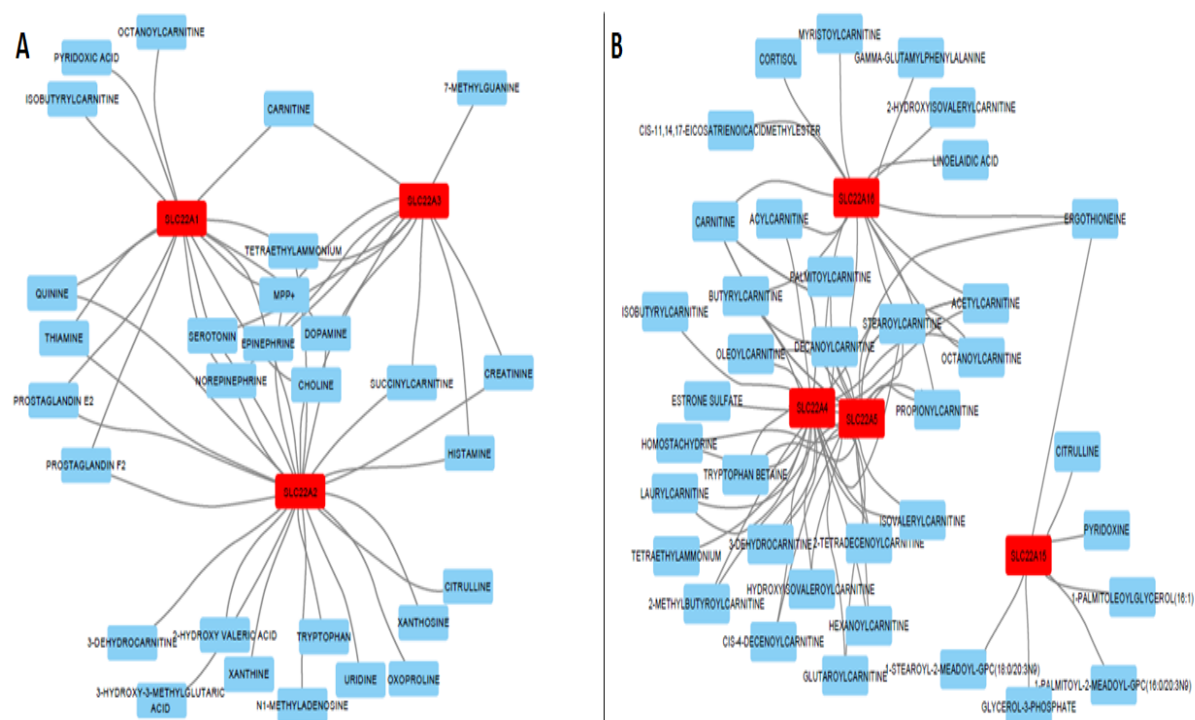
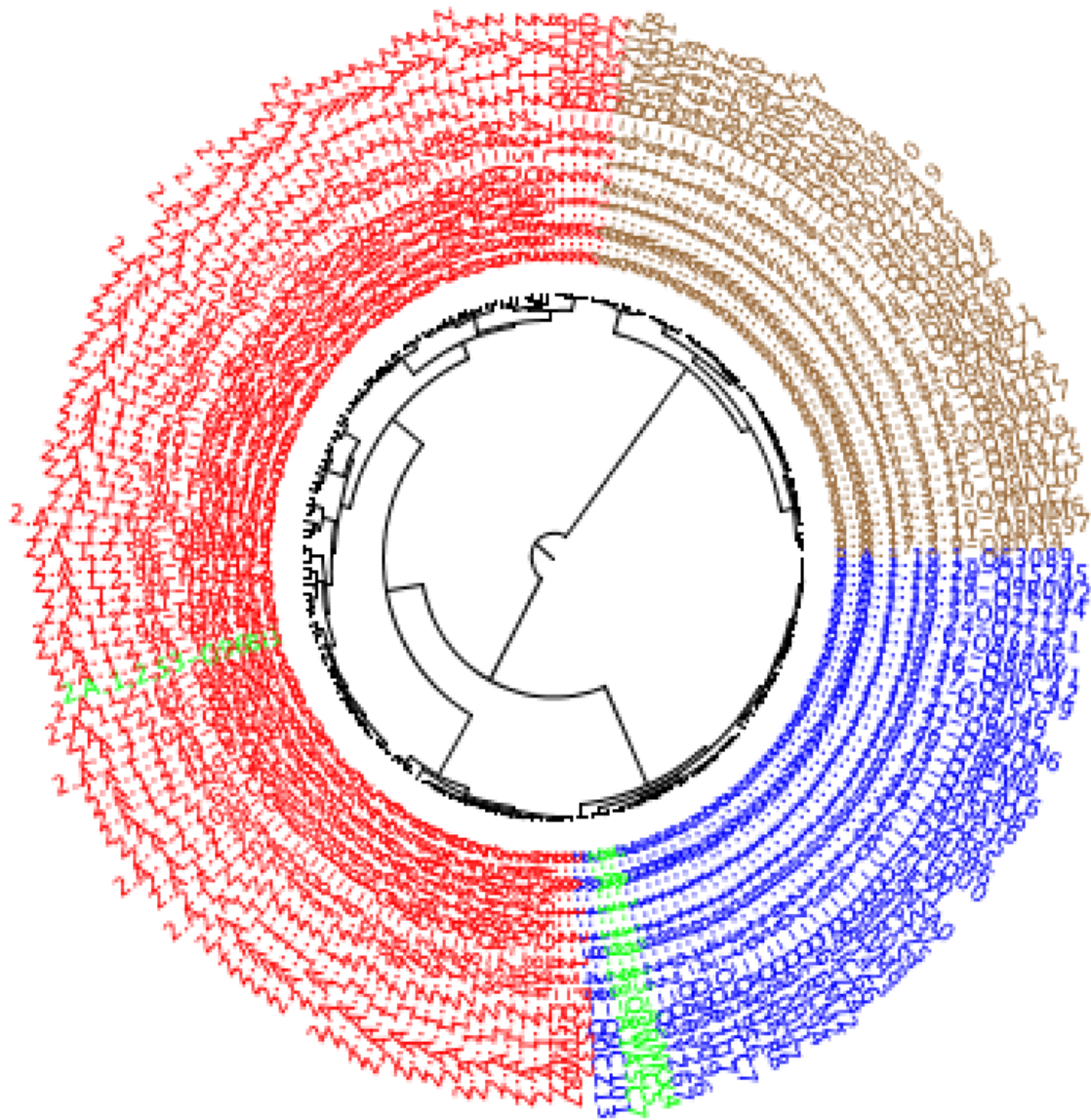


**Figure S1: OATS1-4 Subgroups.** The previously defined OAT major subclade was reconstructed into smaller groups based on additional support. A) OATS1 (SLC22A6, SLC22A8, SLC22A20). B) OATS2 (SLC22A7). C) OATS3 (SLC22A11, SLC22A12, SLC22A22). D) OATS4 (SLC22A9, SLC22A10, SLC22A24, SLC22A25). In each panel, the SLC22 family members are red nodes, the metabolites are blue nodes, and the edges connecting them are evidence of interaction between the protein and the metabolite.



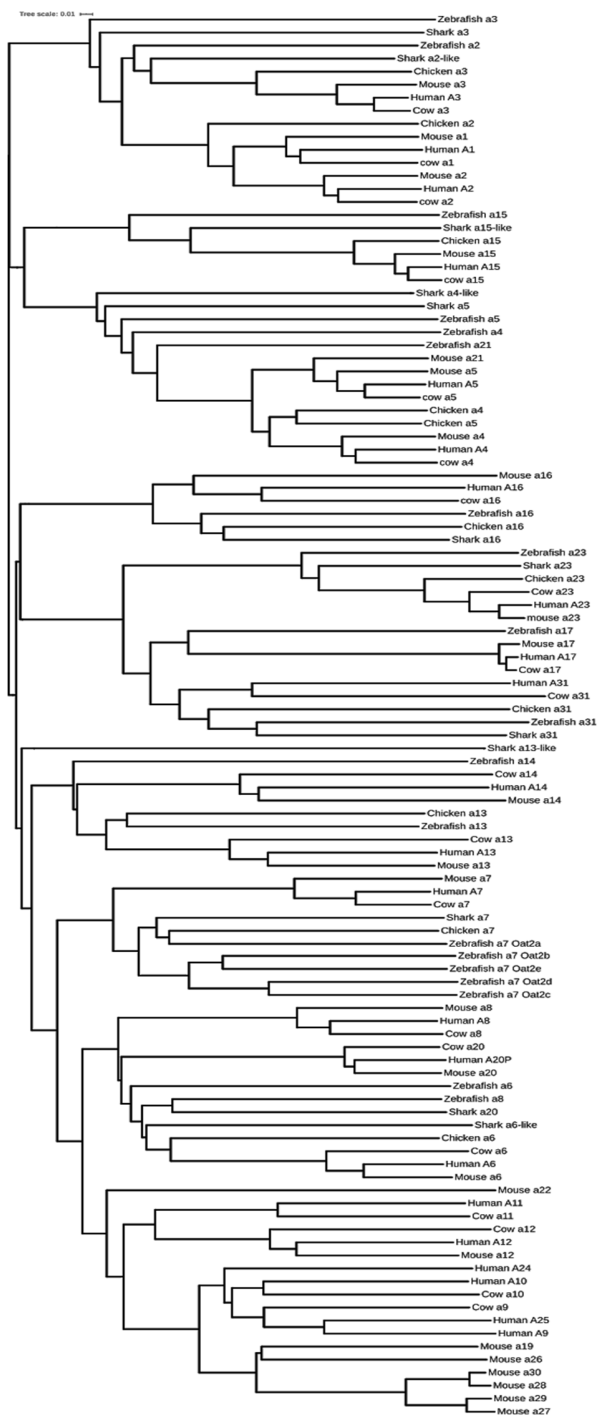
**Figure S2: OCT and OCTN/OCTN-related subgroups.** The previously defined OCT major subclade was reconstructed into new groups based on additional support. A) OCT (SLC22A1, SLC22A2, SLC22A3). B) OCTN/OCTN-Related (SLC22A4, SLC22A5, SLC22A15, SLC22A16). In each panel, the SLC22 family members are red nodes, the metabolites are blue nodes, and edges connecting them are evidence of interaction between the protein and the metabolite.



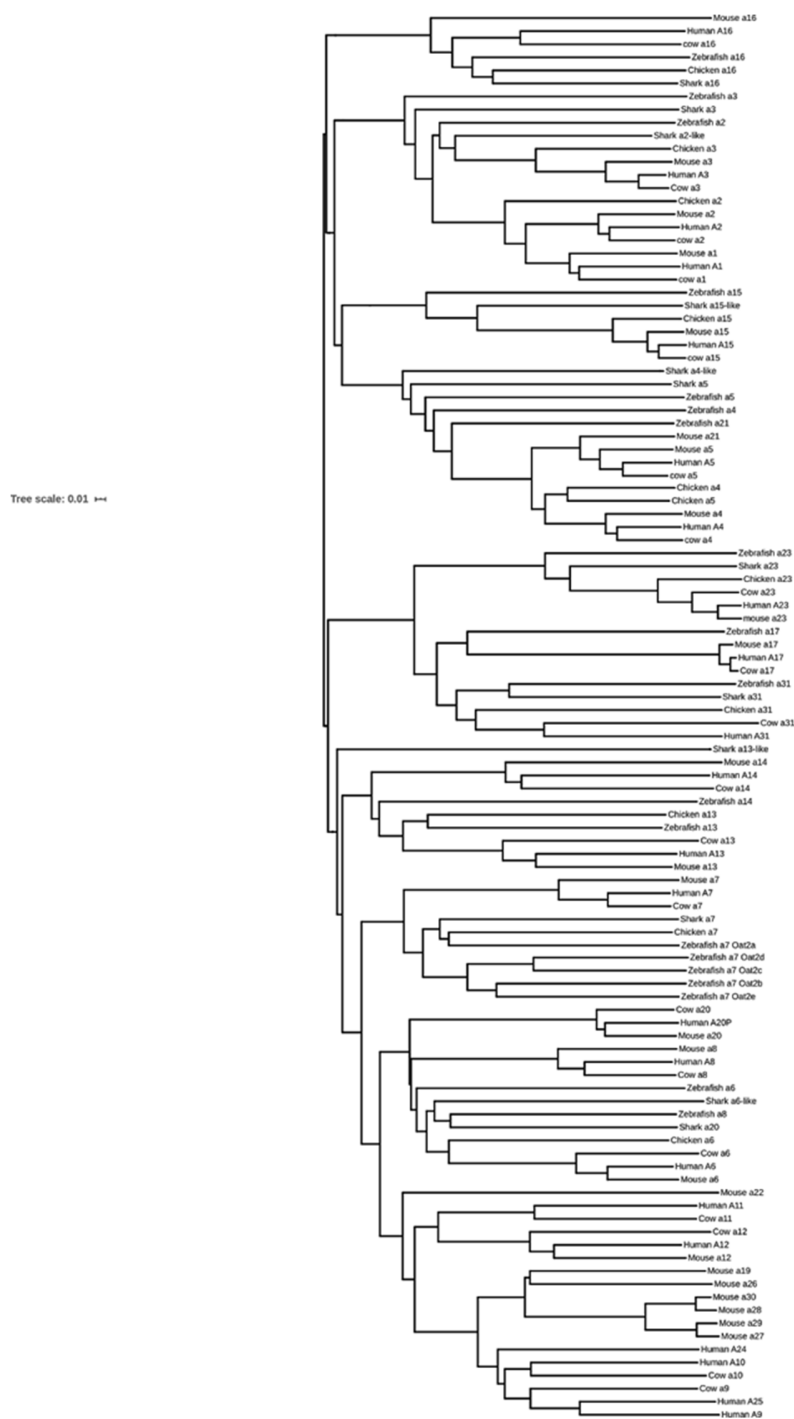


**Figure S4: SSearch36 homology results show Slc22a18 within the DHA family.** The DHA family is shown in red, with SLC22A18 highlighted in green. The SLC22 family is shown in blue, with the other Oat-related subclade members (SLC22A17, SLC22A23, and SLC22A31) highlighted in green. The POT transporter family outgroup is shown in brown.





**Figure S5: MAFFT multiple sequence alignment. Phylogenetic tree of previously defined OAT subclade.** 90 sequences were aligned using MAFFT and viewed on the Interactive Tree of Life (iTOL). Branch lengths indicate the number of amino acid changes per residue between the sequences and the most recent ancestor. This analysis supports the formation of 4 functionally distinct subgroups from the OAT subclade.



**Figure S6: Clustal-Omega multiple sequence alignment.** All SLC22 sequences from human, mouse, cow, chicken, shark, and zebrafish were aligned using Clustal-Omega. Tree was visualized using iTOL.

Oat subclade	Motif	Region	% Present	MEME#	p-value	Sequence
	A	1-20	0.97	12	2.27E-20	MAFNDLLQQVGGVGRFQQIQ
	B	33-52	0.99	2	1.23E-22	SHNTLQNFTAAIPTHHCRPP
	C	67-86	0.99	5	8.88E-19	LPRDRQQQPESCLRFTSPQW
	D	99-118	0.99	1	7.82E-21	TGATEPCTDGWYDNSTFPS
	E	123-142	0.99	3	3.01E-20	EWDLVCSHRALRQLAQSLYM
	F	143-162	1	6	5.34E-18	VGVLGAMVFGYLADRLGRR
	G	177-196	1	13	1.09E-20	TCAAFAPNFPIYCAFRLLSG
	H	230-249	0.99	10	5.99E-21	YSLGQFLLAGVAYAVPHWRH
	I	261-275	0.95	11	2.59E-16	FFIYSWFFIESARWH
	J	279-298	0.95	7	6.4E-17	GRLDLTLRALQRVARINGKR
	K	328-338	0.86	15	1.69E-09	ELLRCPTLRHL
	L	349-368	0.97	9	1.28E-21	TSFAYYGLVMDLQGFGVSIY
	M	376-395	0.97	16	5.25E-18	AVDLPAKLVGFLVINSLGRR
	N	423-437	0.86	14	2.1E-16	RTSLAVLGKGCCLAAS
	O	438-457	0.93	8	2.02E-23	FNCIFLYTGELYPTMIRQTG
	P	503-522	0.97	4	8.46E-20	LLPETLGQPLPDTVQDLESR
Oat subgroup 1	Motif	Region	% Present	MEME #	p-value	Sequence
	1	163-176	1	12	2.92E-22	KVLILNYLQTAVSG
	2	211-229	1	9	4.90E-25	VEWMPIHTRACVGTIGYV
	3	250-252	1	6	1.39E-23	LQL
	4	255-260	1	5	1.14E-23	SAPFFA
	5	299-307	1	7	1.65E-23	EEGAKLSME
	6	346-348	1	3	2.32E-24	WFA
	7	369-375	1	10	4.42E-22	LIQVIFGAVDLPAKLVG
	8	415-422	1	13	1.34E-21	IPQDQSIV

**Table S2: Evolutionarily conserved Oat subclade and Oat subgroup 1 motifs.** Table describing the Oat Subclade-specific (blue) and OATS1-specific (Slc22a6, Slc22a8, and Slc22a20; red) conserved motifs that have been identified within the hOAT1 (hSLC22A6) sequence. This table lists the motif letter, prevalence, MEME#, p-value and amino acid sequence of hOAT1 associated with the particular motif letter.

Oat Subclade	Motif	Region	% Present	MEME #	p-value	Sequence
	A	43485	0.97	12	5.3E-18	MGFEELLEQVGGFGPFQLRN
	B	33-52	0.99	2	4.6E-17	LHFLLPIFLAAPAHRCALP
	C	69-88	0.99	5	7.5E-16	LPREPDGTLSSCLRFAYPQA
	D	107-126	0.99	1	5.3E-20	EPATVPCSQGWEYDHSEFSS
	E	133-152	0.99	3	1.1E-16	QWDLVCEQKGLNRAASTFFF
	F	153-172	1	6	8.6E-21	AGVLVGAVAFGYLSDRFGRR
	G	187-206	1	13	1.2E-11	LASAASVSYVMFAITRTLGT
	H	240-259	0.99	10	4.4E-17	WTGGVMMLLALVGYLIRDWRW
	I	271-285	0.95	11	1.3E-14	GILSLWWVPESARWL
	J	289-318	0.95	7	1.5E-14	GHVKEAHRYLLHCARLNGRP
	K	336-346	0.86	15	1.4E-12	DLFRTPLRLHI
	L	357-376	0.97	9	1.1E-17	VNFSYYGLSLDVSGLGLNVY
	M	384-403	0.97	16	1.3E-15	AVELPSKLLVYLSVRYAGRR
	N	431-445	0.86	14	9.3E-12	STVLAVMGKAFSEAA
	O	446-465	0.93	8	6.6E-21	FTTAYLFTSELYPTVLRQTG
	P	511-530	0.97	4	8.5E-20	LLPETRQAQLPETIQDVERK
Oat subgroup 2	Motif	Region	% Present	MEME #	p-value	Sequence
	1	127-131	1	4	4.61E-26	TIATE
	2	207-211	1	14	1.05E-23	SALAG
	3	214-233	1	9	3.18E-25	IIVMPLELEWLDVEHRTVAG
	4	286-288	1	2	2.51E-26	LTQ
	5	347-356	1	5	2.29E-26	SLCCVVVWFG
	6	377-383	1	10	4.05E-23	QTQLLFGAVELPSK
	7	466-481	0.93	15	2.44E-22	MGLTALVGRLGGSLAP

**Table S3: Evolutionarily conserved Oat subclade and Oat subgroup 2 motifs.** Table describing the Oat Subclade-specific (blue) and OATS2-specific (Slc22a7; red) conserved motifs that have been identified within the hOAT2 (hSLC22A7) sequence. This table lists the motif letter, prevalence, MEME#, p-value and amino acid sequence of hOAT2 associated with the particular motif letter.

Oat Subclade	Motif	Region	% Present	MEME #	p-value	Sequence
	A	1-20	0.97	12	6.05E-20	MAFSELLDLVGGLGRFQVLQ
	B	33-52	0.99	2	7.53E-19	TQSMLENFSAAVPSHRCWAP
	C	77-96	0.99	5	7.02E-23	IPPGPNQRPHQCRRFRQPQW
	D	110-129	0.99	1	4.49E-25	EADTEPCVDGWVYDRSIFTS
	E	134-153	0.99	3	3.36E-19	KWNLVCDSHALKPMAQSIYL
	F	154-173	1	6	2.27E-18	AGILVGAAACGPASDRFGRR
	G	188-207	1	13	1.50E-17	TAAAFAPAFPVYCLFRFLA
	H	241-260	0.99	10	1.64E-13	FSFGHGLTAAVA YGV RDWTL
	I	272-286	0.95	11	1.06E-17	CFLYSWWLAESARWL
	J	290-309	0.95	7	1.41E-16	GRLDWGLQELWRVAAINGKG
	K	339-349	0.86	15	1.34E-07	TLLRMPGLRFR
	L	360-379	0.97	9	2.17E-16	FGFTFFGLALDLQALGSNIF
	M	387-406	0.97	16	1.92E-17	VVDIPAKMGALLLSHLGRR
	N	434-448	0.86	14	2.87E-11	RSALAVLGLGGVGAA
	O	449-468	0.93	8	4.70E-19	FTCITYSSELFPTVLRMTA
	P	514-533	0.97	4	2.33E-20	LLPETQSLPLPDTIQDVQNQ
Oat subgroup 3	Motif	Region	% Present	MEME #	p-value	Sequence
	1	53-57	1	3	7.75E-25	LLDNS
	2	98-109	0.85	15	5.94E-19	LLDPNATATSWs
	3	130-132	1	1	4.79E-27	TIV
	4	174-182	1	8	3.61E-22	LVLTSYSLQ
	5	185-187	1	12	2.53E-21	VMG
	6	261-263	1	13	7.90E-20	LQL
	7	313-332	0.95	14	3.34E-20	DTLTPEVLLSAMREELSMGQ
	8	380-382	0.95	10	1.65E-21	LLQ
	9	417-433	0.9	16	2.86E-23	GLCILANTLVPHEMGAL

**Table S4: Evolutionarily conserved Oat subclade and Oat subgroup 3 motifs.** Table describing the Oat Subclade-specific (blue) and OATS3-specific (Slc22a11 and Slc22a12; red) conserved motifs that have been identified within the hURAT1 (hSLC22A12) sequence. This table lists the motif letter, prevalence, MEME#, p-value and amino acid sequence of hOAT3 associated with the particular motif letter.



Oat Subclade	Motif	Region	% Present	MEME #	p-value	Sequence
	A	1-20	0.97	12	2.41E-15	MDFDEILHHVGDGRFQICM
	B	33-52	0.99	2	7.07E-18	PHDVLENFTAAIPAHHCIN
	C	76-95	0.99	5	9.03E-21	IPMGPNQKPEQCRRFRYTQW
	D	109-128	0.99	1	1.34E-20	ELETEPCLDGWTYDHSVFTS
	E	133-152	0.99	3	1.64E-14	EWDLVCDFQSFKYAQAATSL
	F	153-172	1	6	1.13E-13	AGHLVSCPLSGIISDRFGRK
	G	187-206	1	13	3.93E-16	TYCAFAPNFSVYCVLRFLS
	H	240-259	0.99	10	7.52E-15	NSIGQGVLGGLAYVISDWHL
	I	271-285	0.95	11	3.33E-12	FFVLFCWVPESVRWL
	J	289-308	0.95	7	1.12E-17	GKTDQAWKELQRIASINGKK
	K	338-348	0.86	15	1.17E-07	DIFINPLIRKI
	L	359-378	0.97	9	4.39E-12	ELFSFVGLLLDVQLLGKNMF
	M	386-405	0.97	16	1.20E-12	AIDVPSKSLTYFTIRNVSR
	N	433-447	0.86	14	4.15E-10	RTIIFILGKGCFAAF
	O	513-532	0.97	4	7.45E-16	FLPETFNLPHTDIIKDMEKR
Oat subgroup 3	Motif	Region	% Present	MEME #	E-value	Sequence
	1	53-57	1	3	2.67E-16	LDNSR
	2	129-131	1	2	1.62E-24	TIV
	3	173-181	1	8	1.57E-16	PLLMYCSLA
	4	184-186	1	12	4.47E-18	AVG
	5	260-262	1	13	2.32E-17	LQL
	6	267-270	1	4	1.73E-18	PFFI
	7	312-331	1	14	8.23E-14	QNLTTEDLRSLKKDVNSTG
	8	379-381	1	11	3.17E-15	LTQ
	9	416-432	1	16	2.34E-12	GSCITITIFISEEMYVL
	10	450-469	1	10	5.19E-13	ISTTYINELSPVELRSTLNG

**Table S5: Evolutionarily conserved Oat subclade and Oat subgroup 3 motifs.** Table describing the Oat Subclade-specific (blue) and OATS3-specific (Slc22a11, Slc22a12, and Slc22a22; red) conserved motifs that have been identified within the mOat-pg (mSlc22a22) sequence. This table lists the motif letter, prevalence, MEME#, p-value and amino acid sequence of mOat-pg associated with the particular motif letter.

Oat Subclade	<b>Motif</b>	<b>Region</b>	<b>% Present</b>	<b>MEME #</b>	<b>p-value</b>	<b>Sequence</b>
	A	1-20	0.97	12	4.45E-17	MAFQDLLGHAGDLWRFQILQ
	B	33-52	0.99	2	1.24E-21	LHFMLENFTAFIPGHRWCWVH
	C	77-96	0.99	5	1.62E-24	IPLDSNMRPEKCRRFVHPQW
	D	110-129	0.99	1	5.65E-21	DADMEPCVDGWVYDRISFSS
	E	134-153	0.99	3	5.02E-20	EWDLVCDSQSLTSVAKFVFM
	F	154-173	1	6	1.32E-19	AGMMVGGILGGHLSDRFGRR
	G	188-207	1	13	3.15E-19	TCAALAPTFLIYCSLRFLSG
	H	241-260	0.99	10	3.35E-14	SGIAFMTLAGLAFAIRDWHI
	I	272-286	0.95	11	1.16E-13	IFLTSSWLLESARWL
	J	290-309	0.95	7	9.21E-19	NKPEEGLKELRKAHRSGMK
	K	361-380	0.97	9	9.18E-17	NFMAYFGLNLHVQHLGNNVF
	L	388-407	0.97	16	2.04E-13	AVILLANCVAPWALKYMNRR
	M	435-449	0.86	14	1.11E-09	REVLATLGLGASALA
	N	450-469	0.93	8	1.77E-13	NTLAFAHGNEVIPTIIRARA
	O	515-534	0.97	4	2.09E-19	LLPETRNKPLFDTIQDEKNE
Oat subgroup 4	<b>Motif</b>	<b>Region</b>	<b>% Present</b>	<b>MEME #</b>	<b>p-value</b>	<b>Sequence</b>
	1	53-57	1	3	6.06E-27	ILDND
	2	62-76	0.96	14	1.06E-16	NDTGALSQDALLRIS
	3	100-109	1	13	8.06E-17	HLNGTFPNTS
	4	130-133	1	1	7.76E-25	TIVT
	5	174-182	1	8	1.39E-23	FVLRWCYLQ
	6	261-268	1	10	9.11E-23	LQLVVSVP
	7	287-289	0.92	5	2.20E-25	IIN
	8	310-315	0.92	15	1.28E-16	NARDTL
	9	333-352	0.92	12	2.41E-18	KKKPSLCEMLHMPNICKRIS
	10	418-434	0.88	16	2.51E-21	AICLLAIFVPQEMQTL
	11	488-507	0.92	11	1.70E-23	MILSVYSPPLPWIIYGVFPF

**Table S6: Evolutionarily conserved Oat subclade and Oat subgroup 4 motifs.** Table describing the Oat Subclade-specific (blue) and OATS4-specific (Slc22a9, Slc22a10, Slc22a24, Slc22a25, Slc22a19, Slc22a26, Slc22a27, Slc22a28, Slc22a29, and Slc22a30; red) conserved motifs that have been identified within the hOAT7 (hSLC22A9) sequence. This table lists the motif letter, prevalence, MEME#, p-value and amino acid sequence of hOAT7 associated with the particular motif letter.

Oat Subclade	Motif	Region	% Present	MEME #	p-value	Sequence
	A	1-20	0.97	12	6.05E-20	MSFQELLNQVGS LGRFQILQ
	B	33-52	0.99	2	1.44E-21	PHIAMENFTAAIPNHRCWVP
	C	77-96	0.99	5	1.59E-23	IPLDSNLRPEKCRRAQPPQW
	D	110-129	0.99	1	8.62E-25	EPDTEPCVDGWVYDRSNFLS
	E	134-153	0.99	3	3.89E-20	EWDLVCE SQALNSVTKFSFM
	F	154-173	1	6	3.19E-18	IGLFIGGIICGHLSDRLGRK
	G	188-207	1	13	1.96E-20	TCVAFAPSFYICSLRFLAG
	H	241-260	0.99	10	5.73E-15	PNIGYMISAGLAFLFRIWHH
	I	272-286	0.95	11	1.06E-13	FLILTRWLS SARWL
	J	290-309	0.95	7	8.47E-24	NKPQKGLKELRKVAHMNGMK
	K	338-348	0.86	15	1.76E-11	DLFHTSILRKR
	L	359-378	0.97	9	1.08E-13	FTVSIFGLAVHLQHLSSNII
	M	386-405	0.97	16	2.05E-12	ALAILVSVIGPFVLNHIGRR
	N	448-467	0.93	8	1.10E-12	VGVSR LHTNELLPTTLRATA
	O	513-532	0.97	4	2.90E-19	LLPETKNQPLPDSTHDVGND
Oat subgroup 4	Motif	Region	% Present	MEME #	p-value	Sequence
	1	53-57	1	3	2.87E-27	ILDND
	2	58-76	1	8	1.88E-24	TASDNGSRILSQDDLRLIS
	3	130-133	1	6	7.81E-26	TIVT
	4	174-178	1	12	1.44E-23	FILTC
	5	181-187	1	7	2.59E-26	LQFAITE
	6	215-234	1	14	2.03E-24	VNSHLLMLEWTSPKFLTMM
	7	261-268	1	9	9.82E-25	LQLTMSVP
	8	287-289	1	5	2.26E-26	IVT
	9	310-316	1	10	1.41E-25	NSGDLTM
	10	331-337	1	11	2.08E-24	KTKPSLR
	11	406-412	1	15	2.00E-24	ITYLVLM
	12	489-508	1	13	2.12E-24	ATYYANMPWIFYGGFSIFNA

**Table S7: Evolutionarily conserved Oat subclade and Oat subgroup 4 motifs.** Table describing the Oat Subclade-specific (blue) and OATS4-specific (Slc22a19, Slc22a26, Slc22a27, Slc22a28, Slc22a29, and Slc22a30; red) conserved motifs that have been identified within the mouse Slc22a27 sequence. This table lists the motif letter, prevalence, MEME#, p-value and amino acid sequence of mSlc22a27 associated with the particular motif letter.