Supporting Information

Characterization of Differential Dynamics, Specificity, and Allostery of Lipoxygenase Family Members

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Supplementary Figures

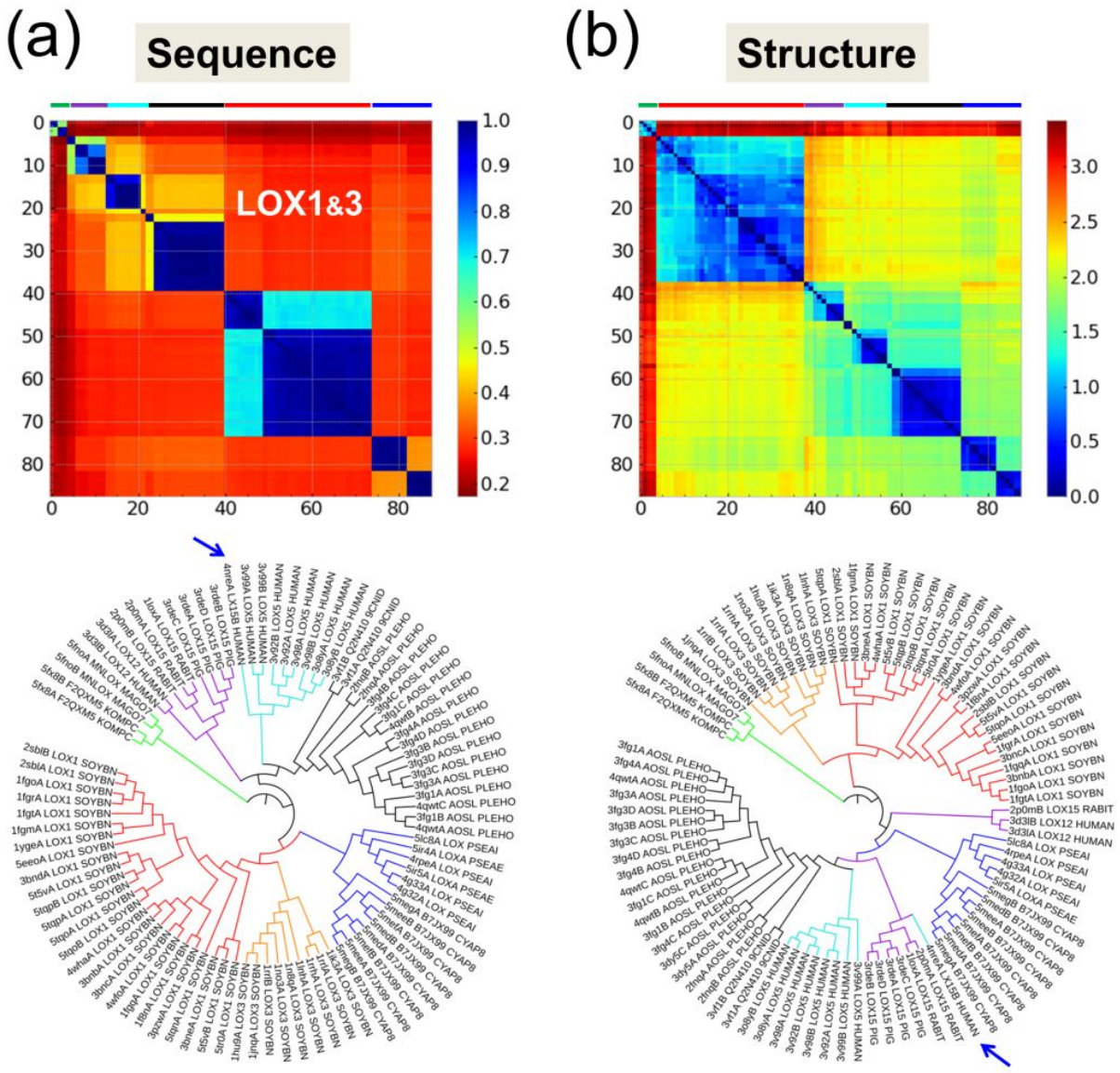

Figure S1: Matrices and dendrograms showing the sequence (a) and structural (b) differences between the 88 LOXs in the PDB. (a) The pairwise fractional sequence identity (SID) is shown in the matrix (*top*) and the Hamming distance (1 – SID) is used for the sequence dendrogram (*bottom*). (b) The pairwise root mean-square deviation (RMSD) in Å is shown in the matrix and used for the dendrogram. Note that human LX15B (also known as 15LO2) is clustered together with human LOX5 in the sequence-based dendrogram (*left*, shown by the arrow), while it is closer to rabbit and pig LOX15 (or 15LO1) in terms of its structure (*arrow* in *right* dendrogram).

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sp|P18054|LOX12_HUMAN/1-663     1 MGRYRIRVA----TGAWLFSGSYNRVQLWLVGTRGEAELE----LQLRPARGEEEEFDHDVAEDLGLLQFVR 64
sp|P16050|LOX15_HUMAN/1-662     1 MGLYRIRVS----TGASLYAGSNNQVQLWLVGQHGEAALG----KRLWPARGKETELKVEVPEYLGPLLFVK 64
sp|O15296|LX15B_HUMAN/1-676     1 MAEFRVRVS----TGEAFGAGTWDKVSVSIVGTRGESPPLPLDNLGKEFTAGAEEDFQVTLPEDVGRVLLLR 68
sp|Q8RNT4|LOX_PSEAI/1-685       1 MKRRSVLLSGVALSGTALANDSIFFSPLKYLGAEQQRSIDASRSLLDNLIPPSLPQYDN-LAGKLARRAVLT 71

sp|P18054|LOX12_HUMAN/1-663    65 LRKH-------HWLVDDAWFCDRITVQGPGACAEVAFPCYRWVQGEDILSLPEGTARLPGDNALDMFGKHRE 129
sp|P16050|LOX15_HUMAN/1-662    65 LRKR-------HLLKDDAWFCNWISVQGPGAGDEVRFPCYRWVEGNGVLSLPEGTGRTVGEDPQGLFQKHRE 129
sp|O15296|LX15B_HUMAN/1-676    69 VHKAPPVLPLLGPLAPDAWFCRWFQLTPP-RGGHLLFPCYQWLEGAGTLVLQEGTAKVSWADHHPVLQQQRQ 139
sp|Q8RNT4|LOX_PSEAI/1-685      72 SKKL--------VYVWTENFANVKGVPMARSVPLGELPNVDWLLKTAGVIVELIVNFVASLPASAAAQFERI 135

sp|P18054|LOX12_HUMAN/1-663   130 KELKDRQQIYCWATWKEGLPLTIAADRKDDLPPNMRFHEEK-RLDFEWTLKAGALEMALKRVYTLLSSWNCL 200
sp|P16050|LOX15_HUMAN/1-662   130 EELEERRKLYRWGNWKDGLILNMAGAKLYDLPVDERFLEDK-RVDFEVSLAKGLADLAIKDSLNVLTCWKDL 200
sp|O15296|LX15B_HUMAN/1-676   140 EELQARQEMYQWKAYNPGWPHCLDEKTVEDLELNIKYSTAK-NANFYLQAGSAFAEMKIKGLLDRKGLWRSL 210
sp|Q8RNT4|LOX_PSEAI/1-685     136 AAGLSG-DLEAARQVHEALLEEAKNDPAAAGSLLLRFTELQTRVIALLTRVGLLVDDILKSASNLVTQGGQG 206

sp|P18054|LOX12_HUMAN/1-663   201 EDFDQIFWGQKSALAEKVRQCWQDDELFSYQFLNGANPMLLRRSTSLPSRLVLPSGMEELQA----QLEKEL 268
sp|P16050|LOX15_HUMAN/1-662   201 DDFNRIFWCGQSKLAERVRDSWKEDALFGYQFLNGANPVVLRRSAHLPARLVFPPGMEELQA----QLEKEL 268
sp|O15296|LX15B_HUMAN/1-676   211 NEMKRIFNFRRTPAAEHAFEHWQEDAFFASQFLNGLNPVLIRRCHYLPKNFPVTDAMVASVLGPGTSLQAEL 282
sp|Q8RNT4|LOX_PSEAI/1-685     207 DGLNRFRAVFGTLRLPEVADSFRDDEAFAYWRVAGPNPLLIRRVDALPANFPLGEEQFRRVMGADDSLLEAA 278

sp|P18054|LOX12_HUMAN/1-663   269 QNGSLFEADFILLDGIPAN----VIRGEKQYLAAPLVMLKMEP-NGKLQPMVIGIQPPNPSSPTPTLFLPSD 335
sp|P16050|LOX15_HUMAN/1-662   269 EGGTLFEADFSLLDGIKAN----VILCSQQHLAAPLVMLKLQP-DGKLLPMVIGLQLPRTGSPPPPLFLPTD 335
sp|O15296|LX15B_HUMAN/1-676   283 EKGSLFLVDHGILSGIQTN----VINGKPQFSAAPMTLLYQSPGCGPLLPLAIGLS--QTPGPNSPIFLPTD 348
sp|Q8RNT4|LOX_PSEAI/1-685     279 ASRRLYLLDYAELGKLAPSGAVDKLLTGTGFAYAPIALFALGKDRAGLLPVAIQCG--QDPATHPMFVRPAE 348

sp|P18054|LOX12_HUMAN/1-663   336 PP----LAWLLAKSWVRNSDFQLHEIQYHLLNTHLVAEVIAVATMRCLPGLHPIFKFLIPHIRYTMEINTRA 403
sp|P16050|LOX15_HUMAN/1-662   336 PP----MAWLLAKCWVRSSDFQLHELQSHLLRGHLMAEVIVVATMRCLPSIHPIFKLIIPHLRYTLEINVRA 403
sp|O15296|LX15B_HUMAN/1-676   349 DK----WDWLLAKTWVRNAEFSFHEALTHLLHSHLLPEVFTLATLRQLPHCHPLFKLLIPHTRYTLHINTLA 416
sp|Q8RNT4|LOX_PSEAI/1-685     349 SESDLYWGWQMAKTVVQVAEENYHEMFVHLAQTHLVSEAFCLATQRTLAPSHPLHVLLAPHFEGTLFINEGA 420

sp|P18054|LOX12_HUMAN/1-663   404 RTQLISDGGIFDKAVSTGGGGHVQLLRRAAAQLTYCSLCPPDDLADRGLLG---LPGALYAHDALRLWEIIA 472
sp|P16050|LOX15_HUMAN/1-662   404 RTGLVSDMGIFDQIMSTGGGGHVQLLKQAGAFLTYSSFCPPDDLADRGLLG---VKSSFYAQDALRLWEIIY 472
sp|O15296|LX15B_HUMAN/1-676   417 RELLIVPGQVVDRSTGIGIEGFSELIQRNMKQLNYSLLCLPEDIRTRGVED---IPGYYYRDDGMQIWGAVE 485
sp|Q8RNT4|LOX_PSEAI/1-685     421 ARILLPSAGFIDVMFAAPIQDTQATAGGNRLGFDFYRGMLPESLKARNVDDPAALPDYPYRDDGLLVWNAIR 492

sp|P18054|LOX12_HUMAN/1-663   473 RYVEGIVHLFYQRDDIVKGDPELQAWCREITEVGLCQAQDRGFPVSFQSQSQLCHFLTMCVFTCTAQHAAIN 544
sp|P16050|LOX15_HUMAN/1-662   473 RYVEGIVSLHYKTDVAVKDDPELQTWCREITEIGLQGAQDRGFPVSLQARDQVCHFVTMCIFTCTGQHASVH 544
sp|O15296|LX15B_HUMAN/1-676   486 RFVSEIIGIYYPSDESVQDDRELQAWVREIFSKGFLNQESSGIPSSLETREALVQYVTMVIFTCSAKHAAVS 557
sp|Q8RNT4|LOX_PSEAI/1-685     493 QWAADYVAVYYASDGDVTADVELAAWVGEVIGSGKVAG-----FRPITGRSQLVEVLTMVIFTASAQHAAVN 559

sp|P18054|LOX12_HUMAN/1-663   545 QGQLDWYAWVPNAPCTMRMPPPTTKEDVTMATVMGSLPDVRQACLQMAISWHLS----RRQPDMVPLGHHKE 612
sp|P16050|LOX15_HUMAN/1-662   545 LGQLDWYSWVPNAPCTMRLPPPTTK-DATLETVMATLPNFHQASLQMSITWQLG----RRQPVMVAVGQHEE 611
sp|O15296|LX15B_HUMAN/1-676   558 AGQFDSCAWMPNLPPSMQLPPPTSKGLATCEGFIATLPPVNATCDVILALWLLS----KEPGDQRPLGTYPD 625
sp|Q8RNT4|LOX_PSEAI/1-685     560 FPQPSMMTYAPAICAMSAAPAPDSPSGKSEADWLKMMPPTLVALEKVNIYHLLGSVYHGRLGDYRQTGFPYA 631

sp|P18054|LOX12_HUMAN/1-663   613 KYFSGPKPKAV---LNQFRTDLEKLEKEITARNEQLDWPYEYLKPSCIENSVTI                   663
sp|P16050|LOX15_HUMAN/1-662   612 EYFSGPEPKAV---LKKFREELAALDKEIEIRNAKLDMPYEYLRPSVVENSVAI                   662
sp|O15296|LX15B_HUMAN/1-676   626 EHFTEEAPRRS---IATFQSRLAQISRGIQERNQGLVLPYTYLDPPLIENSVSI                   676
sp|Q8RNT4|LOX_PSEAI/1-685     632 PVFSDRRVTASGGPLERFQARLKEVEATIRTRNQARRKPYEYLLPSRIPASTNI                   685
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Figure S2: Sequence alignment of human LOX12, LOX15 (15LO1), LX15B (15LO2), and *Pseudomonas aeruginosa* LOX (also known as LOXA or pLoxA). Residues conserved in at least three of the four sequences are colored. Hydrophobic residues are *blue*, polar residues are *green*, positively charged residues are *red*, negatively charged residues are *purple*, glycines are *orange*, and prolines are *yellow*. We used the Jalview[1] program for visualization.

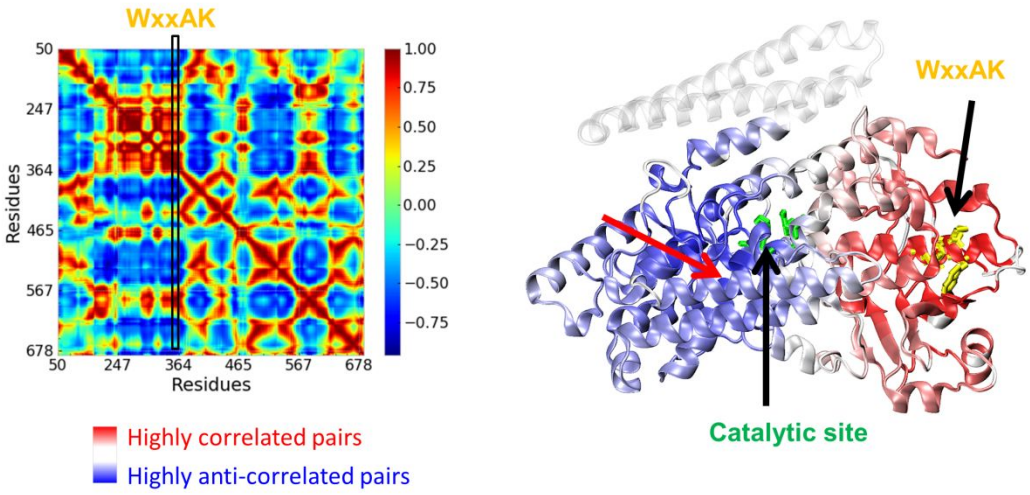

Figure S3: Additional details about generic cross-correlations. The left panel is a reproduction of Figure 3a with the column corresponding to the WxxAK motif highlighted. The right panel shows the values along this row in the context of the 3D structure. Residues in *dark red* show highly correlated (same direction) motions with this motif while regions in *dark blue* show highly anti-correlated (opposite direction) motions. The *red arrow* indicates L383, which corresponds to L367 in 12/15 Lipoxygenase that has been proposed to be near an oxygen access pathway[2].

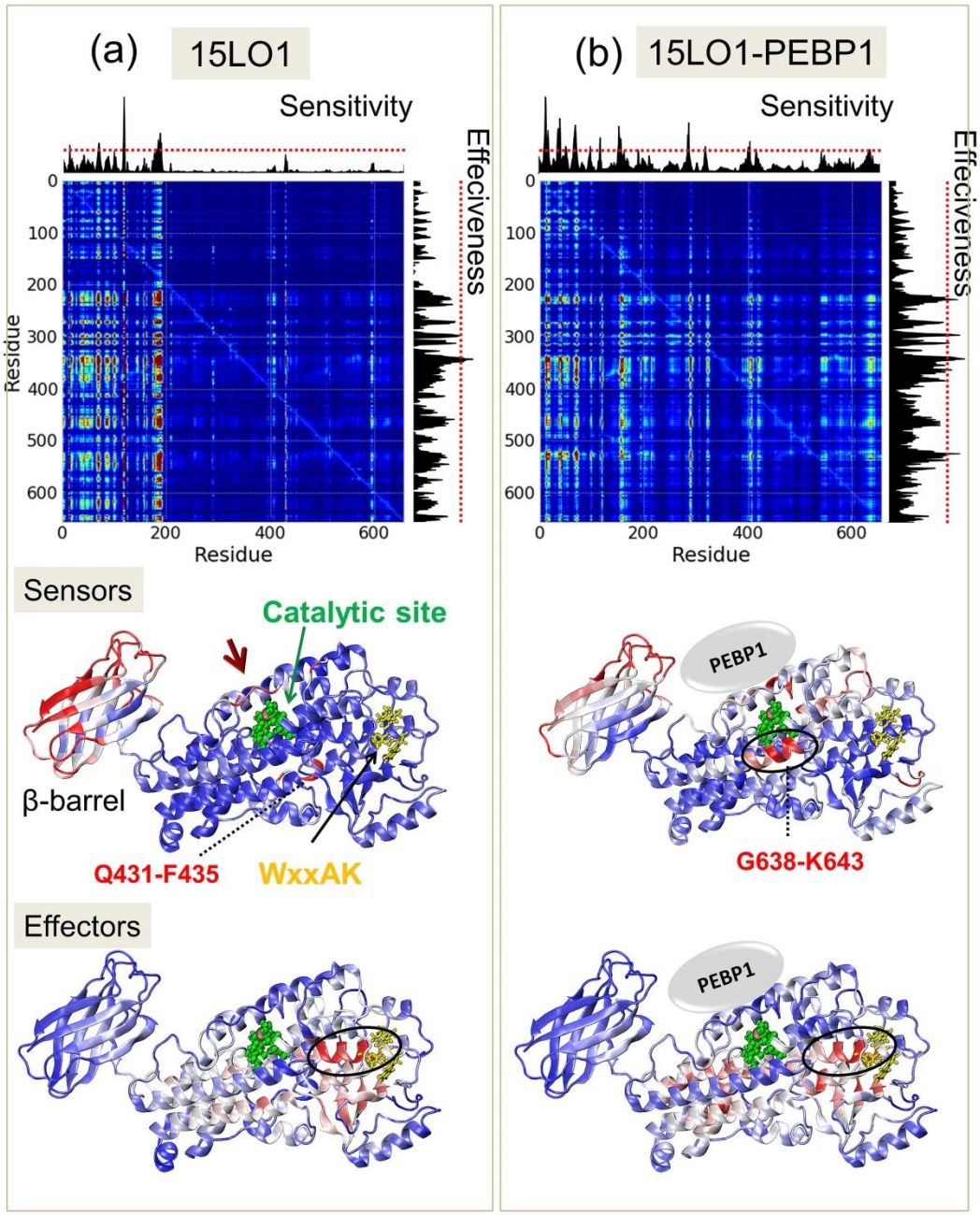

Figure S4: PRS results for 15LO1 alone (a) and in complex with PEBP1 (b). The top panels show the PRS matrices with the bars along the *right* and *top* axes representing the effectiveness and sensitivity, respectively, as in Figure 4. The middle panels show structures colored by sensitivity with the sensors in *red* and the bottom panels are colored by effectiveness with the effectors in *red*. PEBP1 is shown schematically in panel **b** for clarity. For a detailed structure of PEBP1-15LO1 complex see previous work[3].

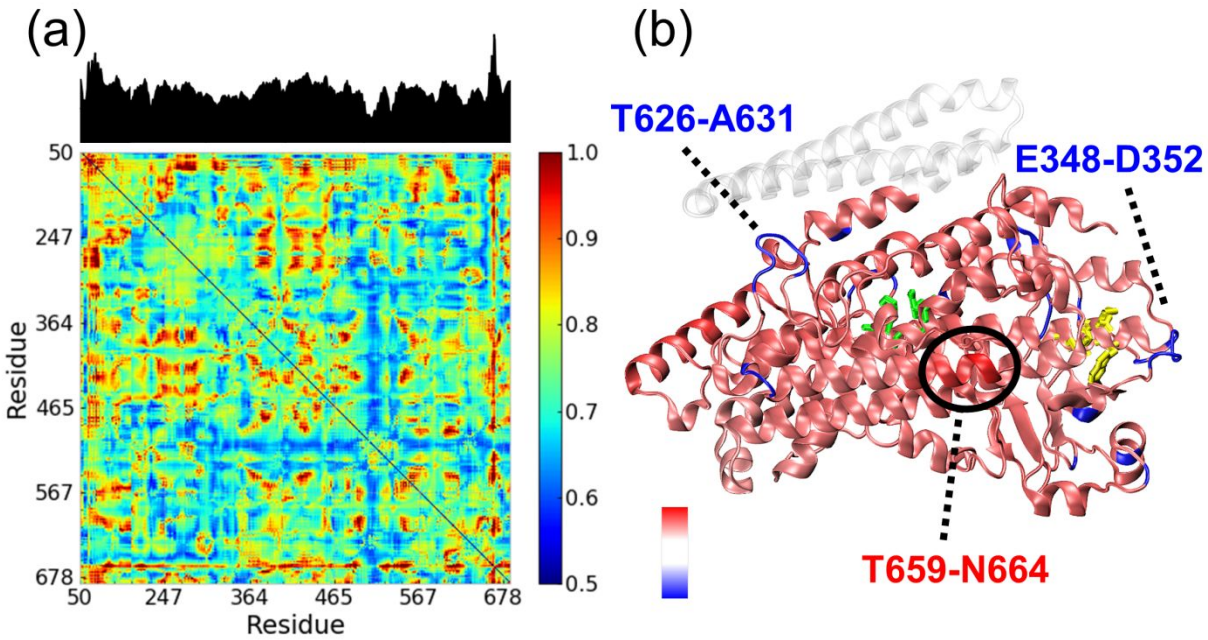

Figure S5: Generic mechanical stiffness properties from 88 LOX structures. (**a**) The mechanical stiffness (MechStiff) matrix shows the effective spring constant associated with uniaxial tension applied to each pair of residues (along the two axes). The entries are colored from *red* (stiffest) to *blue* (most flexible). The *black bars* at the top show the averages over each column, thus providing a residue-based metric for the resistance to deformation. (**b**) Ribbon diagram of LOX core domain (*salmon*). Regions distinguished by the strongest and weakest resistances to deformation are highlighted in *red* and *blue*, respectively, and indicated by the same color labels. Calculations were performed using the MechStiff module in ProDy[4, 5]. The semi-transparent portion displays the helical lid that is not present in mammalian LOXs.

Supplementary Table

Table S1: The 88 Structurally Resolved Lipoxygenases Used in This Study.

	PDB code [a]	UniProtID [b]	Name [c]	# of aligned amino acids [d]	SID [%] [e]	RMSD [Å] [f]
1	5medA	B7JX99_CYAP8	Arachidonate 15-LOX	515	37.3	1.57
2	5megA	B7JX99_CYAP8	Arachidonate 15-LOX	515	36.5	1.53
3	5mefA	B7JX99_CYAP8	Arachidonate 15-LOX	514	36.9	1.59
4	5meeB	B7JX99_CYAP8	Arachidonate 15-LOX	514	36.9	1.59
5	5medB	B7JX99_CYAP8	Arachidonate 15-LOX	513	37.1	1.57
6	5meeA	B7JX99_CYAP8	Arachidonate 15-LOX	515	37.1	1.60
7	5mefB	B7JX99_CYAP8	Arachidonate 15-LOX	515	37.1	1.61
8	5megB	B7JX99_CYAP8	Arachidonate 15-LOX	515	37.5	1.62
9	5ir4A	LOXA_PSEAE	Arachidonate 15-LOX	518	99.6	0.49
10	5lc8A	LOX_PSEAI	Linoleate 9/13-LOX	519	99.6	0.50
11	4g33A	LOX_PSEAI	Linoleate 9/13-LOX	520	100.0	0.44
12	4rpeA	LOX_PSEAI	Linoleate 9/13-LOX	519	99.8	0.43
13	4g32A	LOX_PSEAI	Linoleate 9/13-LOX	520	100.0	0.11
14	**5ir5A**	**LOXA_PSEAE**	**Arachidonate 15-LOX**	**520**	**100.0**	**0.00**
15	3fg4A	AOSL_PLEHO	Allene oxide synthase-LOX	513	30.4	1.84
16	3fg1A	AOSL_PLEHO	Allene oxide synthase-LOX	516	30.8	1.82
17	4qwtA	AOSL_PLEHO	Allene oxide synthase-LOX	517	30.8	1.80
18	4qwtC	AOSL_PLEHO	Allene oxide synthase-LOX	517	30.8	1.78
19	3fg1B	AOSL_PLEHO	Allene oxide synthase-LOX	517	30.8	1.82
20	3fg3C	AOSL_PLEHO	Allene oxide synthase-LOX	517	30.8	1.86
21	3fg3A	AOSL_PLEHO	Allene oxide synthase-LOX	517	30.8	1.87
22	3fg3B	AOSL_PLEHO	Allene oxide synthase-LOX	516	30.8	1.82
23	3fg3D	AOSL_PLEHO	Allene oxide synthase-LOX	517	30.8	1.84
24	3fg1C	AOSL_PLEHO	Allene oxide synthase-LOX	518	30.8	1.83

25	3fg4B	AOSL_PLEHO	Allene oxide synthase-LOX	509	30.2	1.80
26	3fg4C	AOSL_PLEHO	Allene oxide synthase-LOX	514	30.4	1.82
27	3fg4D	AOSL_PLEHO	Allene oxide synthase-LOX	514	30.6	1.85
28	4qwtB	AOSL_PLEHO	Allene oxide synthase-LOX	518	30.8	1.79
29	2fnqB	AOSL_PLEHO	Allene oxide synthase-LOX	514	30.6	1.86
30	2fnqA	AOSL_PLEHO	Allene oxide synthase-LOX	514	30.6	1.86
31	4nreA	LX15B_HUMAN	Arachidonate 15-LOX B	515	30.2	1.85
32	3vf1B	Q2N410_9CNID	11R-LOX	510	27.9	2.11
33	3vf1A	Q2N410_9CNID	11R-LOX	510	27.9	2.11
34	2p0mA	LOX15_RABIT	Arachidonate 15-LOX	505	24.8	2.09
35	1loxA	LOX15_RABIT	Arachidonate 15-LOX	500	24.6	2.12
36	2p0mB	LOX15_RABIT	Arachidonate 15-LOX	496	24.8	2.10
37	3rdeC	LOX15_PIG	Arachidonate 15-LOX	508	25.4	1.88
38	3rdeA	LOX15_PIG	Arachidonate 15-LOX	508	25.4	1.91
39	3rdeD	LOX15_PIG	Arachidonate 15-LOX	509	25.4	1.89
40	3rdeB	LOX15_PIG	Arachidonate 15-LOX	509	25.4	1.89
41	3d3lB	LOX12_HUMAN	Arachidonate 12-LOX, 12S-type	414	22.9	2.29
42	3d3lA	LOX12_HUMAN	Arachidonate 12-LOX, 12S-type	412	22.7	2.13
43	3v92B	LOX5_HUMAN	Arachidonate 5-LOX	515	30.0	2.10
44	3v98A	LOX5_HUMAN	Arachidonate 5-LOX	513	30.0	2.00
45	3v92A	LOX5_HUMAN	Arachidonate 5-LOX	513	30.0	1.97
46	3o8yA	LOX5_HUMAN	Arachidonate 5-LOX	514	30.0	2.02
47	3o8yB	LOX5_HUMAN	Arachidonate 5-LOX	514	30.0	2.02
48	3v98B	LOX5_HUMAN	Arachidonate 5-LOX	514	30.0	1.99

49	3v99A	LOX5_HUMAN	Arachidonate 5-LOX	485	28.8	1.98
50	3v99B	LOX5_HUMAN	Arachidonate 5-LOX	490	29.0	1.78
51	1jnqA	LOX3_SOYBN	Seed linoleate 9S-LOX-3	508	27.7	2.30
52	1hu9A	LOX3_SOYBN	Seed linoleate 9S-LOX-3	508	27.7	2.29
53	1no3A	LOX3_SOYBN	Seed linoleate 9S-LOX-3	506	27.9	2.24
54	1lnhA	LOX3_SOYBN	Seed linoleate 9S-LOX-3	505	27.5	2.28
55	1n8qA	LOX3_SOYBN	Seed linoleate 9S-LOX-3	508	27.9	2.26
56	1rrhA	LOX3_SOYBN	Seed linoleate 9S-LOX-3	507	28.3	2.20
57	1ik3A	LOX3_SOYBN	Seed linoleate 9S-LOX-3	504	28.1	2.20
58	1rrlA	LOX3_SOYBN	Seed linoleate 9S-LOX-3	508	28.5	2.30
59	1fgrA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	505	26.9	2.13
60	1fgoA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	505	27.1	2.13
61	1fgmA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	504	26.9	2.10
62	1ygeA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	507	27.1	2.24
63	2sblA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	505	27.3	2.12
64	2sblB	LOX1_SOYBN	Seed linoleate 13S-LOX-1	506	27.3	2.14
65	3bnbA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	506	27.1	2.16
66	4whaA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	506	26.9	2.16
67	3bncA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	505	27.1	2.15
68	3pzwA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	507	26.9	2.27
69	1f8nA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	508	26.9	2.28
70	5t5vA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	507	27.1	2.17
71	3bndA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	508	26.9	2.20
72	1fgtA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	504	26.9	2.07

73	5eeoA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	504	27.3	2.12
74	5tr0A	LOX1_SOYBN	Seed linoleate 13S-LOX-1	495	26.7	2.11
75	1fgqA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	505	27.5	2.11
76	4wfoA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	505	27.3	2.10
77	3bneA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	503	27.9	2.14
78	5t5vB	LOX1_SOYBN	Seed linoleate 13S-LOX-1	501	28.3	2.07
79	5tqpB	LOX1_SOYBN	Seed linoleate 13S-LOX-1	507	26.5	2.25
80	5tqoB	LOX1_SOYBN	Seed linoleate 13S-LOX-1	505	26.5	2.14
81	5tqoA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	504	26.3	2.13
82	5tqpA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	508	26.7	2.29
83	5tqnA	LOX1_SOYBN	Seed linoleate 13S-LOX-1	504	27.1	2.10
84	1rrlB	LOX3_SOYBN	Seed linoleate 9S-LOX-3	510	27.7	2.33
85	5fx8A	F2QXM5_KOMPC	Manganese LOX	500	21.0	3.34
86	5fnoB	MNLOX_MAGO7	Manganese LOX	503	21.2	3.22
87	5fnoA	MNLOX_MAGO7	Manganese LOX	503	21.5	3.20
88	5fx8B	F2QXM5_KOMPC	Manganese LOX	494	20.8	3.21

[a] The first four characters are the identifier for the structure in the Protein Data Bank[6] (PDB) and the fifth is the chain identifier.
[b] corresponding record in UniProt[7]. The part before the underscore is an identifier that is often an abbreviation for the protein and the part after the underscore corresponds to the organism from which it is derived.
[c] Long names from UniProt.
[d] number of aligned amino acid residues that form the conserved core whose structure and dynamics are compared using PCA and GNM analysis.
[e] Percent sequence identity (SID) of core residues with respect to the pLOXA reference structure in row 14 (bold).
[f] Root-mean-square deviation (RMSD) between core structure and the pLOXA reference structure in row 14 (bold).

Table S2. Key residues dominating the dynamics and allostery of LOX family members[(a)]

pLoxA	15LO1	15LO2	LOX12
H382	H365	H378	H365
H377	H360	H373	H360
H555	H540	H553	H540
N559	H554	S557	N554
I685	I662	I676	I663
W_{357}xxAK_{361}	W340-K344	W353-K357	W340-K344
F228-R248	W222-R242	W232-R252	W222-R242
P242-N243	A236-N237	L246-N247	A236-N237
F_{228}xxD_{231}	W222-D225	W232-D235	W222-D225
P676-I685	P653-I662	P667-I676	P654-I663
I247-F264	L241-E258	I251-V268	L241-E258
N102-I113	C96-S107	C106-V117	C96-S107
L611	Q595	L609	H596
A_{666}RR_{668}	K643-D645	G657-V659	Q644-D646
A240-N243	N234-N237	N244-N247	N234-N237
P561	G546	G559	G546
T362	C345	T358	S645
Q365	R348	R361	R348
E368	D351	E364	D351
E369	F352	F365	F352
E261	P225	D265	S225
E262	G226	A266	G226
D271	-	G275	-
D272	-	T276	-
Q56-V69	E48-F62	D52-L66	E48-F62
E261-E276	P225-K266	D265-A280	S225-K266
D58-G62	K50-E55	Q54-E59	D50-E55
Q365-E369	R348-F252	R361-F365	R348-F352
M565-M566	W550-Y551	S563-C564	W550-Y551
F234-R238	F228-F232	F228-F242	F228-F232
K587	A571	A585	V572
I331	I316	I331	I316
P328	P313	P328	P313
H372	H355	H368	H355
I660	I637	I651	I638
R663	R640	R654	R641
N664	N641	N655	N642
D483	D463	D476	D463

[(a)] *PLoxA residues highlighted in Figs 2-5 and their counterparts in human LOXs 15LO1, 15LO2 and LOX12. Those fully conserved are highlighted in yellow.*

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