GLUCOSE TRANSPORTATION: STRUCTURAL AND FUNCTIONAL ASPECTS OF GLUCOSE TRANSPORTERS

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DECLARATION

I hereby declare that the work presented in this report " Glucose transportation: Structural and Functional Aspects of Glucose Transporters" submitted for partial fulfillment of the requirements for the Master of Science in Biotechnology and Bioinformatics at Jaypee University of Information Technology Waknaghat, is genuine record of my work which is done under the supervision of Dr. Udayabanu, this work has not been submitted elsewhere for the reward of the any other degree/ diploma. Iam responsible for the information of this report.

Suvanshita Sharma

197809

CERTIFICATE

This is to certify that the entitled report on "**GLUCOSE TRANSPORTATION STRUCTURAL & FUNCTIONAL ASPECTS OF GLUCOSE TRANSPORTERS"** presented in this thesis for the fulfillment of the requirements for Master degree in biotechnology and Biotechnology and Bioinformatics at Jaypee university of Information Technology, Waknaghat is an original and legal record for work carried by Suvanshita Sharma 197809 from a period of JAN- 2021 to MAY- 2021 under the supervision of Dr. Udayabhanu sir.

The above statement made is actual to the finest of my knowledge.

Signature of Supervisor ----------

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ABSTRACT

The predominance of diabetes mellitus, metabolic disorder has expanded unevenly throughout the long term and the pattern is proceed to developing at disturbing rate. This illness entanglements are related with number of components making it as significant wellbeing concern. Till now individuals are zeroing in on drug disclosures which can be solid to diabetic patients actually characterized medications are missing, not just identified with insulin, it likewise influencing brain and the diabetes caused to the infants, so researchers are focusing on underlying factors for this problem and that can be start from managing energy requests and energy prerequisites, in this review the main focus is around glucose transportation. Glut 1 to 14 establishing as significant carrier family which works as per as the facilitated diffusion of glucose transport are been talked about alongside SGLT2 active transport members, the role of genetic analysis for assurance of glucose carriers, functions and specifications has been centered, likewise through the accumulated examinations in various organisms has been discussed to get system, likeness or other patterns like rest, diet or glucose take-up. Comparative studies give another knowledge into confirmations which can be demonstrate to similarity, difference might be because of transformations. As specialists are likewise focusing on ligand screening and docking reads for excesses as significant potential targets, however on the other side the job of biomarkers has been examined.

1Introduction: cells regulate biochemical pathways in our body, glucose molecules relatively are polar and larger in size to diffuse across the membranes, they need special membranes proteins called glucose transporters which depends on different transport mechanism which is active or facilitative diffusion , these glucose transporters are transmembrane alpha helices they allow the movement of glucose down its concentration gradient, important glucose transporters are GLUT 1- 5 they differs in substrate specificity and mechanism of distribution over the time researchers are gaining interest in their role in expression of diabetes.

Facilitated glucose transport: the family of gluts that function in this transport includes at least 14 members out of which glut1-5 are usually expressed, glucose transport occurs from an area of higher concentration to an area of lower concentration. Sugar molecules binds to glut protein then sugar is released to the other side of the membrane, after sugar dissociation, the glut changes its orientation and the cycle continues.

Insulin- sensitive glucose transport: expression of GLUT 4 on the membrane surface plays a role in glucose utilization by skeletal muscles and adipose cells. This includes intracellular signaling pathways by insulin binding of glut4 from internal membranes to membrane surfaces. After glucose transport glut4 are transferred from the plasma membrane by the process of endocytosis and recycled back.

Most cells do not require insulin they require only a concentration gradient for glucose because glut proteins are expressed on their surfaces already such as erythrocytes, brain cells, liver and leucocytes and this is also insulin independent manner.

Active transport of glucose: three main locations where glucose is present at higher concentration are choroid plexus, proximal convoluted tubules of the kidney and epithelial cells of small intestinal brush border. The apical membranes facing of the epithelial cells contain sodium glucose transport proteins, catalyze transport of glucose against its concentration gradient.

GLUT1 transporters are present on cell surfaces and their transportation is from higher concentration to lower concentration taking about glut4 they are insulin dependent in skeletal muscles or liver, they don't reside for cell surface proteins there are some others transporters which transport fructose like glut5 not much specific about glut7 and glut9; as it considered to be urate transporter but sodium glucose transporters transport glucose against its concentration gradient. Insulin promotes movement through the intracellular vesicles, it is not involved in any kind of active transport, insulin does not promote ATP hydrolysis that's why for insulin receptor binding receptors and phosphorylation is required. Skeletal muscles are insulin dependent.

Sodium ion gradient is generated and regulated by sodium potassium ATPase which drives the transport of glucose against its concentration gradient into the cells of epithelial but here it required glut2 for transport across the epithelial membrane, glucose is transported from symport not by antiport. In each cycle the inward transport requires two sodium ions and one glucose molecule, it is a form of secondary transport because of non-directly hydrolysis of ATP. Though this process is inhibited because in diabetes patients elevated blood glucose levels requires greater amount of glucose for filtration, in type 2 diabetes it is needed to decreased reabsorption of glucose.

GLUT	MOL.WT	FUNCTION	BINDING SITE	MUTAGENESIS	SEQUENCE
Glut1	492	Basal glucose uptake, transport both hexoses and pentoses Present at blood brain barrier	Position -137 cytochalasin b inhibitor, Position-317 monosaccharide	At position -45 N-T loss of glycosylation site	**P11166**
Glut2	524	Transport both glucose and fructose, cotransport with SGLTs	Position- 349 monosaccharide Position 420- monosaccharide	At position 322- I-V reduced fructose transport	**P11168**
Glut3	496	Transport glucose, galactose mannose, but not fructose	Position- 315 monosaccharide Position- 378 monosaccharide	At position 277-279 QLS-HVA confers moderate fructose activity	**P11169**
GLUT 4	509	Insulin regulated transport from cells, non-insulin into muscles and adipocytes	position – 333 monosaccharide position -404 monosaccharide	At position 223- C-S loss of palmitoylation	**P14672**
Glut14	520	Hexose transporter Can transport glucose	Position -339 Fructose Position -410 Fructose	Not identified	**P22732**

Table 1

GLUT	MOL.WT	FUNCTION	BINDING SITES	MUTAGENESIS	SEQUENCE
Glut5	501	Fructose transporter	Position -32 fructose Position -167	Increased activity leads to prostate and breast cancer	**P22732**
Glut7	512	Probable sugar transport, not confirmed about transport of glucose	Position -331 monosaccharide	At position -302 I-S Does not affect glucose or fructose transport	**Q6PXP3**
Glut9	540	Urate transporter Does not transport glucose, fructose	Position – 90 Glycosylation	Genetic variation in SLCA29 causes excess serum accumulation of uric acid.	**Q9NRM0**
Glut 11	496	Expressed in heart and skeletal muscle	Position -47 Glycosylation	Not defined	**Q9BYW1**

Table 2

GLUT	MOL.WT	FUNCTION	BINDING SITES	MUTAGENESIS	SEQUENCE
Glut6	507	Sugar transporter, does not transport glucose	Position-418 monosaccharide	Not defined	**Q9UGQ3**
Glut8	477	Insulin regulated hexose transporter, transport glucose& fructose	position- 394	Not defined	**Q9NY64**
Glut10	541	Glucose transporter required for cardiovascular system	Position- 432	Arterial tortuosity syndrome caused by gene variants	**095528**
Glut12	617	Insulin independent glucose transporter	Position-617	Not defined	**Q8TD20**

Table 3

1.2 **SGLTs-** Membrane proteins which transport glucose, amino acids and vitamins towards the apical and epithelial membrane across the opening side within the small intestines and renal tubule.

SGLT1 [SLC5A1] is liable for absorption of glucose within the intestine, but SGLT2 [SLC5A2] is liable for reabsorption of glucose in parts of kidney. SGLT3 [SLC5A4] is present in intestine kidney, liver and striated muscle. Other SGLT has been reported but their physiologically basis remains unclear. High diet level up the expression of SGLT1; the first stage transport glucose across the apical membranes, the concentration gradient of glucose is generated between cell and membrane and it requires glut2 for entry and exit from the membrane towards the plasma. During the second stage sodium potassium pump is generated which requires three sodium ions for every two-potassium ion and this maintains sodium gradient, across the apical membrane by pumping sodium towards plasma. mechanism of this SGLT1 mediated glucose transport is liable for post prandial hypoglycemia in diabetes. In type 2 as a result of the expanded glucose shifted load, there's an expanded articulation of SGLT2 and an expanded reabsorption of glucose; this is often a contribution factor adding to hyperglycemia. SGLT inhibition is required to take care of blood- glucose levels.

During the SGLT transport coupled with the movement of two sodium ions and one glucose molecule for each kinetic cycle, cotransport of sodium and glucose with both SGLT1 and SGLT2 generates an electric current,

activation of sugar is observed in the presence of sodium which is identical to the rate of sodium transport when talking about SGLTs currents are generated by voltage gradient in the presence and absence of sodium, when sugar is not present these currents are due to the movement caused by charged or polar amino residues of SGLT1 in the membrane of electric field. As x ray structure confirmations of these SGLTs had been introduced earlier but in this review about structure framework was demonstrated used by sequence identities and similarities, sglt1, and sglt2 were compared with other homologue while comparison in sglt1 the helices of transmembrane which is bounded to residues at outer ends are illustrated, in case of sglt2 the residues which leads to formation of glucose bound between the ends were emphasized [1]. Particular SGLT2 inhibitors – dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, luseogliflozin and tofogliflozin – are endorsed in the treatment leading to type 2 diabetes. These inhibitors of SGLT2 lessen the levels of plasma glucose by an alternate system than other antidiabetic drugs, including an involvement of the glucose discharge by SGLT2 in the proximal tubule for initiating less harm in glucose levels. As glucose support from the small intenstine is typically handled by SGLT1 an advancement in overstated ascent in blood glucose levels with SGLT1inhibitor would be a major treatment in diabetic rodents, a particular nit of KGa-2727 of SGLT inhibitor demonstrated to improved the postprandial hyperglycemia and its saving administration lessens hemoglobin A1C levels [2].

SWEET Proteins- a replacement class of glucose transporters encoded by SLC50 gene. classified according to the expression in Arabidopsis thaliana genes which codes for membrane proteins. The homolog of SWEET1 is encoded by SLC50A1 gene in human also. SWEET1 encoding for humans shows this level of expression among the organs like the oviduct, epididymis, and intestines [3].

1.3 **GLUT1**; **GLUT**1 has a place with the super group of significant facilitator super family, these carriers share a preserved area that includes 12 transmembrane fragments coordinated into areas, which are amino and carboxyl spaces. In the GLUT1 structure, buildups 9–455 comprise the sanctioned MFS overlap while the C-terminal section was undetectable likely because of its intrinsic adaptability in this compliance. Intriguingly, the ICH area was additionally seen in the constructions of the sugar porter individuals XylE and GlcP, however not in different MFS carriers, proposing that ICH might be an interesting component of the sugar porter subfamily. the design examination of glucose uniporter GLUT1 by homology displaying gives a knowledge into advancement of possibly going about as helpful agents [4]**.**

By Meckler et al the secondary structure of GLUT1 was first proposed, noticed to have α-helical spaces in 12 transmembrane structures, they similarly saw that over part of the developments are hydrophobic and recommended that amphipathic helices Transmembrane residues consisting

from 3, 5, 7, 8, and 11 may shape a central watery channel allowing glucose to be traveled through the membrane [4] .

Property of glucose subordinate vehicle is routinely seen through the part of trans-speed increment. First saw in a long time, tests were driven in which hexose was separated streaming clearly against its obsession tendency from the side i, e. cis towards the trans side of layers. Regardless, a couple of examinations have been driven on this part relates to the confirmation plan of GLUT1, another assessment similarly battled the presence of ATP mediated rule in this trans-speed increment.

It was also observed between the confirmations that N domain might be not responsible for ligand binding but may be C domain provide some binding sites. Usually transmembrane domain and intracellular helices domain is responsible for structural modifications in GLUT1, It tracked down that the transmembrane residue 6 of GLUT1 contains buildups fundamental for trans-speed increase with glucose-glucose trade and is answerable for con-stressing the unwinding of GLUT1, yet not immediate restricting or movement of substrate during translocation of substrate during transport [5].

At the blood-brain barrier, GLUT1 is found as a high thickness in both luminal and abluminal layers in the endothelial cells as intensely

glycosylated, with high weight structure (55 kda). The isoform of GLUT1 is likewise found in erythrocytes of human. a couple of investigations utilizing in vitro models of the blood-cerebrum boundary have proposed that the world and systemization of hexokinase can change the proportion of GLUT1 at the luminal and abluminal films [6].

In podocytes, GLUT1 directs glucose take-up at the basal stage however strangely, it's likewise been seemed to react to insulin incitement in these cells. The protective job of GLUT1 is upheld by the finding that peroxisome proliferator-initiated receptor (PPAR) γ agonist rosiglitazone, seemed to act considerably for kidney infection when assessed TIDM for mouse model [7].

Glucose transporters along the blood – brain barrier carried glucose, impairment of glut1 cause deficiency syndrome of glut1 several studies are reported for drugs treatment for controlling seizures in GLUT1 but other findings show animal models are necessary. during this study genetic analysis of mouse was identified. positron emission tomography was used earlier in vitro kinetic analysis for glucose transport. Location of mutation within the mice model was defined. for phenotypic analysis background gene comparison was used to determine glucose intake by comparison with wild type was done using PET, sleep wake analysis of untamed type and heterozygote's of GLUT1 has been reported. In previous

studies in patient's glucose uptake has been reported, notably, glucose hypo metabolism was noticed in thalamic, cerebral & neocortex regions. during this GLUTDS1 model shows high glucose utilization within the brain, this mouse has abnormal glucose metabolism which shows dysfunctional transporter under conscious conditions. Real time monitoring of glucose kinetics allowed using positron emission tomography Further it is often concluded that symptoms and complications of GLUT1 are various. This study conducted missense mutation of T310I, which is nearby to GLUT`RG200, and effects 8th protein transmembrane domain causes down glucose levels, learning disorders and seizures. this GLUT1 mutant are often helpful for developing drugs of GLUT1DS [8].

1.4 GLUT2 Glucose carrier isoform 2 (GLUT2) addresses the many individuals from the GLUT family in beta cells of pancreas and hepatocytes but on the opposite hand is plentiful in alimentary canal, kidney, and therefore the focal sensory system. due to its interestingly low proclivity for glucose (Km ~ 17 mmol/L), GLUT2 assumes a critical part in sorting of cells in glucose detect which is testing a good scope of blood sugar focuses. Notwithstanding GLUT2, glucokinase is likewise significant for maintaining blood sugar levels at a gentle centralization of concentration of 5 mmol/L (in people) and hereditary transformations not only in GLUT2 but also in

glucokinase, are related towards aggravations in and diabetes type 2 and glycemia 1DM [9].

GLUT2 gene is especially expressed in pancreatic β-cells; and liver however, the protein containing domains and regulatory sequence elements regulating the expressed genes of the GLUT2 were not defined. A study was conducted using different cell lines using hepatomas, pancreatic and fibroblasts cells for the differences in activity of promoter gene; the study was conducted for organic phenomenon of glut2 and regulation of glucose homeostasis [10].

GLUT2 is predominantly liable for the basolateral exit of glucose in proximal convoluted tubules. additionally, the failure in GLUT2 transport leads to functional mutations which results in the Fanconi-Bickel syndrome, this mainly includes a proximal complication characterized by glycosuria, phosphaturia, aminoaciduria, proteinuria, and hyperuricemia. GLUT2 is communicated within the central nervous system of rodents [11] mammals and in zebra fish In nervous system glucose sensing is glut2 dependent as required for the traditional control in nervous activity, in sympathetic and parasympathetic manner as it plays major role in encouraging the cell proliferation [12].

Mechanism; GLUT2 works in correlation with sglt2 transporters, inside epithelial cells glucose is modified with glucose-6-phosphate by hexokinase which forestalls the outward movement of levels of glucose

and supported vehicle to the cell, while glucose enters the glycolysis, as glucose 6 phosphate which brings about the creation of ATP atoms, due to consistent supply of glucose the ATP levels are expanding, this effects the potassium channel which create hindrance with the surge of potassium ions from the cell being hindered, k+ ions increments inside the cell, which get electropositive until the process on the layer are adjusted and the depolarization occurs, depolarization actuates the voltage- gated calcium channel, advancing the convergence of Ca2+ ions into the cell, Ca2+ ions create the exocytosis which promotes divert situated within the layer of insulin releasing vesicles, instigating the movement into the cell wall and deliver the substance.

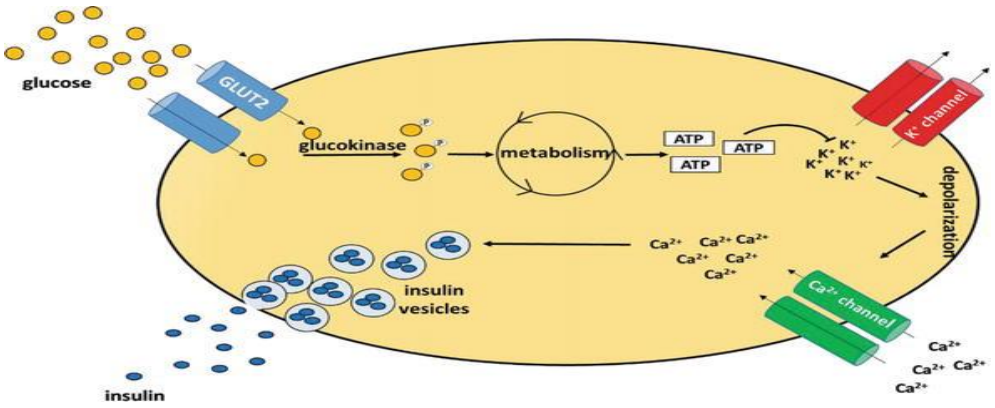

Fig from https://www.intechopen.com/books/blood-glucose-levels/role-of-pi3k-akt-pathway-in-insulin-mediated-glucose-uptake

1.5 STUDY; In this study zebra fish model is employed to look at the physiological role of GLUT2 this study is especially defined for glucose sensing in regions of brain. Zebra fish Glut2 is present in brain, liver, neurons progenitors, pancreas to review function of GLUT2 deprivation on organic phenomenon in zebra fish embryos, a genomic analysis of zebrafish morphant embryos was compared with control embryos. The abolishment of Glut2 caused considerable changes within the expression pattern of perineural genes marked within the hindbrain region during the initial development in zebrafish, this model demonstrates that glucose sensing mechanism with GLUT2 present in zebrafish brain provide experimental tool for examining the function of glut2 in glucose sensing. Demonstrated that glut2 is required during the neuron's developments by progenitors for GABAergic and glutamatergic neurons, recommending the

existence of a glucose-sensing region within the zebrafish brain. Had proposed that the shortage of glut2 in brain areas within the mutant embryos of zebrafish causing increased apoptotic necrobiosis which can be due to loss of glut2 that believe to be the underlying factor for the concerned variations in the brain development. Factors liable for variation in metabolism of FBS patients have also been discussed [10].

1.6 GLUT3 is mostly present within the brain. it's high affinity for glucose, a property which is according to its function to transfer glucose into cells having a better requirement of glucose as it can also binds with mannose [13] A study has been conducted on conformational changes between glut1 and glut3 to know the mechanism of Sugar porter kinetics. A structure analysis of glut1 reveals binding site in which chloride ion is responsible between the motifs as A and SP of N domain and therefore the site for lipid/ glucose binding. The model emphasis on single gene mutation within the region of SP motif which will be converted glut1 into glut3. The chloride ion is maintained by several residues of the A motif within the N domain including arginine residues, interactions are often observed in SP and A motif. This SP motif has role in generating network, the residue of Glut3 EC07 stabilizes the SP-A network, some lipids has been suggested to interact during a motif. During the analysis of GLUT1 C-domain have SP motif and Lys456 as a key residue in molecular modulations, The closely related modification of Arg to Lys residues (and

vice-versa) differentiated that an interconnected network plays role for the transportation activities, interactions were identified between intracellular modulators i.e., glucose/lipid within the SP motif of N domain which shows some role in defining the binding confirmations Further in several members of the MFS family sequences has been analyzed. Concluded that SP motif may be a probe for transport kinetics [14]**.**

1.7 GLUT4; may be a a part of glucose transporter proteins containing 12 transmembrane proteins. Predominantly expressed in striated muscle and fat, where it's liable for insulin stimulated glucose uptake. Glut4 is liable for providing energy demands during exercise to skeletal muscles. Insulin binds to the insulin receptor found on the cell surface, causing a conformational change which initiates its tyrosine- kinase area intracellularly, which may be a sort of signaling pathway for PI3K. Other pathway is mediated by dimeric complex of adaptor proteins associated to maneuver into lipid rafts on the cell surface. it's an activation process for Tc10, insulin dependent process which translocate GLUT4. Another transportation is noninsulin mediated during this contraction happens within the skeletal muscles which activates protein kinase, further which trans locates GLUT4 to cell surfaces to mediate glucose transport. [E Vargas 2019 google NCBI. books]

The Akt kinases are helpful in cell signaling, in adipocytes the main work of Akt is to transport Glut4 towards the cell wall. PDPK1 phosphorylation states of Akt2 is required for insulin dependent translocation however in some studies the mTCORC2 phosphorylation has role in Akt substrate selection. The role of phosho-S474 Akt in substrate selection but not in glut4 instead of glut1. The deficiency of capacity T309A transformation and therefore the increase of capacity S474D change give extra proof that insulin actuation of Akt is vital and capable incite GlUt4 rearrangement to the plasm layer of adipocytes. The movement of S474D without insulin incitement illustrates that Akt are often enacted hooked in to the unstimulated levels of PI3 kinase and PDPK1 exercises. Those discoveries mention the difficulty of whether the initiated levels of PI3 kinase and PDPK1 incitement deciding the degree of Akt enactment accomplished [15]**.**

1.8 STUDY

A study was directed utilizing human initiated pluripotent foundational stem cells inferred cardiomyocytes utilized as a model of evaluating cardiomyocytes in glut4. IPSC-cm model was set up in the year 2007 anyway the outflow of insulin animated glucose take-up was not perceived. cell cultures were acquired, cardiomyocytes were communicated to survey glucose take-up, immunoblotting was utilized to infer proteins that assumes a part in excess invigorated dealing. Moreover, both plasma film

transmembrane proteins known to intercede the mixture of vesicles containing Glut4 with the surface of fat cells and muscle cells, Syntaxin 4 a protein expressed by gene of STX4 present in different tissues, and Synaptosomal associated protein 23, are communicated in these cells. While insulin invigorated glucose take-up is often observed in contractions of heart muscle this reaction is significantly less amazing than that reported from tranquil disconnected cells that make heart muscle. an identical evaluation was performed somewhere within the range of glut1 and glut4 and as indicated by information reports glut4 articulation is more fragile than glut1, notwithstanding articulation another technique for hindrance was picked to asses glucose transport utilizing iPSC-cm in request to accumulate further knowledge past this protein articulation information, the impact of GLUT1 and GLUT4inhibition upon these defined cells glucose transport was surveyed. To accomplish this the recommended medication [BAY-876] was used. As indicated by the factual examination information it had been recommended that whether glut4 is in charge of glucose take-up, however the outflow of those cells is autonomous towards glut4 and subject to glut1.Therefore, inside the present investigation these derived cells were maintained in medium enhanced with a scope of biologically pertinent convergences of T 3. Nonetheless, this neglected to fundamentally change iPSC-CM glut expression [16]. However, studies have been suggested the balance between lipid and glucose metabolism, the energy kinetics and

associations of glucose substrates in pathways which is contributing to increase of glucose**.** However, several attempts and factors were modified for enhancing the glut4 expression but new insight further suggests molecular modulation to understand the expression of GLUT4 in iPSC- cm cells. Studies are emphasizing on glut4 translocation is linked to type 2 diabetes. In some studies people are concerning about glucose uptake is regulated by glucose concentration and cell permeability. Two different study provides conflicting information about insulin kinetics and insulin flux, but the most question is glucose transportation through the tissues. The competition model for substrate transitions has been tested on mouse model using carnitine palmitoyltransferase-1 (CPT-1) activity. An enzyme which works in biological process of lipid metabolism to determine frequent causes the biological significance for the inhibition of this enzyme was also done. However, studies are suggested the balance between lipid and glucose metabolism, the energy kinetics and associations of glucose substrates in pathways which is contributing to extend of glucose.[17]

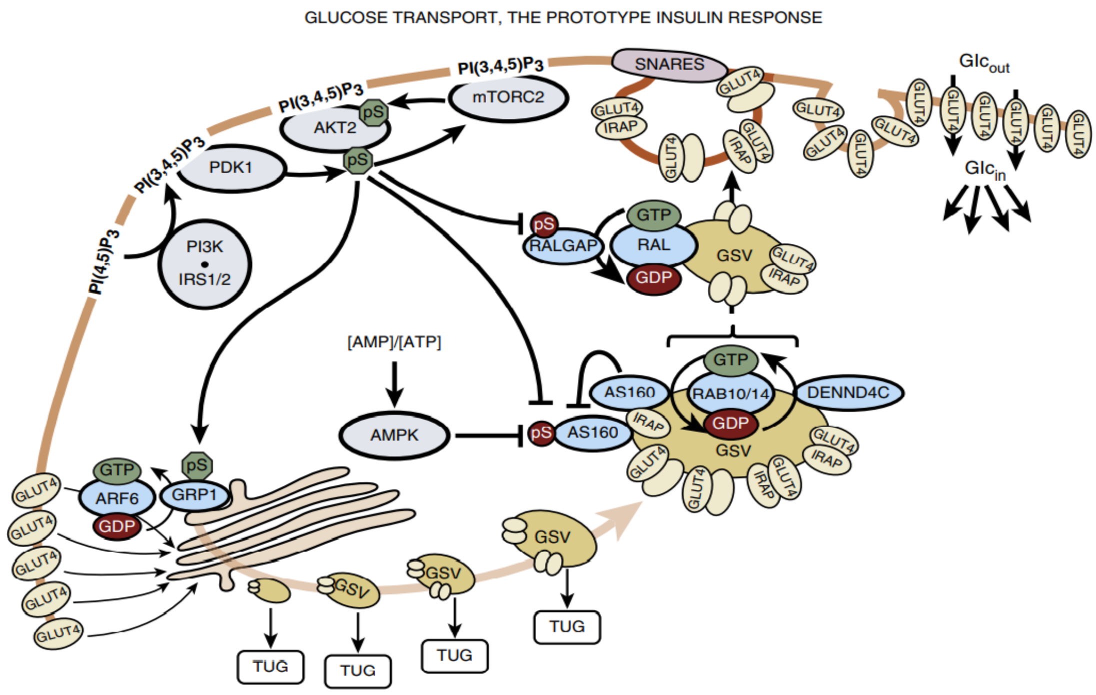

fig from [**Morris F. White and Kyle D. Coop]** Insulin stimulated glucose transport

1.9 Mechanism; A system of insulin-animated transport of glucose ; during insulin stimulation intracellular vesicles containing Glut4 is moved from cytosol to the cell membrane, insulin receptor beta subunits contain tyrosine kinase which phosphorylates insulin receptor subunits to bind and activate phoshpotidylinositol-3 kinase which is transferred to plasma membrane and converts phosphatidylinositol-3,4, 5 triphosphate into phosphatidylinositol 4, 5- bisphosphate, on plasma membrane Phosphoinositide3- kinase activates protein dependent kinase which activates AKT.

Akt activation triggers vesicle fusion, translocation of Glut4, containing vesicles from intracellular compartments to plasma membrane, the elevation of GLUT4 on the membrane leads to increase of glucose entry into cells, after insulin stimulation completion glut4 is transferred back to cytosol from plasma membrane, in non-insulin state mostly glut4 is present in vesicles of muscles and adipocytes where it maintains glucose stability.

2 GLUT5: GLUT5 is present in intestinal areas, testes and may be in kidney where it plays biological role. it's fructose transporter; its increased expression relates to prostate and carcinoma. these compounds; Rubusoside and astragalin-6-glucoside are proposed to have GLUT5 inhibitory activity. These molecules assist in the identification for binding of the ligand's differences between GLUT1 and GLUT5. supported this, another substrate (MSNBA) [N-4-methylsulfonyl-2-nitrophenyl-1,3benzodioxol-5-amine] was experimentally suggested as potent and particular GLUT5 inhibitor [13]. there are some studies during which comparison of GLUT 5 structure confirmations has been reported in rat and bovine Glut5, through the data structural mutants seemed to play a binding approach to glucose transport in central binding sites, when observed through the confirmations, in inner facing confirmation no transmembrane bundle between the salt bridges were formed but there's a formation between the outward facing confirmation, at the cytoplasmic ends further it's concluded that GLUT 5 is controlled by rocker switch

mechanism but through gated movements in the N domain and towards the C domain TMs 7 and 10 show some confirmations and substitutions within the aminoalkanoic acid residues contributing to different glucose affinity and transport kinetics [18].

2.1 GLUT 6: it is derived from GLUT3 it was cloned from leukocytes, consists of 507 amino acid residues. It is mostly detected in brain spleen and particularly in peripheral leukocytes. However it appears to have no facilitation of glucose , it's function is to transport hexose molecules, but the regulation and physiology of glut6 seems to be unknown.[L Szablewski books.google.com] in some studies generation of knockout model for GLUT 6 activity has been generated for molecular characterization however through the results it has been demonstrated through gene expression that the deletion of GLUT 6 from the mouse body has little contribution in few tissues brain, and spleen, may be some patters to humans but it not has such role in glucose metabolism or it has less impact on whole body physiology. [19]

in other studies the expression of GLUT6 in gene knockout mouse through different genomic and metabolic analysis it was reported in results that regulation of this transporter in inflammatory macrophages, further through the analysis activity of different pathways leading to GLUT6 metabolism it was suggested that GLUT6 shows glycolytic activity in inflammatory macrophages, reporting as lysosomal transporter, not showing any activity in glucose transport in different cells. [20]

2.2 GLUT7: it is expressed in high levels within some organs such as colon and small intestine or may be in low levels in testis and prostate. It encodes for 524 amino acid protein and it's like GLUT 5. it's sugar transporter glucose or fructose transporter with somewhat showing high affinity for glucose or not. Mutations has been reported during this gene resulting in cancer [21].

The human GLUT7 was cloned using an intestinal cDNA library by method of PCR-based strategy. Previously as mentioned GLUT7 is highly expressed in the small intestine and colon, although mRNA has been identified in the testes and prostate as well. through alignment data Between fructose and non-fructose transporting isoforms of Glut identified a set of protein residue in GLUT7 that has possibility to validate the ability of fructose transport [22].

2.3 GLUT 8:

it's expressed among several tissues like testis and brain, might be in liver, spleen, kidney, heart, but highly in testis and brain It specifies to move glucose and fructose. Its transport is somewhat like that of GLUT 4, when expressed in gene knockout mice the hepatic GLUT 8 expression associated with circulating insulin. Not much known about the monosaccharides but According to some studies it is able to transport

trehalose a disaccharide which is non oxidized type sugar and mostly found among the plants varieties and different categories of insects, GLUT 8 defective mice when exposed to trehalose induced AMPK phosphorylation signifies its role in autophagy,signalling [9].

2.4 Glut9; GLUT9 of human was isolated using PCR amplification from a cDNA library representing human kidney on the basis of information of sequences which is from short sub sequences and with the help of genomic sequences The glut9 mRNA is detected almost unaccompanied in the kidney and liver and at lower levels in leucocytes, small intestine, placenta and lung [22] it is urate transporter and it's has no affinity for glucose and fructose it's primarily expressed in liver and kidney consistent with polymorphisms it affects uric metabolism. Its genetic variants are related to hyperuricemia [13].

2.5 GLUT 10: encoded by slc2a10 gene, with chain length of 541 and mol, wt. of 57kda, glucose transporter required for cardiovascular system like glut8, in some studies centered towards Golgi in adipocytes. When talking about mouse and rat cells, seems to be abounding in mitochondria where it shows Dehydroxy ascorbic uptake but in silico studies disapproved mitochondrial DHA transport, studies described glut10 in endomembranes, others found around the nuclear regions in human fibroblasts, in the Glut10 is employed as a reference during which vitamin C is employed as

a ligand to further identify transport link in oxidized form, gene mappings of glut 10 mutations result on rare multiorgan animal tissue order, some studies show vitamin C increased hydromethylation levels of DNA in fibroblasts, but gene analysis discloses changes in ATS patients [23].

2.6 GlUT11:

it is associated with Glut5 on similarity basis and in various tissues, mostly expressed in skeletal muscles and heart, similar proteins have being identified on mRNA levels, it's transport activity was inhibited by fructose, immunohistochemical analysis revealed localization of glut11 in muscle fibers, but it's molecular abilities of substrate defining and mechanism in striated muscle remains still unidentified [9].

2.7 Glut12: Class member protein mostly expressed in human and mouse brains alongside heart, prostate and placenta, it is more restricted to tissues like striated muscles, adipocytes and may be in kidney. though it's transcripts has been identified which is very expressed in adult mice and rats, but it's role in glucose regulation remain unclear and there's no confirmation about glut12 localization in CP[choroid plexus] [24].

2.8 Glut13: unlike others Myoinositol transporter which is H+ dependent,

low levels of expression in kidney and adipose cells but expressed predominantly in brain and brain parts, including small region of brain, major components of brain including cerebellum and brain stem [25] Screening of public communicated arrangement data sets with the glut8 protein was cloned by PCR identified according to cloning between human and rat variant, though functionally defined between organisms like *Xenopus laevis* and mammals for various mutations and in no affinity for glucose because of myoinositol transport, it is key regulator for signaling pathways, HMIT is dominatingly communicated within the cerebrum, with high articulation found in brain major regions, nerve center, also in cerebellum&brainstem[22].

intracellularly located, and its activation in brain cells occurs through cellular compartments which is depolarization and protein kinase activation, it's main transporter associated with inositol 3 phosphate, which helps in regulating signaling pathways and disturbances during this pathway leads to various brain disorders [25].

2.9 Comparative study between avian and mammalian glucose transporters; among this specially chicken is chosen and it's concluded that similarity of glut1 amino acid residues is 80% with humans, during this analysis orthologs has been examined in several organisms. Glut3 shows 70%

sequence similarity with humans, but when taking about glut4 there's no such expression present. However, characteristics of human and chicken were summarized and from previous studies glut1-2-3-5-8-9 has been identified in chicken. evolutionary relationships of gluts were also examined during this paper for scaling the relative number of site specific substitutions Through the sequence analysis and RT-qpcr glut 9 and glut11 seems to be similar in chicken genes in comparison to humans.[26]

3 The study examined importance of hydrophobic residues; these interactions strengthen hydrogen interactions between charged groups by decreasing the entropy of in any case openly turning polar or charged side chains and establishing a water- lessen non polar environment. i, e. tryptophan and isoleucine residues chosen for urate transporter and trans acceleration of urate/ hexose exchange, point mutations was introduced on hslc2A9 proteins were assessed and expressed in Xenopus oocytes by the utilization of flux measurements in radiotracers and electrical recording techniques Biotinylating and western blot analyses were performed, immune staining protocol was used to determine expression of proteins in X oocytes membranes. Urate kinetics measurements in oocytes were reported, the structural comparison of glut1 and glut9 was reported, trans-acceleration studies for urate uptake into oocytes loaded with fructose or urate were reported. consistent with data reports Isoleucine -residue of glut 9 is important for urate/fructose trans acceleration, whereas Trp110 interacts with urate/fructose transportation. Hydrophobic residues has role in structural

confirmations when defining model binding and subsequently substrate specificity[27].

3.1 The further study emphasis on functional specifications of intestinal fructose transporters to know fructose transport of glucose transporters. Glut2, GLUT5, GLUT7, GLUT9 were expressed in African clawed frog oocytes, NXI motif role in glut2 and glut5 variants were tested. transport of sugar was measured using recommended assays, or genomics analysis of cell extracts was performed. Western blotting, fluorescence microscopy and statistical analysis was used for demonstration of results, however in results GLUT7 and GLUT9 was did not show activity for fructose. showed that glut7 cannot transport fructose, it can't be declared that amino acids are liable for fructose transport. moreover substrate specificity for these transporters got to be identified [28].

3.2 A recent study on yeast cell system is generated by functional expression of human Glut2 & Glut3 in a plasmid, to verify the localization of modified transporters fluorescence microscopy was used, structural models for glut2 , glut3 were generated, according to structural analysis constructs show sequence identity and homology, Gluts expression in yeast system declared to have specific role when concerning about transport activities, these variants were investigated according to inward and outward confirmations, mutants shows variations between N and C domains, mutants were also

identified in the coil between Transmembrane region of inner and outer residues. However, glut2 expression was used as a strategy for observation in yeast cells. In summary despite of essential changes in their succession concerning as sensitive towards known inhibitors, phloretin and quercetin. the yeast system can be used for high throughput screening**.** [29]

3.3 The role of biomarkers in diabetes; Adipokines has part in lipid and glucose digestion there are some adipokines; retinol binding protein4, adipocyte fatty acid binding protein vaspin, chemerin regulates insulin resistance**.** [30]

Adiponectin is a metabolic regulator it is included in fatty acid oxidation and gluconeogenesis; it has insulin sensitizing anti-inflammatory and anti-atherogenic functions and it is shown to be independent predictor of diabetes. in some studies, hyperinsulinemia euglycemic clamp and intravenous glucose resistance test showed that adiponectin levels were straightforwardly associated with higher insulin sensitivity and indirectly associates with insulin complications**.** [31]

Retinal binding protein 4 acts as a carrier in blood stream through fat tissues, muscles and liver, when overexpressed in fat tissues down manages the production of glut4 which prompts late response of glucose from blood, some studies had reported electrochemical immune sensor for adiponectin detection, in earlier studies measurements of retinol binding protein can be used as functional biomarker for determination of insulin sensitivity**.** [30]

In some condition's glucose is used through hexosamine biosynthesis pathway. During this process utilization can effectively increase product formed N- glycan structure which considered to be responsible for increase in plasma levels in type1 and type2 diabetes**.** [32]

N -glycosylation is the main process for different glycosyl transferases in this process uridine diphosphate N-acetylglucosamine serves as substrate when talking about eukaryotes, the process occurs by block of 14 sugar transfer corresponding to specific asparagine residues in endoplasmic reticulum. However, glucose transporters have N- glycosylation sites present in loops, in some studies reduced glut2 expression was observed for the effect of high fat diet, in this both diet and genetic change was observed. Glycosyltransferases catalyzes the synthesis of glut2 by lectin- glycan binding, the process leads to GLUT2 endocytosis, which caused diabetes complications. However, this transport can be maintained by the process of N-glycosylation. Currently NMR based biomarker known as GlyCA; originated from Nacetyl -methyl or N -acetylglucosamine residues can be used as a marker for systematic inflammation may be linked to insulin sensitivity. On the other side increased levels of this GlyCA seems to be interlinked with type 2 diabetes**.** [32]

3.4 Conclusion: as the main work of glucose transporters is regulating glucose metabolism but researchers are interested in defining glut roles in other diseases like Alzheimer and cancer and some studies are also targeting on GLUTs as potential targets, where in some studies the structure of glut1, Glut2, glut 3 has been discussed through conformational studies on the other hand studies are reported about glut4 expression in different tissues, Glut5 role and it's affinity had been discussed in some studies but main mechanism is unclear, talking about GLUT6 metabolism it is associated to be a lysosomal transporter and its role in endomembranes has been discussed along with glut8, 10. While glut9 serves to be urate transporter still it's mechanism remain unclear, talking about GlUT11, 12 and 13 it's expression and localization is somewhat clear but questions remain about its translocation and mechanisms, studies are emphasizing on genetic analysis and tentative models to link the factors responsible for these gluts mechanisms and mutations so far till studies are reflecting main focus on different glycolytic activity in different cells or the search of biomarkers for disease predictions and correlating complications.

3.5 Performed multiple sequence alignment;

CLUSTAL O (1.2.4) multiple sequence alignment

```
NP_006507.2          -------------------------------------------MEP-SSKKLTGRLMLAV 16
NP_001265587.1       ------------------------------------------------------------
NP_008862.1          -------------------------------------------M-GTQKVTPALIFAI 14
NP_001033.1          ------------------------MPSGFQQ----IGSEDGEP-PQQRVTGTLVLAV 28
AAB60641.1           ---------------------------------MEQQ---------------------- 4
SP|Q9UGQ3|GTR6_HUMAN ------------MQEPLLGAEGPDYDTFPEKPP---PS---PGDRARVGTLQNKRVFLAT 42
NP_997303.2          --------------------------------MENKEAGTPPPIPSREGRLQPTLLLAT 27
AAH19043.1           -----------------MTPEDPEET-QPLLGP--------PG----GSAPRGRRVFLAA 30
```

```
AAI10415.1          MARKQNRNSKELGLVPLTDDTSHARPPGPGRALLECDHLRSGVPGGRRRKDWSCSLLVAS 60
NP_110404.1          ----------------------------------------MGHSPPVLPLCA------- 12
SP|Q9BYW1|GTR11_HUMAN ----------------------------------------MRALRRLIQGRILLLTI 17
NP_660159.1          ------------MVPVENTEGPSLLNQKGTAV---ETEGSGSRHPPWARGCGMFTFLSS 44
SP|Q8TDB8|GTR14_HUMAN --------------MEFHNG-GH--VSGIGGFLV----SLTSRMKP-HTLAVTPALIFAI 38


NP_006507.2          GGAVL-GSLQFGYNTGVINAPQKVIEEFYNQTWVVHRYGE----SILPTTLTTLWSLSVAI 71
NP_001265587.1         ------------------------------------------------------------
NP_008862.1          TVATI-GSFQFGYNTGVINAPEKIIKEFINKTLTDKGNA----PPSEVLLTSLWSLSVAI 69
NP_001033.1          FSAVL-GSLQFGYNIGVINAPQKVIEQSYNETWLGRQGPEGPSSIPPGTLTTLWALSVAI 87
AAB60641.1          -DQSM--KEGMGTTWLLSTPQHWLMQQFYNETYYGRTGE----FMEDFPLTLLWSVTVSM 57
SP|Q9UGQ3|GTR6_HUMAN FAAVL-GNFSFGYALVYTSPVIPALERSL--------------DPDLHLTKSQASWFGSV 87
NP_997303.2          LSAAFGSAFQYGYNLSVVNTPHKVFKSFYNETYFERHAT----FMDGKLMLLLWSCTVSM 83
AAH19043.1           FAAAL-GPLSFGFALGYSSPAIPSLQRAA--------------PPAPRLDDAAASWFGAV 75
AAI10415.1          LAGAFGSSFLYGYNLSVVNAPTPYIKAFYNESWERRHGR----PIDPDTLTLLWSVTVSI 116
NP_110404.1          SVSLL-GGLTFGYELAVISGALLPLQLDF------------------GLSCLEQEFLVGS 53
SP|Q9BYW1|GTR11_HUMAN CAAGIGGTFQFGYNLSIINAPTLHIQEFTNETWQARTGE----PLPDHLVLLMWSLIVSL
73
NP_660159.1          VTAAV-SGLLVGYELGIISGALLQIKTLL------------------ALSCHEQEMVVSS 85
SP|Q8TDB8|GTR14_HUMAN TVATI-GSFQFGYNTGVINAPETIIKEFINKTLTDKANA----PPSEVLLTNLWSLSVAI 93


NP_006507.2          FSVGGMIGSFSVGLFVNRFGRRNSMLMMNLLAFVSAVLMGFSKLGKSFEMLILGRFIIGV 131
NP_001265587.1         ----------------MHLNRIKAMLVANILSLVGALLMGFSKLGPSHILIIAGRSISGL 44
NP_008862.1          FSVGGMIGSFSVGLFVNRFGRRNSMLIVNLLAVTGGCFMGLCKVAKSVEMLILGRLVIGL 129
NP_001033.1          FSVGGMISSFLIGIISQWLGRKRAMLVNNVLAVLGGSLMGLANAAASYEMLILGRFLIGA 147
AAB60641.1          FPFGGFIGSLLVGPLVNKFGRKGALLFNNIFSIVPAILMGCSRVATSFELIIISRLLVGI 117
SP|Q9UGQ3|GTR6_HUMAN FTLGAAAGGLSAMILNDLLGRKLSIMFSAVPSAAGYALMAG---
AHGLWMLLLGRTLTGF 144
NP_997303.2          FPLGGLLGSLLVGLLVDSCGRKGTLLINNIFAIIPAILMGVSKVAKAFELIVFSRVVLGV 143
AAH19043.1           VTLGAAAGGVLGGWLVDRAGRKLSLLLCSVPFVAGFAVITA---AQDVWMLLGGRLLTGL 132
AAI10415.1          FAIGGLVGTLIVKMIGKVLGRKHTLLANNGFAISAALLMACSLQAGAFEMLIVGRFIMGI 176
NP_110404.1          LLLGALLASLVGGFLIDCYGRKQAILGSNLVLLAGSLTLGL---AGSLAWLVLGRAVVGF 110
SP|Q9BYW1|GTR11_HUMAN YPLGGLFGALLAGPLAITLGRKKSLLVNNIFVVSAAILFGFSRKAGSFEMIMLGRLLVGV
133
NP_660159.1          LVIGALLASLTGGVLIDRYGRRTAIILSSCLLGLGSLVLIL---SLSYTVLIVGRIAIGV 142
SP|Q8TDB8|GTR14_HUMAN
FSVGGMIGSFSVGLFVNRFGRRNSMLIVNLLAATGGCLMGLCKIAESVEMLILGRLVIGL 153
                              .*  :::          :    .    :: .*   *

NP_006507.2          YCGLTTGFVPMYVGEVSPTALRGALGTLHQLGIVVGILIAQVFGLDSIMGNKDLWPLLLS 191
NP_001265587.1         YCGLISGLVPMYIGEIAPTALRGALGTFHQLAIVTGILISQIIGLEFILGNYDLWHILLG 104
NP_008862.1          FCGLCTGFVPMYIGEISPTALRGAFGTLNQLGIVVGILVAQIFGLEFILGSEELWPLLLG 189
NP_001033.1          YSGLTSGLVPMYVGEIAPTHLRGALGTLNQLAIVIGILIAQVLGLESLLGTASLWPLLLG 207
AAB60641.1          CAGVSSNVVPMYLGELAPKNLRGALGVVPQLFITVGILVAQIFGLRNLLANVDGWPILLG 177
```

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SP|Q9UGQ3|GTR6_HUMAN AGGLTAACIPVYVSEIAPPGVRGALGATPQLMAVFGSLSLYALGLL-L---PWRWLAVAG
200
NP_997303.2         CAGISYSALPMYLGELAPKNLRGMVGTMTEVFVIVGVFLAQIFSLQAILGNPAGWPVLLA 203
AAH19043.1          ACGVASLVAPVYISEIAYPAVRGLLGSCVQLMVVVGILLAYLAGWV-L---EWRWLAVLG 188
AAI10415.1          DGGVALSVLPMYLSEISPKEIRGSLGQVTAIFICIGVFTGQLLGLPELLGKESTWPYLFG 236
NP_110404.1         AISLSSMACCIYVSELVGPRQRGVLVSLYEAGITVGILLSYALNYA-LAGTPWGWRHMFG 169
SP|Q9BYW1|GTR11_HUMAN
NAGVSMNIQPMYLGESAPKELRGAVAMSSAIFTALGIVMGQVVGLRELLGGPQAWPLLLA 193
NP_660159.1         SISLSSIATCVYIAEIAPQHRRGLLVSLNELMIVIGILSAYISNYA-FANVFHGWKYMFG 201
SP|Q8TDB8|GTR14_HUMAN FCGLCTGFVPMYIGEISPTALRGAFGTLNQLGIVIGILVAQIFGLELILGSEELWPVLLG
213
                .:    :*:.*    ** .       * .   . :    * : .

NP_006507.2         IIFIPALLQCIVLPFCPESPRFLLINRNEENRAKSVLKKLRGTADVTHDLQEMKEESRQM 251
NP_001265587.1        LSGVRAILQSLLLFFCPESPRYLYIKLDEEVKAKQSLKRLRGYDDVTKDINEMRKEREEA 164
NP_008862.1         FTILPAILQSAALPFCPESPRFLLINRKEEENAKQILQRLWGTQDVSQDIQEMKDESARM 249
NP_001033.1         LTVLPALLQLVLLPFCPESPRYLYIIQNLEGPARKSLKRLTGWADVSGVLAELKDEKRKL 267
AAB60641.1          LTGVGAALQLLLLPFFPESPRYLLIQKKDEAAAKKALQTLRGWDSVDREVAEIRQEDEAE 237
SP|Q9UGQ3|GTR6_HUMAN E--APVLIMILLLSFMPNSPRFLLSR-GRDEEALRALAWLRGTDVDVHW--EFEQIQDNV
255
NP_997303.2         LTGVPALLQLLTLPFFPESPRYSLIQKGDEATARQALRRLRGHTDMEAELEDMRAEARAE 263
AAH19043.1          C--VPPSLMLLLMCFMPETPRFLLTQ-HRRQEAMAALRFLWGSEQ--GW--EDPPIGA-- 239
AAI10415.1          VIVVPAVVQLLSLPFLPDSPRYLLLEKHNEARAVKAFQTFLGKADVSQEVEEVLAESRVQ 296
NP_110404.1         WATAPAVLQSLSLLFLPAGTDETATH--------KDLIPLQG------G--E---APKLG 210
SP|Q9BYW1|GTR11_HUMAN SCLVPGALQLASLPLLPESPRYLLIDCGDTEACLAALRRLRGSGDLAGELEELEEERAAC
253
NP_660159.1         LVIPLGVLQAIAMYFLPPSPRFLVMK-GQEGAASKVLGRLRALSDTT-E--ELTVIKSSL 257
SP|Q8TDB8|GTR14_HUMAN
FTILPAILQSAALPCCPESPRFLLINRKKEENATRILQRLWGTQDVSQDIQEMKDESARM 273
                  :   :  *             : : .      :

NP_006507.2         MREKKVTILELFRSPA-YRQPILIAVVLQLSQQLSGINAVFYYSTSIFEKAGVQQ---PV 307
NP_001265587.1        SSEQKVSIIQLFTNSS-YRQPILVALMLHVAQQFSGINGIFYYSTSIFQTAGISK---PV 220
NP_008862.1         SQEKQVTVLELFRVSS-YRQPIIISIVLQLSQQLSGINAVFYYSTGIFKDAGVQE---PI 305
NP_001033.1         ERERPLSLLQLLGSRT-HRQPLIIAVVLQLSQQLSGINAVFYYSTSIFETAGVGQ---PA 323
AAB60641.1          KAAGFISVLKLFRMRS-LRWQLLSIIVLMGGQQLSGVNAIYYYADQIYLSAGVPE-EHVQ 295
SP|Q9UGQ3|GTR6_HUMAN RRQSSRVSWAEARAPH-VCRPITVALLMRLLQQLTGITPILVYLQSIFDSTAVLLPP--K
312
NP_997303.2         RAEGHLSVLHLCALRS-LRWQLLSIIVLMAGQQLSGINAINYYADTIYTSAGVEA-AHSQ 321
AAH19043.1          ---EQSFHLALLRQPG-IYKPFIIGVSLMAFQQLSGVNAVMFYAETIFEEAKFK-DS--S 292
AAI10415.1          RSIRLVSVLELLRAPY-VRWQVVTVIVTMACYQLCGLNAIWFYTNSIFGKAGIPL-AKIP 354
NP_110404.1         PGRPRYSFLDLFRARDNMRGRTTVGLGLVLFQQLTGQPNVLCYASTIFSSVGFHGGSSAV 270
SP|Q9BYW1|GTR11_HUMAN QGCRARRPWELFQHRA-LRRQVTSLVVLGSAMELCGNDSVYAYASSVFRKAGVPE-
AKIQ 311
NP_660159.1         KDEYQYSFWDLFRSKDNMRTRIMIGLTLVFFVQITGQPNILFYASTVLKSVGFQSNEAAS 317
SP|Q8TDB8|GTR14_HUMAN SQEKQVTVLELFRVSS-YRQPIIISIVLQLSQQLSGINAVFYYSTGIFKDAGVQQ---PI 329
                            :    :: *  : *  :  . .
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NP_006507.2          YATIGSGIVNTAFTVVSLFVVERAGRRTLHLIGLAGMAGCAILMTIALA---------- 356
NP_001265587.1         YATIGVGAVNMVFTAVSVFLVEKAGRRSLFLIGMSGMFVCAIFMSVGLV---------- 269
NP_008862.1          YATIGAGVVNTIFTVVSLFLVERAGRRTLHMIGLGGMAFCSTLMTVSLL---------- 354
NP_001033.1          YATIGAGVVNTVFTLVSVLLVERAGRRTLHLLGLAGMCGCAILMTVALL---------- 372
AAB60641.1          YVTAGTGAVNVVMTFCAVFVVELLGRRLLLLLGFSICLIACCVLTAALA---------- 344
SP|Q9UGQ3|GTR6_HUMAN DDAAIVGAVRLLSVLIAALTMDLAGRKVLLFVSAAIMFAANLTLGLYIH---------- 361
NP_997303.2          YVTVGSGVVNIVMTITSAVLVERLGRRHLLLAGYGICGSACLVLTVVLL---------- 370
AAH19043.1          LASVVVGVIQVLFTAVAALIMDRAGRRLLLVLSGVVMVFSTSAFGAYFK---------- 341
AAI10415.1          YVTLSTGGIETLAAVFSGLVIEHLGRRPLLIGGFGLMGLFFGTLTITLT---------- 403
NP_110404.1          LASVGLGAVKVAATLTAMGLVDRAGRRALLLAGCALMALSVSGIGLVSFAVPMDSGPSCL 330
SP|Q9BYW1|GTR11_HUMAN YAIIGTGSCELLTAVVSCVVIERVGRRVLLIGGYSLMTCWGSIFTVALC---------- 360
NP_660159.1          LASTGVGVVKVISTIPATLLVDHVGSKTFLCIGSSVMAASLVTMGIVNLNIHMNFTHICR 377
SP|Q8TDB8|GTR14_HUMAN YATISAGVVNTIFTLLSLFLVERAGRRTLHMIGLGGMAFCSTLMTVSLL---------- 378
                     * .  . :  :: * : :  .        :

NP_006507.2          --------------------------LLEQ----------------------------- 360
NP_001265587.1         --------------------------LLNK----------------------------- 273
NP_008862.1          --------------------------LKDN----------------------------- 358
NP_001033.1          --------------------------LLER----------------------------- 376
AAB60641.1          --------------------------LQDT----------------------------- 348
SP|Q9UGQ3|GTR6_HUMAN --------------FGPRPLSPNST---------------------------------- 372
NP_997303.2          --------------------------FQNR----------------------------- 374
AAH19043.1          --------------LTQGGPGNSSH---------------------------------- 352
AAI10415.1          --------------------------LQDH----------------------------- 407
NP_110404.1          AVPNATGQ---------TGLPGDSGLLQDSSLPPIPRTNEDQREPILSTAKKTKPHPRSG 381
SP|Q9BYW1|GTR11_HUMAN --------------------------LQSS----------------------------- 364
NP_660159.1          SHNSINQSLDESVIYGPGNLSTNNNTLRDH-FKGIS---SHSRSSLMPLRND---VDKRG 430
SP|Q8TDB8|GTR14_HUMAN --------------------------LKNH----------------------------- 382


NP_006507.2          --------------------------LPWMSYLSIVAIFGFVAFFEVGPGPIPWFIVAE 393
NP_001265587.1         --------------------------FSWMSYVSMIAIFLFVSFFEIGPGPIPWFMVAE 306
NP_008862.1          --------------------------YNGMSFVCIGAILVFVAFFEIGPGPIPWFIVAE 391
NP_001033.1          --------------------------VPAMSYVSIVAIFGFVAFFEIGPGPIPWFIVAE 409
AAB60641.1          --------------------------VSWMPYISIVCVISYVIGHALGPSPIPALLITE 381
SP|Q9UGQ3|GTR6_HUMAN ---------AGLESESWGDLAQPLAAPAGYLTLVPLLATMLFIMGYAVGWGPITWLLMSE
423
NP_997303.2          --------------------------VPELSYLGIICVFAYIAGHSIGPSPVPSVVRTE 407
AAH19043.1          ---------VAIS---APVSAQPVDASVGL-AWLAVGSMCLFIAGFAVGWGPIPWLLMSE 399
AAI10415.1          --------------------------APWVPYLSIVGILAIIASFCSGPGGIPFILTGE 440
NP_110404.1          DPSAPPRLA--L-SSALPGPPLPARG-HALLRWTALLCLMVFVSAFSFGFGPVTWLVLSE 437
SP|Q9BYW1|GTR11_HUMAN --------------------------FPWTLYLAMACIFAFILSFGIGPAGVTGILATE 397
NP_660159.1          ETTSASLLNAGLSHTEYQIVTDPGDV-PAFLKWLSLASLLVYVAAFSIGLGPMPWLVLSE 489
SP|Q8TDB8|GTR14_HUMAN --------------------------YNGMSFVCIGAILVFVACFEIGPGPIPWFIVAE 415
                                    :    : .  * . : .: *
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NP_006507.2          LFSQGPRPAAIAVAGFSNWTSNFIVGMCFQYVEQLCGPY-VFIIFTVLLVLFFIFTYFKV 452
NP_001265587.1       FFSQGPRPAALAIAAFSNWTCNFIVALCFQYIADFCGPY-VFFLFAGVLLAFTLFTFFKV 365
NP_008862.1          LFSQGPRPAAMAVAGCSNWTSNFLVGLLFPSAAHYLGAY-VFIIFTGFLITFLAFTFFKV 450
NP_001033.1          LFSQGPRPAAMAVAGFSNWTSNFIIGMGFQYVAEAMGPY-VFLLFAVLLLGFFIFTFLRV 468
AAB60641.1          IFLQSSRPSAFMVGGSVHWLSNFTVGLIFPFIQEGLGPY-SFIVFAVICLLTTIYIFLIV 440
SP|Q9UGQ3|GTR6_HUMAN VLPLRARGVASGLCVLASWLTAFVLTKSFLPVVSTFGLQVPFFFFAAICLVSLVFTGCCV
483
NP_997303.2          IFLQSSRRAAFMVDGAVHWLTNFIIGFLFPSIQEAIGAY-SFIIFAGICLLTAIYIYVVI 466
AAH19043.1          IFPLHVKGVATGICVLTNWLMAFLVTKEFSSLMEVLRPYGAFWLASAFCIFSVLFTLFCV 459
AAI10415.1          FFQQSQRPAAFIIAGTVNWLSNFAVGLLFPFIQKSLDTY-CFLVFATICITGAIYLYFVL 499
NP_110404.1          IYPVEIRGRAFAFCNSFNWAANLFISLSFLDLIGTIGLSWTFLLYGLTAVLGLGFIYLFV 497
SP|Q9BYW1|GTR11_HUMAN LFDQMARPAACMVCGALMWIMLILVGLGFPFIMEALSHF-
LYVPFLGVCVCGAIYTGLFL 456
NP_660159.1          IFPGGIRGRAMALTSSMNWGINLLISLTFLTVTDLIGLPWVCFIYTIMSLASLLFVVMFI 549
SP|Q8TDB8|GTR14_HUMAN LFSQGPRPAAMAVAGCSNWTSNFLVGLLFPSAAYYLGAY-VFIIFTGFLITFLAFTFFKV
474
                .   : * .   *  : :  *            :  :  :

NP_006507.2          PETKGRTFDEIASGFRQGGASQS-DKTP---EELFHPLGADSQV---------- 492
NP_001265587.1       PETKGKSFEEIAAEFQKKSGSAHRPKA----AVEMKFLGATETV---------- 405
NP_008862.1          PETRGRTFEDITRAFEGQAHGADRSGKD--GVMEMNSIEPAKETTTNV---------- 496
NP_001033.1          PETRGRTFDQISAAFHRTPSLLEQEVKP---STELEYLGPDEND---------- 509
AAB60641.1          PETKAKTFIEINQIFTKMNKVSEVYPEK----EELKELPPVTSEQ---------- 481
SP|Q9UGQ3|GTR6_HUMAN PETKGRSLEQIESFFRTGRRSFLR---------- 507
NP_997303.2          PETKGKTFVEINRIFAKRNRVKLPEEKE----ETIDAGPPTASPAKETSF---------- 512
AAH19043.1          PETKGKTLEQITAHFEGR---------- 477
AAI10415.1          PETKNRTYAEISQAFSKRNKAYPPEEKI----DSAVTDGKINGRP---------- 540
NP_110404.1          PETKGQSLAEIDQQFQKRRFTLS---FGHRQNSTGIPYSRIEISAAS---------- 541
SP|Q9BYW1|GTR11_HUMAN PETKGKTFQEISKELHRLNFPRRAQGPT------WRSLEVIQSTEL---------- 496
NP_660159.1          PETKGCSLEQISMELAKVNYVKNNICFMSHHQEELVPKQPQKRKPQEQLLECNKLCGRGQ 609
SP|Q8TDB8|GTR14_HUMAN PETRGRTFEDITRAFEGQAHGADRSGKD--GVMGMNSIEPAKETTTNV----------
520
                ***: : :*  :

NP_006507.2          --------
NP_001265587.1       --------
NP_008862.1          --------
NP_001033.1          --------
AAB60641.1          --------
SP|Q9UGQ3|GTR6_HUMAN --------
NP_997303.2          --------
AAH19043.1          --------
AAI10415.1          --------
NP_110404.1          --------
SP|Q9BYW1|GTR11_HUMAN --------
NP_660159.1          SRQLSPET 617
SP|Q8TDB8|GTR14_HUMAN --------
```

A multiple sequence alignment showing similarity of human GLUT family members from glut1-14. Lines detect identification of amino acids paired dots signifies much related sequences and single dots indicate may be half related residues.

IDENTICAL POSITIONS = 23
SIMILAR POSITIONS= 61
IDENTITY= 3.443%

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