

Supplemental S1: List of abbreviations.

- ACMG : American College of Medical Genetics
- AMP : American College of Pathologist
- CADD : Combined Annotation Dependant Depletion
- Cer : ceramides
- dhCer : dihydroceramides
- dSA : deoxysphinganine
- HSAN1 : Hereditary Sensory and Autonomic Neuropathy type 1
- LR : Likelihood Ratios
- ORMDL3 : ORMDL sphingolipid biosynthesis regulator 3
- PLP : pyridoxal 5'-phosphate
- REVEL : Rare Exome Variant Ensemble Learner
- SPT : Serine Palmitoyl Transferase
- SPTLC1 : serine palmitoyltransferase long chain base subunit 1
- SPTLC2 : serine palmitoyltransferase long chain base subunit 2
- ssSPTa/b : serine palmitoyltransferase small subunit A/B
- VUS : Variants of Unknown Significance

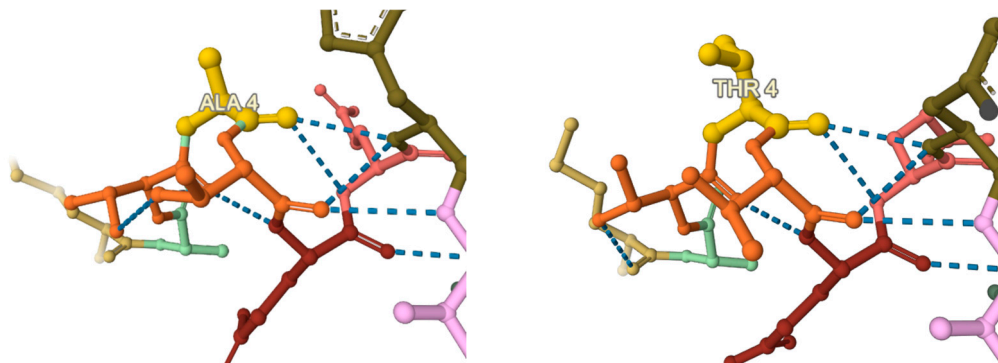
Supplemental S2: Genes list of the CMT Panel.

NM	Gene	NM	Gene	NM	Gene
NM_001605	AARS	NM_000166	GJB1	NM_002677	PMP2
NM_015600	ABHD12	NM_021629	GNB4	NM_000304	PMP22
NM_015270	ADCY6	NM_000183	HADHB	NM_007254	PNKP
NM_014629	ARHGEF10	NM_002109	HARS	NM_021619	PRDM12
NM_015915	ATL1	NM_005340	HINT1	NM_002764	PRPS1
NM_015459	ATL3	NM_000188	HK1	NM_020956	PRX
NM_000052	ATP7A	NM_002148	HOXD10	NM_004637	RAB7A
NM_004281	BAG3	NM_001540	HSPB1	NM_001164730	REEP1
NM_001003800	BICD2	NM_006308	HSPB3	NM_001034850	RETREG1
NM_032667	BSCL2	NM_014365	HSPB8	NM_002972	SBF1
NM_152269	C12orf65	NM_002180	IGHMBP2	NM_030962	SBF2
NM_012073	CCT5	NM_001031714	INF2	NM_014139	SCN11A
NM_213720	CHCHD10	NM_005548	KARS	NM_002977	SCN9A
NM_003632	CNTNAP1	NM_001244008	KIF1A	NM_001113491	SEPT9
NM_004373	COX6A1	NM_015074	KIF1B	NM_015046	SETX
NM_004715	CTDP1	NM_004984	KIF5A	NM_024577	SH3TC2
NM_018122	DARS2	NM_004862	LITAF	NM_005866	SIGMAR1
NM_015726	DCAF8	NM_170707	LMNA	NM_133647	SLC12A6
NM_004082	DCTN1	NM_138361	LRSAM1	NM_021815	SLC5A7
NM_006400	DCTN2	NM_004990	MARS	NM_006941	SOX10
NM_032564	DGAT2	NM_030973	MED25	NM_025137	SPG11
NM_018706	DHTKD1	NM_014874	MFN2	NM_006415	SPTLC1
NM_001039550	DNAJB2	NM_022765	MICAL1	NM_004863	SPTLC2
NM_004945	DNM2	NM_000902	MME	NM_003172	SURF1
NM_001130823	DNMT1	NM_014941	MORC2	NM_177402	SYT2
NM_183380	DST	NM_002437	MPV17	NM_006070	TFG
NM_001376	DYNC1H1	NM_000530	MPZ	NM_015271	TRIM2
NM_000399	EGR2	NM_016156	MTMR2	NM_021625	TRPV4
NM_003640	ELP1	NM_001077186	MYH14	NM_000371	TTR
NM_006329	FBLN5	NM_006096	NDRG1	NM_007126	VCP
NM_030793	FBXO38	NM_006158	NEFL	NM_003384	VRK1
NM_139241	FGD4	NM_002506	NGF	NM_018979	WNK1
NM_014845	FIG4	NM_001007792	NTRK1	NM_003680	YARS
NM_002047	GARS	NM_001142386	PDK3		
NM_018972	GDAP1	NM_020631	PLEKHG5		

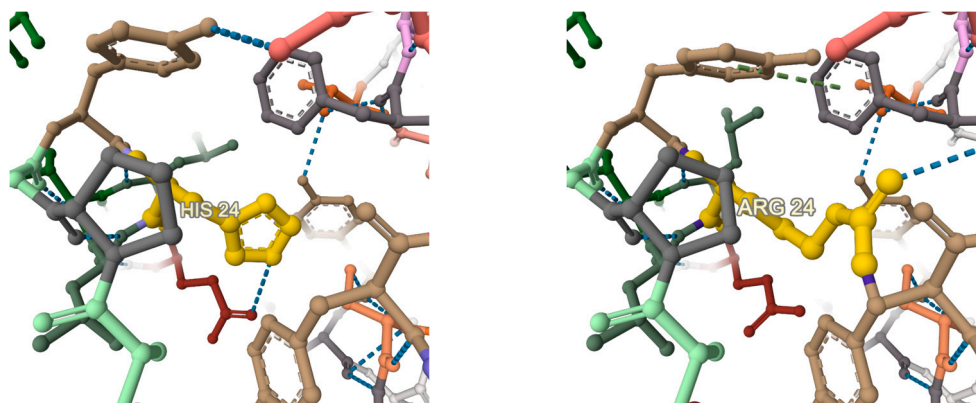
Supplemental S3: Miztli predicted impact of *SPTLC1* p.Ala4Thr, p.His24Arg and p.Arg151Cys variants on structure and interactions within the SPT enzymatic complex.

A : Predicted impact of *SPTLC1* p.Ala4Thr variant. B : Impact of *SPTLC1* p.His24Arg variant. C : Impact of *SPTLC1* p.Arg151Cys variant.

A

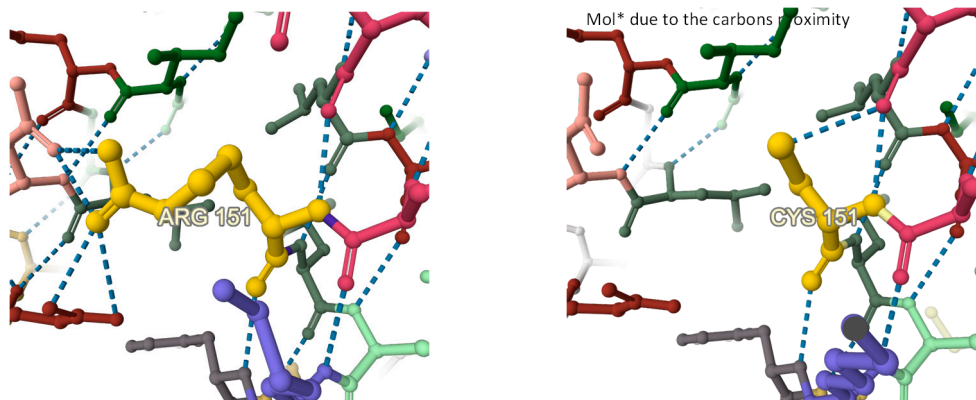


B



the apparent covalent bond is an artefact created by Mol* due to the carbons proximity

C



----- Hydrogen bond

Supplemental S4 : Quantification of ceramides and dihydroceramides species in plasma by tandem mass spectrometry. High levels of Cer of dhCer are shown in red and low levels in light blue.

		Individual ID					
	Controls	P1 p.A4T	P2 p.H24R	P3 p.R151C	P4 p.S331F	P5 p.Q333R	P6 p.A339T
Ceramides (μmol/L)							
Cer (d18:1/16:0)	1.66 ±0.42	1,24	1,91	1,16	1,51	1,87	3,16
Cer (d18:1/18:0)	0.55 ±0.08	0,53	0,35	0,60	0,24	0,62	0,61
Cer (d18:1/20:0)	0.22 ±0.12	0,42	0,25	0,46	0,28	0,49	0,11
Cer (d18:1/22:0)	1.36 ±0.10	1,17	1,85	1,62	1,29	1,44	0,77
Cer (d18:1/24:0)	3.72±1.26	3,21	3,76	4,82	2,98	4,26	2,54
Total Cer	7.51±1.73	6,57	8,12	8,66	6,30	8,68	7,19
Dihydroceramides (μmol/L)							
dhCer(d18:0/16:0)	0.19 ±0.05	0,27	0,29	0,14	0,16	0,26	0,11
dhCer (d18:0/18:0)	0.07 ±0.02	0,11	0,09	0,14	0,14	1,10	0,88
dhCer (d18:0/20:0)	0.17 ±0.07	0,15	0,11	0,35	0,22	1,54	1,22
dhCer (d18:0/22:0)	0.27 ±0.07	0,20	0,19	0,36	0,86	1,98	1,65
dhCer (d18:0/24:0)	0.90 ±0.23	0,95	0,93	1,11	1,22	2,54	2,03
Total dhCer	1.60±0.50	1,67	1,61	2,10	2,60	7,42	5,89