Supporting Information

Insights into substrate and inhibitor selectivity among human GLUT transporters through comparative modeling and molecular docking

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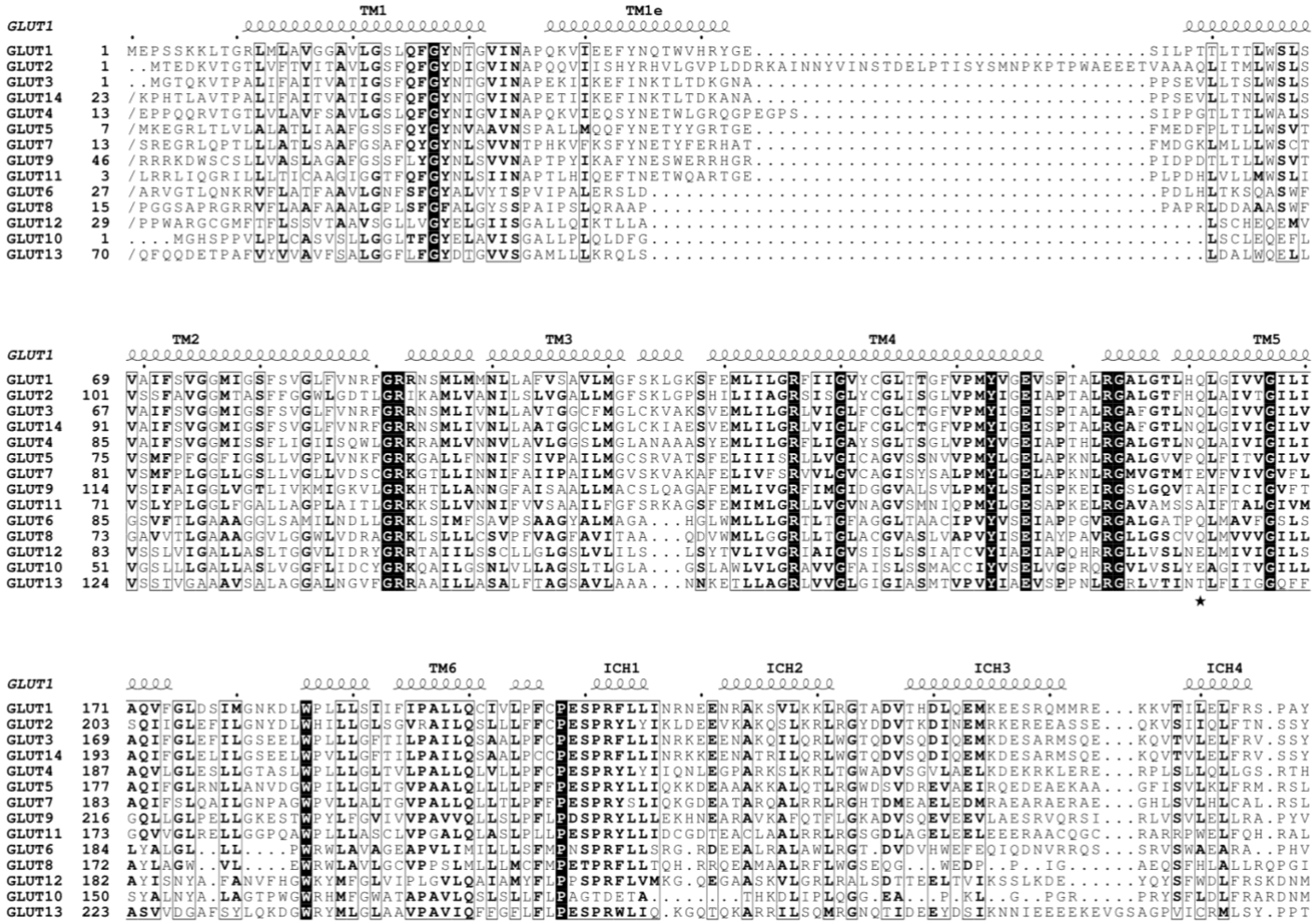
Figure S1. Sequence alignment of GLUT1-14. Alignment performed with T-COFFEE and adjusted with Vito. N-terminal and C-terminal regions from several sequences are not shown, as indicated by slashes. TM1-12 indicate transmembrane helices, while ICH1-4 indicate helices from the intracelular helical domain. Stars indicate positions that hydrogen bond to glucose in PDB 4ZW9. Figure prepared with ESPript 3.0.[1]



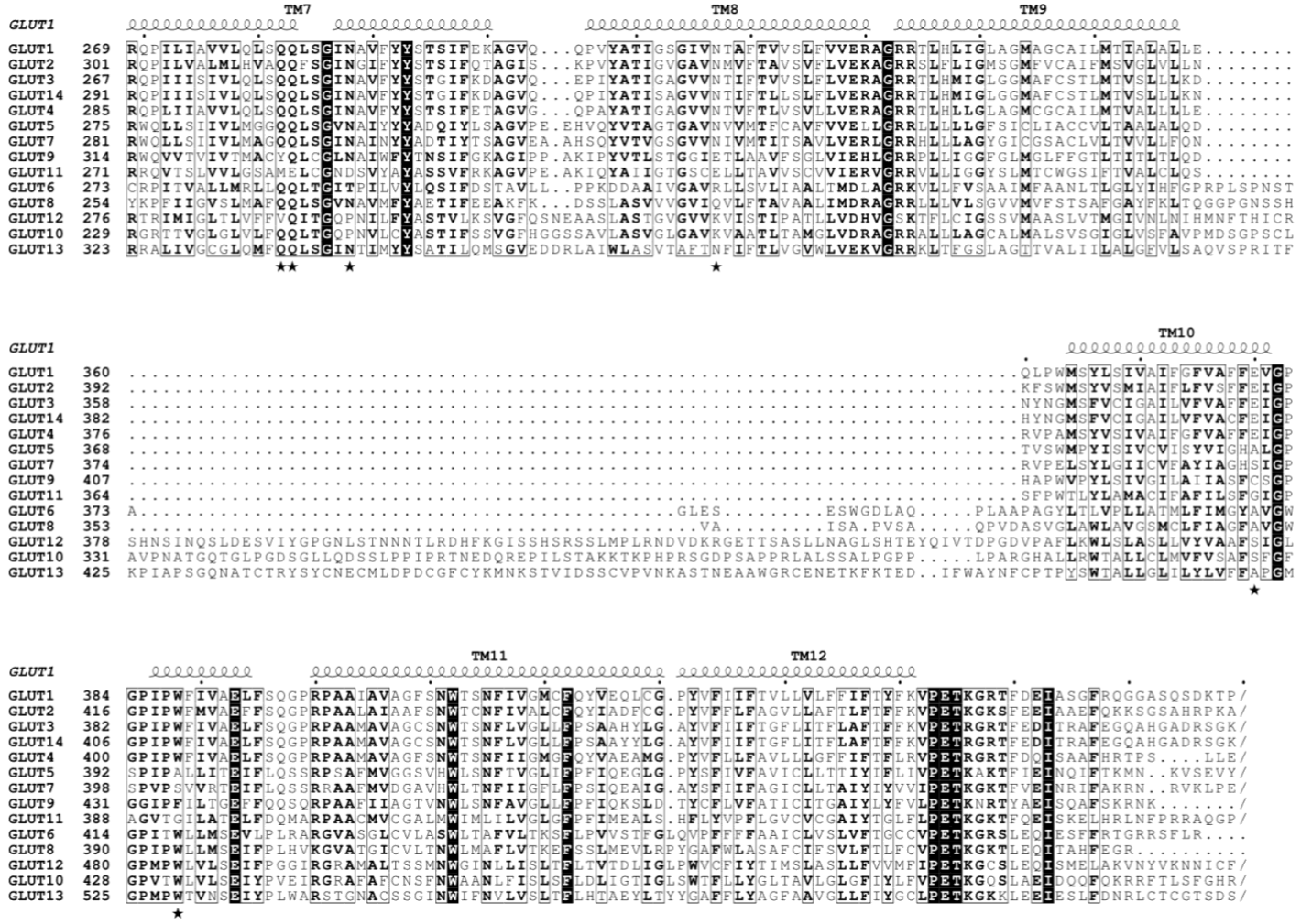

TM7
TM8
TM9
TM10
TM11
TM12
GLUT1
GLUT2
GLUT3
GLUT14
GLUT4
GLUT5
GLUT7
GLUT9
GLUT11
GLUT6
GLUT8
GLUT12
GLUT10
GLUT13

Table S1. Sequence identity matrix for GLUT1-14, obtained after sequence alignment with Clustal Omega.

	GLUT1	GLUT2	GLUT14	GLUT3	GLUT4	GLUT11	GLUT9	GLUT7	GLUT5	GLUT6	GLUT8	GLUT13	GLUT10	GLUT12
GLUT1	100.0	55.8	61.6	63.5	65.5	35.1	36.9	38.0	41.1	28.6	29.7	26.0	26.0	26.1
GLUT2	55.8	100.0	50.2	52.0	54.3	31.6	30.3	35.7	40.2	28.3	29.2	31.1	27.1	28.6
GLUT14	61.6	50.2	100.0	94.6	55.6	32.4	33.9	36.6	37.4	26.4	31.4	28.4	24.9	26.4
GLUT3	63.5	52.0	94.6	100.0	57.6	33.4	34.7	38.0	39.1	27.0	32.7	29.4	24.6	26.8
GLUT4	65.5	54.3	55.6	57.6	100.0	35.6	35.8	38.9	42.4	28.5	31.6	28.2	27.5	27.3
GLUT11	35.1	31.6	32.4	33.4	35.6	100.0	40.2	40.5	40.5	23.3	25.9	21.6	23.4	21.1
GLUT9	36.9	30.3	33.9	34.7	35.8	40.2	100.0	42.6	43.7	24.4	26.4	23.1	21.3	20.2
GLUT7	38.0	35.7	36.6	38.0	38.9	40.5	42.6	100.0	59.3	25.1	27.1	25.6	27.1	25.3
GLUT5	41.1	40.2	37.4	39.1	42.4	40.5	43.7	59.3	100.0	27.0	29.1	26.8	26.3	23.9
GLUT6	28.6	28.3	26.4	27.0	28.5	23.3	24.4	25.1	27.0	100.0	42.8	27.5	29.9	25.4
GLUT8	29.7	29.2	31.4	32.7	31.6	25.9	26.4	27.1	29.1	42.8	100.0	31.2	30.0	29.2
GLUT13	26.0	31.1	28.4	29.4	28.2	21.6	23.1	25.6	26.8	27.5	31.2	100.0	31.0	29.0
GLUT10	26.0	27.1	24.9	24.6	27.5	23.4	21.3	27.1	26.3	29.9	30.0	31.0	100.0	40.1
GLUT12	26.1	28.6	26.4	26.8	27.3	21.1	20.2	25.3	23.9	25.4	29.2	29.0	40.1	100.0

Table S2. Reported substrates for GLUT1-14.

	REPORTED SUBSTRATES*[2]											
Receptor	**glucose**	**galactose**	**2-desoxyglucose**	**mannose**	**glucosamine**	**fructose**	**xylose**	**urate**	**trehalose**	**dehydroascorbic acid**	**alfa-MG (alfa-methyl-glucose)**	**myo-inositol**
GLUT1	3 mM[3]	YES		YES	YES					YES		
GLUT2	17 mM[3]	YES		YES	YES	YES						
GLUT3	1.4 mM[3]	YES		YES			YES			YES[4]		
GLUT4	5 mM[3]				YES					YES[3]		
GLUT14	YES	YES		YES			YES			YES		
GLUT5	NO					YES[5]				NO[4]		
GLUT7	YES	NO				YES[5]	NO			NO[4]		
GLUT9	0.6 mM[3]					0.4 mM[3]		0.9 mM[3]		NO[4]		
GLUT11	YES	NO				YES				NO[4]		
GLUT6	YES									NO[4]		
GLUT8	2 mM[3]	YES				YES			YES[6]	YES[4]		
GLUT10	YES	YES								NO[4]		
GLUT12	YES[7]	YES[7]	YES[7]			YES[7]				YES[8]	YES[7]	
GLUT13	NO											100 μM[3]

*Unless another reference is especified. data was extracted from Yan. 2017.[2] For cases where a K_d value was reported. the affinity is indicated. Otherwise. YES indicated the substrated is transported. NO indicates it is not transported. and blank cells indicates that no data was found.

Table S3. Conservation of exofacial GLUT10 binding site in 250 homologous sequences.

Statistics after Clustal Omega alignment	Residue						
	E140	Q242	Q243	P248	K280	S424	W432
% conservation	100	100	100	100	100	100	97.2
Occupancy*	250	250	250	250	250	250	247

*number of aligned sequences among a total of 250 sequences considered.

Table S4. Conservation of exofacial GLUT12 binding site in 250 homologous sequences.

Statistics after Clustal Omega alignment	Residue						
	E172	V289	Q290	P295	K327	S476	W484
% conservation	99.6	100	99.6	100	100	100	88
Occupancy*	249	250	250	250	250	250	236

*number of aligned sequences among a total of 250 sequences considered.

Table S5. Myo-inositol binding site residues and their conservation within GLUTs.

		Selected residues in the binding site								
Reference protein	**GLUT13**	T213	**Q220**	**Q336**	**Q337**	**N342**	N374	A521	**W529**	**N552**
Other GLUTs	**GLUT1**	Q161	I168	Q282	Q283	N288	N317	E380	W388	N411
	GLUT2	Q193	I200	Q314	Q315	N320	N349	E412	W420	N443
	GLUT3	Q159	I166	Q280	Q281	N286	N315	E378	W386	N409
	GLUT4	Q177	I184	Q298	Q299	N304	N333	E396	W404	N427
	GLUT5	Q167	I174	Q288	Q289	N294	N325	A380	A396	H419
	GLUT6	Q174	S181	Q286	Q287	T292	R322	A410	W418	S441
	GLUT7	E173	V180	Q294	Q295	N300	N331	S394	S402	H425
	GLUT8	Q162	I169	Q267	Q268	N273	Q302	A386	W394	N417
	GLUT9	A206	V213	Y327	Q328	N333	E364	C427	F435	N458
	GLUT10	E140	I147	Q242	Q243	P248	K280	S424	W432	N455
	GLUT11	A163	I170	M284	E285	D290	E321	G384	G392	M415
	GLUT12	E172	I179	V289	Q290	P295	K327	S476	W484	N507
	GLUT14	Q183	I190	Q304	Q305	N310	N339	E402	W410	N433
Top 250 Blastp hits	**% conservation**	96.4	99.6	100	100	99.6	99.6	96.8	96.8	96.4
	occupancy	249	249	250	250	250	250	243	243	242

*GLUT13 residues which are predicted to hydrogen bond to myo-inositol are shown in bold. For all other receptors. Cells are colored red if the residue differs from the one found in GLUT13 and green otherwise.

Table S6. Urate binding site residues and their conservation within GLUTs.

		Selected residues in predicted urate binding site						
Reference protein	**GLUT9**	Y71	**Y327**	**Q328**	**N333**	**W336**	C427	F435
Other GLUTs	**GLUT1**	F26	Q282	Q283	N288	F291	E380	W388
	GLUT2	F24	Q314	Q315	N320	F323	E412	W420
	GLUT3	F24	Q280	Q281	N286	F289	E378	W386
	GLUT4	F38	Q298	Q299	N304	F307	E396	W404
	GLUT5	Y32	Q288	Q289	N294	Y297	A380	A396
	GLUT6	F52	Q286	Q287	T292	L295	A410	W418
	GLUT7	Y38	Q294	Q295	N300	N303	S394	S402
	GLUT8	F40	Q267	Q268	N273	M276	A386	W394
	GLUT10	F22	Q242	Q243	P248	L251	S424	W432
	GLUT11	F28	M284	E285	D290	Y293	G384	G392
	GLUT12	V54	V289	Q290	P295	L298	S476	W484
	GLUT13	F95	Q336	Q337	N342	M354	A521	W529
	GLUT14	F48	Q304	Q305	N310	F313	E402	W410
top 250 GLUT9 Blastp hits	**% conservation**	95.6	100	100	100	99.6	99.6	99.7
	occupancy	243	250	250	250	249	250	249

*GLUT9 residues which are predicted to hydrogen bond to urate are shown in bold. For all other receptors. Cells are colored red if the residue differs from the one found in GLUT9 and green otherwise.

Table S7. Conservation of exofacial GLUT11 binding site in 250 homologous sequences.

Statistics after Clustal Omega alignment	Residue							
	A163	M284	E285	N289	D290	E321	G384	G392
% conservation	90.8	88.0	92.0	92.5	96.0	92.0	98.8	97.2
Occupancy*	250	246	246	246	246	231	248	247

*number of aligned sequences among a total of 250 sequences considered.

Table S8. Reported complexes analyzed by comparative docking or docking with PLANTS.

Protein	Ligand	Study type/ Study name	Template/ Anchor
GLUT5	Cytochalasin B	Comparative docking/ Raw transfer	5EQI/ 5RH
GLUT7	Cytochalasin B	Comparative docking/ Raw transfer	5EQI/ 5RH
GLUT9	Cytochalasin B	Comparative docking/ Raw transfer	5EQI/ 5RH
GLUT11	α-D-Glucose	Docking with PLANTS/ GLUT11ligsAnchor3	4ZW9/GLC_A_5 (best LPE)
GLUT11	D-Glucosamine	Docking with PLANTS/ GLUT11ligsAnchor3	4ZW9/GLC_A_5 (best pKd)
GLUT11	N-Acetyl-glucosamine thiazoline	Docking with PLANTS/ GLUT11ligsAnchor3	4ZWC/MAL_A_5 (best pKd)
GLUT9	Urate	Docking with PLANTS/ GTR9uratePLANTS0constraint	4GC0/6BG_A
GLUT3	Myo-inositol	Docking with PLANTS/ GTR3allPLANTS	4ZW9/GLC_A_5 (best LPE)
GLUT13	Myo-inositol	Docking with PLANTS/ GTR13allPLANTSupload	4ZW9/GLC_A_5 (best LPE)

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