<http://genetics.bwh.harvard.edu/pph2/>).

2.4 PROVEAN:

PROVEAN (Protein Variation Effect Analyzer), is an algorithm, which accurately predicts the impact of single amino acid substitutions, multiple substitutions, insertions and deletions(37). The tool accepts a protein sequence and amino acid variations as input, performs a BLAST to identify homologous sequences, and generates the scores. A variant is predicted to be 'deleterious' if the final score is below -2.5 , and is predicted to be 'neutral' otherwise (37, 38). It is available at (<http://provean.jcvi.org/index.php>).

2.5 PHD-SNP:

Predictor of Human Deleterious Single Nucleotide Polymorphisms; is an online Support Vector Machine SVM-based classifier. It predicts whether the amino acid substitution is deleterious or neutral (39). It is available at (<http://snps.biofold.org/phd-snp/phd-snp.html>).

2.6 SNPs&GO:

Single Nucleotide Polymorphism Database & Gene Ontology is a support vector machine (SVM) based method. The information derived from the protein sequence, structure, and protein function; it needs a whole protein in FASTA sequence, and/or its three-dimensional structure, a target SNP and its functional Gene Ontology (GO) terms to be an input option. The output provides, for each protein variation, the probabilities to be disease or neutral. The score of predicted variants is 82% accurate with Matthews's correlation coefficient of 0.63 and if it is > 0.5 this is defined as a 'disease' (39-41). It is freely available at (<http://snps.biofold.org/snps-and-go/snps-and-go.html>)

2.7 PANTHER:

Protein Analysis through evolutionary relationships, is used for analysis of variants, it utilizes hidden Markov model (HMM) based statistical methods and multiple sequence alignments which create the substitution position-specific evolutionary conservation score (subPSEC). The SNPs is considered deleterious with score (< -3) and neutral with (score > -3) (39). It is available at (<http://www.pantherdb.org/>)

2.8 P-Mut:

P-Mut is an online tool annotates and predicts the damaging mutations. Pmut is rely on sequence information of any protein to identify the mutations. It delivers a very simple output: a yes/no answer and a reliability index. Its methods performance is 84 % overall success rate, and 67 % improvement over random (42-44). It is available at (<http://mmb.irbbarcelona.org/PMut/>).

2.9 I-Mutant 3.0:

I-Mutant is a neural-network-based tool for prediction of protein stability and modulation upon single amino acid substitution. The protein sequence and variant position is needed for input data. The output is the predicted free energy change (DDG), which classifies the prediction into: 'large decrease' ($DDG < -0.5$ kcal/mol), 'large increase' ($DDG > 0.5$ kcal/mol), or 'neutral' ($-0.5 < DDG < 0.5$ kcal/mol) (39, 44). It is available at (<http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi>).

2.10 MUPro:

A support vector machine-based bioinformatics tool, MUPro, is used for predicting the stability changes of a protein upon nonsynonymous SNPs. The value of the energy change is assumed, and a confidence score among -1 and 1 for measuring the confidence of the assumption is calculated. A score <0 shows that the variable reduces the protein stabilization and vice versa (45). It is available at (<http://mupro.proteomics.ics.uci.edu/>).

2.12 Project HOPE

Have Our Protein Explained, is an online next-generation tool used for mutant analysis. HOPE's layout demonstrates the molecular origin of disease's phenotype which results from protein mutation. The Web services and DAS servers are used to collect the data. The sources from which HOPE gathers the data are 'Protein's 3D structure' and the 'UniProt database', of well-annotated protein sequences. For each protein, this data is stored in a PostgreSQL-based information system. The data is processed and used to predict the mutation impact on the 3D structure and the function of the protein. The report is generated, is supported with figures and clarify the effects of mutation. Lastly the report can be utilized to design follow-up experiments, better diagnostic & medicines (46). Available at (<http://www.cmbi.ru.nl/hope/input/>).

2.11 RaptorX

Since the human *SLC25A15* protein's 3D structure is unavailable in the Protein Data Bank, RaptorX software was used to obtain the 3D structural model for wild-type of SLC25A15. RaptorX is a bioinformatics web server predicts the structural property of a protein sequence without the need of any templates. It surpasses other servers, chiefly for proteins without close homologs in PDB or with very sparse sequence profile (47). It is available at (<http://raptorx.uchicago.edu/>).

2.12 UCSF Chimera:

This desktop application is for the interactive visualization and analysis of molecular structures and related data. The application features are expanded due to incorporation of the web access with desktop tool. The features include the accomplishing computationally intense work and is able to connect to databases. Chimera is subdivided into a 'Core', which is responsible for basic services and visualization, and 'Extensions', that contain new features with higher functionality.

These extensions are Multialign Viewer, docking, trajectories, visualize large-scale molecular assemblies, etc. chimera images with high resolution. This application can generate an animation (48). Chimera is available at (<http://www.cgl.ucsf.edu/chimera/>).

2.13 GeneMANIA:

GeneMANIA is an online server generating proposition about gene function, investigating gene lists and prioritizing genes for functional assays. It expands the query list with functionally similar genes that recognizes by using available genomics and proteomics data. The high accuracy of the GeneMANIA prediction algorithm and large database make the GeneMANIA an useful tool for any biologist (49, 50) . It is available at (<http://genemania.org/>).

Figure 1: Diagrammatic representation of *SLC25A15* gene in silico work flow.

3. Result and discussion:

3.1 Result:

Table (1): Deleterious – damaging (Affected) nsSNPs predicted by various software:

Amino acid change	SIFT		POLYPHEN-2		PROVEAN	
	Prediction	Score	Prediction	Score	Prediction (cutoff=-2.5)	Score
D31H	AFFECTED	0.00	probably damaging	1	Deleterious	-6.651
D31Y	AFFECTED	0.00	probably damaging	1	Deleterious	-8.551
Y64C	AFFECTED	0.00	probably damaging	1	Deleterious	-8.418
G66S	AFFECTED	0.00	probably damaging	1	Deleterious	-5.634
L71Q	AFFECTED	0.00	probably damaging	1	Deleterious	-4.892
G86C	AFFECTED	0.00	probably damaging	1	Deleterious	-8.585
G113C	AFFECTED	0.00	probably damaging	1	Deleterious	-8.512
G168E	AFFECTED	0.00	probably damaging	1	Deleterious	-6.745
T176A	AFFECTED	0.00	probably damaging	1	Deleterious	-4.81
F188S	AFFECTED	0.00	probably damaging	1	Deleterious	-7.651
G216S	AFFECTED	0.00	probably damaging	1	Deleterious	-5.543
G217R	AFFECTED	0.00	probably damaging	1	Deleterious	-5.213
G220R	AFFECTED	0.00	probably damaging	1	Deleterious	-7.39
K234I	AFFECTED	0.00	probably damaging	1	Deleterious	-7.488
Q238R	AFFECTED	0.00	probably damaging	1	Deleterious	-3.795
R275Q	AFFECTED	0.00	probably damaging	1	Deleterious	-3.64
R275L	AFFECTED	0.00	probably damaging	1	Deleterious	-6.303
Y287H	AFFECTED	0.00	probably damaging	1	Deleterious	-4.617

E288K	AFFECTED	0.00	probably damaging	1	Deleterious	-3.773
E288G	AFFECTED	0.00	probably damaging	1	Deleterious	-6.603

Table (2): Disease-associated nsSNPs predicted by various software:

Amino acid change	SNP&GO			PHD-SNP			PANTHER		
	Prediction	RI	Score	Prediction	RI	Score	Prediction	RI	Score
D31H	Disease	4	0.719	Disease	7	0.863	Disease	10	0.992!
D31Y	Disease	7	0.842	Disease	9	0.933	Disease	10	0.995
Y64C	Disease	6	0.797	Disease	8	0.915	Disease	8	0.905
G66S	Disease	6	0.794	Disease	8	0.908	Disease	10	1
L71Q	Disease	5	0.77	Disease	6	0.793	Disease	6	0.82
G86C	Disease	1	0.539	Disease	4	0.721	Disease	5	0.775
G113C	Disease	6	0.801	Disease	8	0.89	Disease	8	0.916
G168E	Disease	7	0.826	Disease	7	0.828	Disease	7	0.85
T176A	Disease	2	0.609	Disease	1	0.574	Disease	0	0.525
F188S	Disease	6	0.78	Disease	8	0.877	Disease	6	0.814
G216S	Disease	4	0.718	Disease	6	0.793	Disease	10	0.988
G217R	Disease	6	0.779	Disease	7	0.874	Disease	2	0.618
G220R	Disease	7	0.841	Disease	8	0.914	Disease	8	0.882
K234I	Disease	6	0.799	Disease	7	0.874	Disease	10	0.999
Q238R	Disease	4	0.7	Disease	6	0.799	Disease	3	0.633
R275Q	Disease	5	0.76	Disease	7	0.847	Disease	10	0.986
R275L	Disease	7	0.851	Disease	9	0.932	Disease	10	0.991
Y287H	Disease	3	0.649	Disease	7	0.868	Disease	3	0.65
E288K	Disease	5	0.743	Disease	9	0.943	Disease	0	0.503
E288G	Disease	1	0.537	Disease	7	0.875	Disease	1	0.558

Table (3): Disease-associated nsSNPs predicted by P-Mut software:

Amino acid change	P-Mut Prediction	P-Mut Score
D31H	Disease	0.85 (91%)
D31Y	Disease	0.86 (91%)
Y64C	Disease	0.85 (91%)
G66S	Disease	0.85 (91%)
L71Q	Disease	0.76 (88%)
G86C	Disease	0.76 (88%)
G113C	Disease	0.86 (91%)
G168E	Disease	0.73 (87%)
T176A	Disease	0.71 (86%)
F188S	Disease	0.86 (91%)
G216S	Disease	0.63 (83%)
G217R	Disease	0.86 (91%)
G220R	Disease	0.86 (91%)
K234I	Disease	0.86 (91%)
Q238R	Disease	0.74 (87%)
R275Q	Disease	0.86 (91%)
R275L	Disease	0.86 (91%)
Y287H	Disease	0.80 (89%)
E288K	Disease	0.85 (91%)
E288G	Disease	0.85 (91%)

Table (4): The effect of the deleterious SNPs on the stability predicted by 2 software:

Amino acid change	I- mutant			MUPRO	
	SVM2 Prediction Effect	RI	DDG Value Prediction	Prediction	Score
D31H	Decrease	-0.16	1	Decrease	-1.1775469
D31Y	Increase	0.46	3	Decrease	-0.68362433
Y64C	Decrease	-1.33	3	Decrease	1.09234
G66S	Decrease	-1.5	9	Decrease	-0.66844573
L71Q	Decrease	-2.24	9	Decrease	-1.8046296
G86C	Decrease	6	-1.12	Decrease	-0.46574415
G113C	Decrease	1	-0.64	Decrease	-0.13197126
G168E	Increase	3	-0.54	Decrease	-0.40969468
T176A	Decrease	8	-1.18	Decrease	-1.526078
F188S	Decrease	7	-1.62	Decrease	-1.740386
G216S	Increase	-0.76	1	Decrease	-0.98156517
G217R	Increase	-0.34	1	Decrease	-1.1923443
G220R	Decrease	-0.39	1	Decrease	-0.50470067
K234I	Decrease	0.19	1	Increase	0.014638836
Q238R	Decrease	-0.22	2	Decrease	-1.0081246
R275Q	Decrease	-0.93	7	Decrease	-0.6423489
R275L	Decrease	-0.32	7	Decrease	-0.007036716
Y287H	Decrease	-1.37	6	Decrease	-1.6533478
E288K	Decrease	-0.75	8	Decrease	-1.1400911
E288G	Decrease	-1.14	7	Decrease	-1.3861129

Table (5): The *SCL25A15* gene function and its appearance in network and genome:

Function	FDR	Genes in network	Genes in genome
alpha-amino acid metabolic process	1.90205E-06	7	142
nitrogen cycle metabolic process	0.001517377	3	12
urea metabolic process	0.001517377	3	11
acute inflammatory response	0.003303863	4	66
cellular amino acid catabolic process	0.009215468	4	90
amide biosynthetic process	0.022215719	3	35
inflammatory response	0.028672552	5	283
complement activation	0.031243953	3	43
cellular modified amino acid metabolic process	0.034067443	4	145
carboxylic acid catabolic process	0.042072255	4	161
organic acid catabolic process	0.042072255	4	161
protein activation cascade	0.059994966	3	61
alpha-amino acid catabolic process	0.067027879	3	65
small molecule catabolic process	0.075684161	4	199

Table (6): The gene co-expressed, shared domain and interaction with *SCL25A15* gene network:

Gene 1	Gene 2	Weight	Network group
<i>G6PC</i>	<i>ARG1</i>	0.013130839	Co-expression
<i>CTH</i>	<i>SLC25A15</i>	0.026114333	Co-expression
<i>ARG1</i>	<i>HAL</i>	0.015584574	Co-expression
<i>BAAT</i>	<i>HAL</i>	0.010479293	Co-expression
<i>BAAT</i>	<i>ARG1</i>	0.010356814	Co-expression
<i>C4BPB</i>	<i>BAAT</i>	0.009120464	Co-expression
<i>MTHFS</i>	<i>SLC25A15</i>	0.025209978	Co-expression
<i>MTHFS</i>	<i>CTH</i>	0.023388306	Co-expression
<i>MBL2</i>	<i>HAL</i>	0.012773992	Co-expression
<i>MBL2</i>	<i>HGD</i>	0.00896276	Co-expression
<i>C5</i>	<i>HAL</i>	0.011430247	Co-expression
<i>C5</i>	<i>ARG1</i>	0.01082647	Co-expression
<i>C5</i>	<i>BAAT</i>	0.00760778	Co-expression
<i>C5</i>	<i>C4BPB</i>	0.009530854	Co-expression

<i>C5</i>	<i>HGD</i>	0.007940412	Co-expression
<i>C5</i>	<i>MBL2</i>	0.009273721	Co-expression
<i>G6PC</i>	<i>HAL</i>	0.011071949	Co-expression
<i>G6PC</i>	<i>BAAT</i>	0.007867279	Co-expression
<i>G6PC</i>	<i>C4BPB</i>	0.009524476	Co-expression
<i>G6PC</i>	<i>HGD</i>	0.007717506	Co-expression
<i>G6PC</i>	<i>MBL2</i>	0.009207115	Co-expression
<i>G6PC</i>	<i>C5</i>	0.008035515	Co-expression
<i>LBP</i>	<i>HAL</i>	0.009203292	Co-expression
<i>LBP</i>	<i>ARG1</i>	0.009164802	Co-expression
<i>LBP</i>	<i>BAAT</i>	0.00658665	Co-expression
<i>LBP</i>	<i>HGD</i>	0.006415015	Co-expression
<i>LBP</i>	<i>MBL2</i>	0.007615251	Co-expression
<i>LBP</i>	<i>C5</i>	0.006644955	Co-expression
<i>LBP</i>	<i>G6PC</i>	0.006901765	Co-expression
<i>SLC17A2</i>	<i>HAL</i>	0.010264788	Co-expression
<i>SLC17A2</i>	<i>BAAT</i>	0.007278958	Co-expression
<i>SLC17A2</i>	<i>C4BPB</i>	0.009022474	Co-expression
<i>SLC17A2</i>	<i>HGD</i>	0.007203176	Co-expression
<i>SLC17A2</i>	<i>MBL2</i>	0.008483202	Co-expression
<i>SLC17A2</i>	<i>C5</i>	0.007472467	Co-expression
<i>SLC17A2</i>	<i>G6PC</i>	0.007659466	Co-expression
<i>SLC17A2</i>	<i>LBP</i>	0.006347752	Co-expression
<i>ORM1</i>	<i>HAL</i>	0.009871504	Co-expression
<i>ORM1</i>	<i>ARG1</i>	0.009783008	Co-expression
<i>ORM1</i>	<i>BAAT</i>	0.007071007	Co-expression
<i>ORM1</i>	<i>C4BPB</i>	0.008490616	Co-expression
<i>ORM1</i>	<i>MBL2</i>	0.008121029	Co-expression
<i>ORM1</i>	<i>C5</i>	0.007148504	Co-expression
<i>ORM1</i>	<i>G6PC</i>	0.007398048	Co-expression
<i>ORM1</i>	<i>LBP</i>	0.006209759	Co-expression
<i>ORM1</i>	<i>SLC17A2</i>	0.006826424	Co-expression
<i>PREP</i>	<i>SLC25A15</i>	0.010442503	Co-expression
<i>SERPINA7</i>	<i>MBL2</i>	0.013247599	Co-expression
<i>CPS1</i>	<i>HAL</i>	0.01234286	Co-expression
<i>ARG1</i>	<i>SLC25A15</i>	0.005247516	Co-expression
<i>ARG1</i>	<i>CTH</i>	0.005402988	Co-expression
<i>BAAT</i>	<i>SLC25A15</i>	0.00938927	Co-expression
<i>BAAT</i>	<i>HAL</i>	0.008351558	Co-expression
<i>BAAT</i>	<i>ARG1</i>	0.004348387	Co-expression
<i>C4BPB</i>	<i>SLC25A15</i>	0.009231251	Co-expression

<i>C4BPB</i>	<i>HAL</i>	0.00814306	Co-expression
<i>C4BPB</i>	<i>BAAT</i>	0.007613069	Co-expression
<i>HGD</i>	<i>HAL</i>	0.013029266	Co-expression
<i>HGD</i>	<i>ARG1</i>	0.006771524	Co-expression
<i>HGD</i>	<i>BAAT</i>	0.012214398	Co-expression
<i>HGD</i>	<i>C4BPB</i>	0.011807794	Co-expression
<i>MBL2</i>	<i>SLC25A15</i>	0.008736178	Co-expression
<i>MBL2</i>	<i>HAL</i>	0.007751754	Co-expression
<i>MBL2</i>	<i>BAAT</i>	0.007231998	Co-expression
<i>MBL2</i>	<i>C4BPB</i>	0.00703362	Co-expression
<i>MBL2</i>	<i>HGD</i>	0.011195325	Co-expression
<i>C5</i>	<i>SLC25A15</i>	0.006322735	Co-expression
<i>C5</i>	<i>HAL</i>	0.005552603	Co-expression
<i>C5</i>	<i>ARG1</i>	0.002911721	Co-expression
<i>C5</i>	<i>BAAT</i>	0.005179715	Co-expression
<i>C5</i>	<i>C4BPB</i>	0.005058356	Co-expression
<i>C5</i>	<i>HGD</i>	0.008068559	Co-expression
<i>C5</i>	<i>MBL2</i>	0.004826631	Co-expression
<i>G6PC</i>	<i>CTH</i>	0.006566833	Co-expression
<i>G6PC</i>	<i>CPS1</i>	0.007564845	Co-expression
<i>G6PC</i>	<i>ARG1</i>	0.002987566	Co-expression
<i>DIO1</i>	<i>ARG1</i>	0.003676503	Co-expression
<i>DIO1</i>	<i>C5</i>	0.004387379	Co-expression
<i>DIO1</i>	<i>G6PC</i>	0.004473042	Co-expression
<i>LBP</i>	<i>BAAT</i>	0.009965218	Co-expression
<i>LBP</i>	<i>C4BPB</i>	0.009667832	Co-expression
<i>LBP</i>	<i>MBL2</i>	0.009191572	Co-expression
<i>LBP</i>	<i>C5</i>	0.006629785	Co-expression
<i>SLC17A2</i>	<i>SLC25A15</i>	0.007915142	Co-expression
<i>SLC17A2</i>	<i>HAL</i>	0.007040063	Co-expression
<i>SLC17A2</i>	<i>CPS1</i>	0.009285137	Co-expression
<i>SLC17A2</i>	<i>BAAT</i>	0.006526508	Co-expression
<i>SLC17A2</i>	<i>C4BPB</i>	0.006351683	Co-expression
<i>SLC17A2</i>	<i>HGD</i>	0.010178178	Co-expression
<i>SLC17A2</i>	<i>MBL2</i>	0.006092981	Co-expression
<i>SLC17A2</i>	<i>C5</i>	0.004395986	Co-expression
<i>SLC17A2</i>	<i>DIO1</i>	0.005542256	Co-expression
<i>SLC17A2</i>	<i>LBP</i>	0.008360203	Co-expression
<i>ORM1</i>	<i>SLC25A15</i>	0.009182534	Co-expression
<i>ORM1</i>	<i>C5</i>	0.005041816	Co-expression
<i>ORM1</i>	<i>G6PC</i>	0.005162204	Co-expression

<i>SERPINA7</i>	<i>SLC25A15</i>	0.007883273	Co-expression
<i>SERPINA7</i>	<i>HAL</i>	0.006906412	Co-expression
<i>SERPINA7</i>	<i>CPS1</i>	0.009286882	Co-expression
<i>SERPINA7</i>	<i>ARG1</i>	0.003641196	Co-expression
<i>SERPINA7</i>	<i>C4BPB</i>	0.006316919	Co-expression
<i>SERPINA7</i>	<i>MBL2</i>	0.005971783	Co-expression
<i>SERPINA7</i>	<i>C5</i>	0.00436016	Co-expression
<i>SERPINA7</i>	<i>DIO1</i>	0.005475692	Co-expression
<i>SERPINA7</i>	<i>SLC17A2</i>	0.005462843	Co-expression
<i>SERPINA7</i>	<i>ORM1</i>	0.006366141	Co-expression
<i>CYP3A5</i>	<i>C4BPB</i>	0.009888263	Co-expression
<i>CYP3A5</i>	<i>MBL2</i>	0.009454532	Co-expression
<i>CYP3A5</i>	<i>C5</i>	0.006786631	Co-expression
<i>CYP3A5</i>	<i>SLC17A2</i>	0.008575552	Co-expression
<i>CYP3A5</i>	<i>ORM1</i>	0.009884344	Co-expression
<i>CYP3A5</i>	<i>SERPINA7</i>	0.008449458	Co-expression
<i>CTH</i>	<i>SLC25A15</i>	0.017681984	Co-expression
<i>HAL</i>	<i>SLC25A15</i>	0.011282469	Co-expression
<i>HAL</i>	<i>CTH</i>	0.018665954	Co-expression
<i>CPS1</i>	<i>SLC25A15</i>	0.014783018	Co-expression
<i>CPS1</i>	<i>CTH</i>	0.021131555	Co-expression
<i>CPS1</i>	<i>HAL</i>	0.01605092	Co-expression
<i>ARG1</i>	<i>SLC25A15</i>	0.01022149	Co-expression
<i>ARG1</i>	<i>CTH</i>	0.014448987	Co-expression
<i>ARG1</i>	<i>CPS1</i>	0.014791401	Co-expression
<i>BAAT</i>	<i>SLC25A15</i>	0.007653142	Co-expression
<i>BAAT</i>	<i>CPS1</i>	0.011089044	Co-expression
<i>BAAT</i>	<i>ARG1</i>	0.009111863	Co-expression
<i>C4BPB</i>	<i>CTH</i>	0.007979206	Co-expression
<i>HGD</i>	<i>SLC25A15</i>	0.009968358	Co-expression
<i>HGD</i>	<i>CTH</i>	0.011085113	Co-expression
<i>HGD</i>	<i>HAL</i>	0.008449321	Co-expression
<i>HGD</i>	<i>CPS1</i>	0.012882358	Co-expression
<i>HGD</i>	<i>ARG1</i>	0.009243058	Co-expression
<i>HGD</i>	<i>BAAT</i>	0.007479178	Co-expression
<i>MTHFS</i>	<i>C4BPB</i>	0.009367498	Co-expression
<i>C5</i>	<i>HAL</i>	0.007322867	Co-expression
<i>C5</i>	<i>MBL2</i>	0.010361436	Co-expression
<i>G6PC</i>	<i>SLC25A15</i>	0.016148888	Co-expression
<i>G6PC</i>	<i>CTH</i>	0.022236109	Co-expression
<i>G6PC</i>	<i>HAL</i>	0.01545969	Co-expression

<i>G6PC</i>	<i>CPS1</i>	0.01768735	Co-expression
<i>G6PC</i>	<i>ARG1</i>	0.012720793	Co-expression
<i>G6PC</i>	<i>BAAT</i>	0.009469871	Co-expression
<i>G6PC</i>	<i>HGD</i>	0.011001362	Co-expression
<i>LBP</i>	<i>C4BPB</i>	0.003940297	Co-expression
<i>LEPR</i>	<i>SLC25A15</i>	0.015385044	Co-expression
<i>LEPR</i>	<i>HAL</i>	0.018157363	Co-expression
<i>LEPR</i>	<i>CPS1</i>	0.021792563	Co-expression
<i>LEPR</i>	<i>ARG1</i>	0.012319317	Co-expression
<i>LEPR</i>	<i>HGD</i>	0.012408955	Co-expression
<i>LEPR</i>	<i>G6PC</i>	0.026779622	Co-expression
<i>SLC17A2</i>	<i>C4BPB</i>	0.006601628	Co-expression
<i>SLC17A2</i>	<i>MTHFS</i>	0.011673527	Co-expression
<i>SLC17A2</i>	<i>LBP</i>	0.004327369	Co-expression
<i>ORM1</i>	<i>C4BPB</i>	0.008727606	Co-expression
<i>ORM1</i>	<i>C5</i>	0.007064989	Co-expression
<i>PREP</i>	<i>SLC25A15</i>	0.013786578	Co-expression
<i>SERPINA7</i>	<i>C5</i>	0.005918165	Co-expression
<i>SERPINA7</i>	<i>ORM1</i>	0.010403195	Co-expression
<i>HGD</i>	<i>CPS1</i>	0.020025367	Co-expression
<i>DIO1</i>	<i>MBL2</i>	0.014330983	Co-expression
<i>LBP</i>	<i>G6PC</i>	0.0091696	Co-expression
<i>CPS1</i>	<i>SLC25A15</i>	0.010167049	Co-expression
<i>CTH</i>	<i>SLC25A15</i>	0.022405656	Co-expression
<i>HAL</i>	<i>SLC25A15</i>	0.024649095	Co-expression
<i>CPS1</i>	<i>SLC25A15</i>	0.011441315	Co-expression
<i>CPS1</i>	<i>CTH</i>	0.011585185	Co-expression
<i>CPS1</i>	<i>HAL</i>	0.012319576	Co-expression
<i>ARG1</i>	<i>SLC25A15</i>	0.020499837	Co-expression
<i>BAAT</i>	<i>SLC25A15</i>	0.01333323	Co-expression
<i>BAAT</i>	<i>CTH</i>	0.01358016	Co-expression
<i>BAAT</i>	<i>CPS1</i>	0.007241853	Co-expression
<i>BAAT</i>	<i>ARG1</i>	0.011780513	Co-expression
<i>C4BPB</i>	<i>SLC25A15</i>	0.010655208	Co-expression
<i>C4BPB</i>	<i>CTH</i>	0.010559047	Co-expression
<i>C4BPB</i>	<i>HAL</i>	0.011841011	Co-expression
<i>C4BPB</i>	<i>CPS1</i>	0.006141116	Co-expression
<i>HGD</i>	<i>CPS1</i>	0.009511196	Co-expression
<i>HGD</i>	<i>BAAT</i>	0.011432248	Co-expression
<i>MBL2</i>	<i>SLC25A15</i>	0.017125212	Co-expression
<i>MBL2</i>	<i>CTH</i>	0.016398663	Co-expression

<i>MBL2</i>	<i>HAL</i>	0.018915584	Co-expression
<i>MBL2</i>	<i>CPS1</i>	0.009279709	Co-expression
<i>MBL2</i>	<i>C4BPB</i>	0.008994715	Co-expression
<i>C5</i>	<i>SLC25A15</i>	0.008921804	Co-expression
<i>C5</i>	<i>CTH</i>	0.008959468	Co-expression
<i>C5</i>	<i>HAL</i>	0.009587029	Co-expression
<i>C5</i>	<i>CPS1</i>	0.005092065	Co-expression
<i>C5</i>	<i>BAAT</i>	0.005769644	Co-expression
<i>C5</i>	<i>C4BPB</i>	0.004815416	Co-expression
<i>C5</i>	<i>HGD</i>	0.007569547	Co-expression
<i>C5</i>	<i>MBL2</i>	0.007248661	Co-expression
<i>G6PC</i>	<i>CTH</i>	0.021676406	Co-expression
<i>G6PC</i>	<i>CPS1</i>	0.010997106	Co-expression
<i>G6PC</i>	<i>BAAT</i>	0.012542194	Co-expression
<i>G6PC</i>	<i>C4BPB</i>	0.009974403	Co-expression
<i>G6PC</i>	<i>HGD</i>	0.017824262	Co-expression
<i>G6PC</i>	<i>C5</i>	0.00849682	Co-expression
<i>LBP</i>	<i>SLC25A15</i>	0.018759409	Co-expression
<i>LBP</i>	<i>HAL</i>	0.02087546	Co-expression
<i>LBP</i>	<i>CPS1</i>	0.009439292	Co-expression
<i>LBP</i>	<i>ARG1</i>	0.018111857	Co-expression
<i>LBP</i>	<i>BAAT</i>	0.010925728	Co-expression
<i>LBP</i>	<i>C4BPB</i>	0.009051763	Co-expression
<i>LBP</i>	<i>MBL2</i>	0.014943773	Co-expression
<i>LBP</i>	<i>C5</i>	0.007415157	Co-expression
<i>LEPR</i>	<i>SLC25A15</i>	0.025149433	Co-expression
<i>LEPR</i>	<i>CTH</i>	0.02639034	Co-expression
<i>LEPR</i>	<i>CPS1</i>	0.012923609	Co-expression
<i>LEPR</i>	<i>BAAT</i>	0.015909543	Co-expression
<i>LEPR</i>	<i>C5</i>	0.010308038	Co-expression
<i>LEPR</i>	<i>LBP</i>	0.020950127	Co-expression
<i>SLC17A2</i>	<i>C4BPB</i>	0.005922639	Co-expression
<i>SLC17A2</i>	<i>C5</i>	0.00483539	Co-expression
<i>ORM1</i>	<i>SLC25A15</i>	0.012226423	Co-expression
<i>ORM1</i>	<i>CTH</i>	0.012432948	Co-expression
<i>ORM1</i>	<i>HAL</i>	0.013200064	Co-expression
<i>ORM1</i>	<i>CPS1</i>	0.006929017	Co-expression
<i>ORM1</i>	<i>BAAT</i>	0.007673539	Co-expression
<i>ORM1</i>	<i>C4BPB</i>	0.00653899	Co-expression
<i>ORM1</i>	<i>HGD</i>	0.010120259	Co-expression
<i>ORM1</i>	<i>MBL2</i>	0.009900892	Co-expression

<i>ORM1</i>	<i>C5</i>	0.005402325	Co-expression
<i>ORM1</i>	<i>G6PC</i>	0.011815394	Co-expression
<i>ORM1</i>	<i>LBP</i>	0.010073603	Co-expression
<i>ORM1</i>	<i>LEPR</i>	0.013810683	Co-expression
<i>SERPINA7</i>	<i>SLC25A15</i>	0.012462362	Co-expression
<i>SERPINA7</i>	<i>HAL</i>	0.01432913	Co-expression
<i>SERPINA7</i>	<i>CPS1</i>	0.00686181	Co-expression
<i>SERPINA7</i>	<i>ARG1</i>	0.01146561	Co-expression
<i>SERPINA7</i>	<i>C4BPB</i>	0.00677565	Co-expression
<i>SERPINA7</i>	<i>MBL2</i>	0.010809767	Co-expression
<i>SERPINA7</i>	<i>C5</i>	0.005448063	Co-expression
<i>SERPINA7</i>	<i>LBP</i>	0.011217129	Co-expression
<i>SERPINA7</i>	<i>SLC17A2</i>	0.006874819	Co-expression
<i>CYP3A5</i>	<i>CPS1</i>	0.01207218	Co-expression
<i>CYP3A5</i>	<i>C4BPB</i>	0.011685826	Co-expression
<i>CYP3A5</i>	<i>C5</i>	0.009578024	Co-expression
<i>CYP3A5</i>	<i>SLC17A2</i>	0.011991991	Co-expression
<i>CYP3A5</i>	<i>ORM1</i>	0.012806383	Co-expression
<i>SLC17A2</i>	<i>G6PC</i>	0.014184606	Co-expression
<i>SERPINA7</i>	<i>C5</i>	0.019346774	Co-expression
<i>CYP3A5</i>	<i>SERPINA7</i>	0.010969018	Co-expression
<i>HGD</i>	<i>SLC25A15</i>	0.006551247	Co-expression
<i>PREP</i>	<i>SLC25A15</i>	0.012394655	Co-expression
<i>SERPINA7</i>	<i>G6PC</i>	0.017327776	Co-expression
<i>CPS1</i>	<i>HAL</i>	0.00694992	Co-expression
<i>ARG1</i>	<i>CTH</i>	0.006446471	Co-expression
<i>ARG1</i>	<i>HAL</i>	0.010185538	Co-expression
<i>ARG1</i>	<i>CPS1</i>	0.006081839	Co-expression
<i>BAAT</i>	<i>ARG1</i>	0.01191919	Co-expression
<i>C4BPB</i>	<i>CPS1</i>	0.00363932	Co-expression
<i>HGD</i>	<i>CPS1</i>	0.008691518	Co-expression
<i>HGD</i>	<i>ARG1</i>	0.010913373	Co-expression
<i>MTHFS</i>	<i>HAL</i>	0.007126623	Co-expression
<i>C5</i>	<i>C4BPB</i>	0.004553121	Co-expression
<i>LBP</i>	<i>ARG1</i>	0.006003315	Co-expression
<i>LBP</i>	<i>C4BPB</i>	0.00376871	Co-expression
<i>LBP</i>	<i>C5</i>	0.005731973	Co-expression
<i>LEPR</i>	<i>CPS1</i>	0.010181712	Co-expression
<i>LEPR</i>	<i>ARG1</i>	0.012883171	Co-expression
<i>LEPR</i>	<i>HGD</i>	0.019583575	Co-expression
<i>SERPINA7</i>	<i>C4BPB</i>	0.006879414	Co-expression

<i>SERPINA7</i>	<i>C5</i>	0.009770601	Co-expression
<i>SERPINA7</i>	<i>DIO1</i>	0.018938221	Co-expression
<i>SERPINA7</i>	<i>SLC17A2</i>	0.021433447	Co-expression
<i>DIO1</i>	<i>C4BPB</i>	0.01167786	Co-expression
<i>DIO1</i>	<i>CTH</i>	0.004786647	Co-expression
<i>DIO1</i>	<i>MBL2</i>	0.007709226	Co-expression
<i>DIO1</i>	<i>C5</i>	0.006562013	Co-expression
<i>HAL</i>	<i>CTH</i>	0.00904644	Co-localization
<i>ARG1</i>	<i>CTH</i>	0.007396141	Co-localization
<i>ARG1</i>	<i>HAL</i>	0.011341748	Co-localization
<i>C4BPB</i>	<i>CTH</i>	0.00882447	Co-localization
<i>C4BPB</i>	<i>HAL</i>	0.009825678	Co-localization
<i>MBL2</i>	<i>ARG1</i>	0.011475822	Co-localization
<i>C5</i>	<i>CTH</i>	0.009882752	Co-localization
<i>C5</i>	<i>HAL</i>	0.012378897	Co-localization
<i>C5</i>	<i>ARG1</i>	0.011783864	Co-localization
<i>C5</i>	<i>MBL2</i>	0.015168445	Co-localization
<i>G6PC</i>	<i>CTH</i>	0.006479372	Co-localization
<i>G6PC</i>	<i>HAL</i>	0.007433198	Co-localization
<i>G6PC</i>	<i>ARG1</i>	0.006618402	Co-localization
<i>G6PC</i>	<i>C4BPB</i>	0.008764179	Co-localization
<i>G6PC</i>	<i>HGD</i>	0.011694877	Co-localization
<i>SERPINA7</i>	<i>CTH</i>	0.007116361	Co-localization
<i>SERPINA7</i>	<i>HAL</i>	0.008624428	Co-localization
<i>SERPINA7</i>	<i>ARG1</i>	0.007838565	Co-localization
<i>SERPINA7</i>	<i>C4BPB</i>	0.009594075	Co-localization
<i>SERPINA7</i>	<i>MBL2</i>	0.011912366	Co-localization
<i>SERPINA7</i>	<i>C5</i>	0.012075914	Co-localization
<i>SERPINA7</i>	<i>G6PC</i>	0.007159275	Co-localization
<i>HAL</i>	<i>SLC25A15</i>	0.014272561	Co-localization
<i>CPS1</i>	<i>SLC25A15</i>	0.013714614	Co-localization
<i>ARG1</i>	<i>SLC25A15</i>	0.01310207	Co-localization
<i>ARG1</i>	<i>CPS1</i>	0.00861983	Co-localization
<i>BAAT</i>	<i>SLC25A15</i>	0.013363565	Co-localization
<i>BAAT</i>	<i>CPS1</i>	0.008450216	Co-localization
<i>BAAT</i>	<i>ARG1</i>	0.008598406	Co-localization
<i>HGD</i>	<i>SLC25A15</i>	0.022047134	Co-localization
<i>HGD</i>	<i>HAL</i>	0.010812771	Co-localization
<i>MTHFS</i>	<i>SLC25A15</i>	0.008358937	Co-localization
<i>MTHFS</i>	<i>HAL</i>	0.004322442	Co-localization
<i>MTHFS</i>	<i>C4BPB</i>	0.009622298	Co-localization

<i>MTHFS</i>	<i>HGD</i>	0.007224194	Co-localization
<i>ADCK2</i>	<i>SLC25A15</i>	0.026127955	Co-localization
<i>ADCK2</i>	<i>BAAT</i>	0.010211586	Co-localization
<i>ADCK2</i>	<i>MTHFS</i>	0.00685143	Co-localization
<i>MBL2</i>	<i>SLC25A15</i>	0.011515018	Co-localization
<i>MBL2</i>	<i>C4BPB</i>	0.012219642	Co-localization
<i>MBL2</i>	<i>MTHFS</i>	0.003996356	Co-localization
<i>MBL2</i>	<i>ADCK2</i>	0.009659463	Co-localization
<i>C5</i>	<i>SLC25A15</i>	0.01863199	Co-localization
<i>C5</i>	<i>HAL</i>	0.009531116	Co-localization
<i>C5</i>	<i>CPS1</i>	0.010474401	Co-localization
<i>C5</i>	<i>ARG1</i>	0.010341191	Co-localization
<i>C5</i>	<i>BAAT</i>	0.010462028	Co-localization
<i>G6PC</i>	<i>SLC25A15</i>	0.016094055	Co-localization
<i>G6PC</i>	<i>HAL</i>	0.008763849	Co-localization
<i>G6PC</i>	<i>CPS1</i>	0.009082945	Co-localization
<i>G6PC</i>	<i>BAAT</i>	0.00880316	Co-localization
<i>G6PC</i>	<i>HGD</i>	0.014180019	Co-localization
<i>G6PC</i>	<i>MTHFS</i>	0.005369584	Co-localization
<i>G6PC</i>	<i>MBL2</i>	0.007431859	Co-localization
<i>G6PC</i>	<i>C5</i>	0.011984772	Co-localization
<i>DIO1</i>	<i>SLC25A15</i>	0.025056243	Co-localization
<i>DIO1</i>	<i>HGD</i>	0.017162617	Co-localization
<i>LBP</i>	<i>SLC25A15</i>	0.014860843	Co-localization
<i>LBP</i>	<i>HAL</i>	0.008506832	Co-localization
<i>LBP</i>	<i>BAAT</i>	0.006969759	Co-localization
<i>LBP</i>	<i>HGD</i>	0.011018015	Co-localization
<i>LBP</i>	<i>MTHFS</i>	0.004518892	Co-localization
<i>LBP</i>	<i>MBL2</i>	0.006218935	Co-localization
<i>LBP</i>	<i>C5</i>	0.010104029	Co-localization
<i>LBP</i>	<i>G6PC</i>	0.009210799	Co-localization
<i>SLC17A2</i>	<i>SLC25A15</i>	0.018329779	Co-localization
<i>SLC17A2</i>	<i>HAL</i>	0.009681415	Co-localization
<i>SLC17A2</i>	<i>BAAT</i>	0.009294453	Co-localization
<i>SLC17A2</i>	<i>HGD</i>	0.013592821	Co-localization
<i>SLC17A2</i>	<i>MTHFS</i>	0.006027925	Co-localization
<i>SLC17A2</i>	<i>ADCK2</i>	0.015540332	Co-localization
<i>SLC17A2</i>	<i>MBL2</i>	0.008607964	Co-localization
<i>SLC17A2</i>	<i>G6PC</i>	0.011782652	Co-localization
<i>SLC17A2</i>	<i>LBP</i>	0.010201342	Co-localization
<i>ORM1</i>	<i>SLC25A15</i>	0.009743731	Co-localization

<i>ORM1</i>	<i>HAL</i>	0.005098609	Co-localization
<i>ORM1</i>	<i>CPS1</i>	0.005120896	Co-localization
<i>ORM1</i>	<i>ARG1</i>	0.004895931	Co-localization
<i>ORM1</i>	<i>BAAT</i>	0.004949312	Co-localization
<i>ORM1</i>	<i>C4BPB</i>	0.009870878	Co-localization
<i>ORM1</i>	<i>HGD</i>	0.007168311	Co-localization
<i>ORM1</i>	<i>MTHFS</i>	0.003196832	Co-localization
<i>ORM1</i>	<i>ADCK2</i>	0.007305417	Co-localization
<i>ORM1</i>	<i>MBL2</i>	0.004552235	Co-localization
<i>ORM1</i>	<i>C5</i>	0.006662394	Co-localization
<i>ORM1</i>	<i>G6PC</i>	0.006180191	Co-localization
<i>ORM1</i>	<i>LBP</i>	0.005398762	Co-localization
<i>ORM1</i>	<i>SLC17A2</i>	0.006999721	Co-localization
<i>SERPINA7</i>	<i>SLC25A15</i>	0.010623649	Co-localization
<i>SERPINA7</i>	<i>CPS1</i>	0.006563142	Co-localization
<i>SERPINA7</i>	<i>ARG1</i>	0.006524967	Co-localization
<i>SERPINA7</i>	<i>BAAT</i>	0.006416609	Co-localization
<i>SERPINA7</i>	<i>MBL2</i>	0.005163964	Co-localization
<i>SERPINA7</i>	<i>C5</i>	0.00801424	Co-localization
<i>SERPINA7</i>	<i>G6PC</i>	0.007043994	Co-localization
<i>SERPINA7</i>	<i>LBP</i>	0.005624746	Co-localization
<i>SERPINA7</i>	<i>SLC17A2</i>	0.007645443	Co-localization
<i>SERPINA7</i>	<i>ORM1</i>	0.004100054	Co-localization
<i>CYP3A5</i>	<i>SLC25A15</i>	0.021976126	Co-localization
<i>CYP3A5</i>	<i>HAL</i>	0.012220652	Co-localization
<i>CYP3A5</i>	<i>CPS1</i>	0.011446337	Co-localization
<i>CYP3A5</i>	<i>BAAT</i>	0.011028161	Co-localization
<i>CYP3A5</i>	<i>MTHFS</i>	0.006549534	Co-localization
<i>CYP3A5</i>	<i>C5</i>	0.015651088	Co-localization
<i>CYP3A5</i>	<i>G6PC</i>	0.01435386	Co-localization
<i>CYP3A5</i>	<i>LBP</i>	0.012599541	Co-localization
<i>CYP3A5</i>	<i>SLC17A2</i>	0.014993709	Co-localization
<i>CYP3A5</i>	<i>ORM1</i>	0.008000645	Co-localization
<i>CYP3A5</i>	<i>SERPINA7</i>	0.008649936	Co-localization
<i>PREP</i>	<i>CTH</i>	0.047972582	Physical Interactions
<i>C4BPB</i>	<i>SLC25A15</i>	0.15971017	Physical Interactions

3D analysis of SLC25A15 gene by UCSF Chimera and Project HOPE:

Figure 2: (G31H) the amino acid Aspartic Acid (green) changes to Histidine (red) at position 31.

Figure 3: (D31Y) the amino acid Aspartic Acid (green) changes to Tyrosine (red) at position 31.

Figure 4: (Y64C) the amino acid Tyrosine (green) changes into a Cysteine (red) at position 64

Figure 5: (G66S) the amino acid Glycine (green) changes into a Serine (red) at position 66.

Figure 6: (L71Q) the amino acid Leucine (green) changes into a Glutamine (red) at position 71.

Figure 7: (G86C) the amino acid Glycine (green) changes into a Cysteine (red) at position 86.

Figure 8: (G113C) the amino Acid Glycine (green) changes into a Cysteine (red) at position 113.

Figure 9: (G168E) the amino acid Glycine (green) changes into a Glutamic Acid (red) at position 168.

Figure 10: (T176A) the amino acid Threonine (green) changes into Alanine (red) at position 176.

Figure 11: (F186S) the amino acid Phenylalanine (green) changes to Serine (red) at position 188.

Figure 12: (G216S) the amino acid Glycine (green) changes to Serine 9 (red) at position 216.

Figure 13: (G217R) the amino acid Glycine (green) change to Arginine (red) at position 217

Figure 14: (G220R) the amino acid Glycine (green) change to Arginine (red) at position 220.

Figure 15: (K234I) the amino acid Lysine (green) changes to Isoleucine (red) at position 234.

Figure 16: (Q238R) the amino acid Glutamine (green) changes to Arginine (red) at position 238.

Figure 17: (R275Q) the amino acid Arginine (green) changes to Glutamine (red) at position 275.

Figure 18: (R275L) the amino acid Arginine (green) change to Leucine (red) at position 275.

Figure 19: (Y287H) the amino acid Tyrosine (green) changes to Histidine (red) at position 287.

Figure 20: (E288K) the amino acid Glutamic Acid (green) changes to Lysine (red) at position 288.

Figure 21: (E288G) the amino acid Glutamic Acid (green) changes into a Glycine (red) at position 288.

Networks

- Physical Interactions
- Co-expression
- Predicted
- Co-localization
- Pathway
- Genetic Interactions
- Shared protein domains

Figure22: Interaction between *SLC25A15* and its related genes.

3.2 Discussion:

Various bioinformatics tools were performed to identify the SNPs impact in the *SLC25A15* protein. 20 mutations have been distinguished to affect the stability and function of *SLC25A15*, 12 out of 20 are considered as novel (D31H, D31Y, Y64C, G66S, G86C, G168E, T176A, F188S, K234I, Y287H, E288K and E288G). To ensure the pathological effect of the mutations at the molecular level, different parameters plus trustworthy information were used, and for more accuracy, numerous methods rather than one method (PolyPhen-2, PROVEAN, PHD-SNP, SNP&GO, PANTHER, P-MUT, I-Mutant3.0, MUpro, Project HOPE, RaptorX, Chimera, and GeneMANIA were used (Figure1)

630 variants of the Homo Sapiens *SLC25A15* gene which situated on the coding region were acquired from dbSNP/NCBI Database. To predict if these variants affect the function of the protein, phenotype and end by disease 220 missense mutations were submitted to SIFT, PolyPhen-2 and PROVEAN software respectively. 57 SNPs were predicted to be 'deleterious' by SIFT software, while by PolypPhen-2; 114 SNPs were predicted to be 'damaging', in which 79 were 'probably damaging' and 35 as 'possibly damaging', and PROVEAN predicted 142 SNPs to be deleterious. The triple positive results of these software were 27 SNPs, and they are affecting the function of the protein (Table 1). These 27 pathogenic SNPs were submitted to PHD-SNP, SNP&GO, PANTHER and P-MUT for further confirmation; 27 deleterious SNPs were predicted by PHD-SNP and SNP&GO while PANTHER predict 25 variants and P-MUT predicted 21 deleterious SNPs (table 2 AND 3). The fourth positive results of these software were 20 pathogenic SNPs, were submitted to I-Mutant and MUpro servers in order to examine the effect of mutation on the stability of the protein. I-Mutant revealed all these 20 pathogenic SNPs decreased the stability of the protein except for 4 SNPs with I-Mutant (D31Y, G168E, G216S, and G217R), but one SNP with MUPRO (K234I) was predicted to increase the stability (Table 4).

Project HOPE revealed that some mutant residues (which are buried in the core of the protein) are larger than the wild-type residues, this makes the new residue in an improper position to make the same hydrogen bond as the original wild-type residue did, while the smaller sized mutants cannot fill the core of the protein. It also showed the mutation may change the charge of the residue and lead to repulsion of ligands or other residues with the same charge, there are 9 variants remain unchanged. In Project HOPE results, 12 variants with mutant residue are more hydrophobic than the wild-type residue, these hydrophobicity variations can affect the hydrophobic interactions with the membrane lipids, and it identified 10 variants with transmembrane domain as well. The amino acid Glycine is the most flexible of all residues, this flexibility might be necessary for the protein's function. Thus mutation of this glycine can abolish this function. For visualization of the wild and mutant types of amino acids in *SLC25A15*, Chimera software was performed (Figures 2-21)

GeneMania disclosed that *SLC25A15* functions in the amide biosynthetic process, nitrogen cycle metabolic process, urea metabolic process, cellular amino acid catabolic process, inflammatory response, complement activation, cellular modified amino acid metabolic process, carboxylic acid catabolic process, organic acid catabolic process, protein activation cascade. Disruption of this function give rise to cytoplasmic ornithine aggregation, citrulline synthesis reduction, impaired ammonia detoxication and increased carbamoyl phosphate(1). The genes co-expressed with; share similar protein domain, or participate to achieve similar function were illustrated by GeneMANIA and shown in figure (22) Tables (5, and 6).

This study is the first in silico analysis to determine the impact of SNPs on the coding region of the *SLC25A15*, other studies relied on molecular work investigated, specifically the effect of mutations on *SLC25A15* that specified and associated with phenotype of HHH syndrome (26). Also, detailed information on HHH was carried out by analysis of *SLC25A15* gene with computational modeling NMR, in order to study and construct the 3D structure and mutated mitochondrial ornithine transporter 1, and also to provide molecular docking to identify substrate binding site followed by dynamic simulation to optimize these model (51).

20 pathogenic SNPs effect on the *SLC25A15* protein function and structure were revealed in this study. 12 of these 20 missense SNPs are proposedly to be considered as novel mutations, while; L71Q, G113C, F188S, G216S, G220R, Q238R, R275Q, and R275L are not originals, due to their previous mentions in studies (1, 11, 12, 26, 52, 53).

NCBI and this study both acknowledge that L71Q, G113S, G220R, and R275Q SNPs to be pathogenic, in addition to, this study also found further 16 other pathogenic SNPs. However underneath NCBI pathogenic results; G27R was to be positive, while in this study G27R resulted as not pathogenic SNP.

Overexpression of *SLC25A15* may enhance the melanoma proliferation, which might affect the melanoma prognosis and future orientation for melanoma therapy (53).

The diagnosis of HHH associates with clinical manifestation of the syndrome, while treatment may improve with protein free diet and administration of arginine, however liver transplant may still be required (54). This new study, it is not only costless, but can rapidly identify the pathogenic SNPs, specifically targeting mutant *SLC25A15* and may aid in biomarker diagnosis of the disease thus allowing safe novel gene therapy to be performed, from the alternative liver transplant.

4. Conclusions:

In this study 20 pathogenic SNPs (D31Y, Y64C, G66S, L71Q, G86C, G113C, G168E, T176A, F188S, G216S, G217R, G220R, K234I, Q238R, R275Q, R275L, Y287H, E288K, and E288G) were found in *SLC25A15* gene through a combination of different in silico bioinformatics tools. Their impact on *SLC25A15* gene functions and structure were also analyzed, thus providing knowledge as a starting point for innovation of new, useful SNP markers for medical testing and a safer medication to treat the most common demoralizing disorders of *SLC25A15* in urea cycle.

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