Supplemental Data

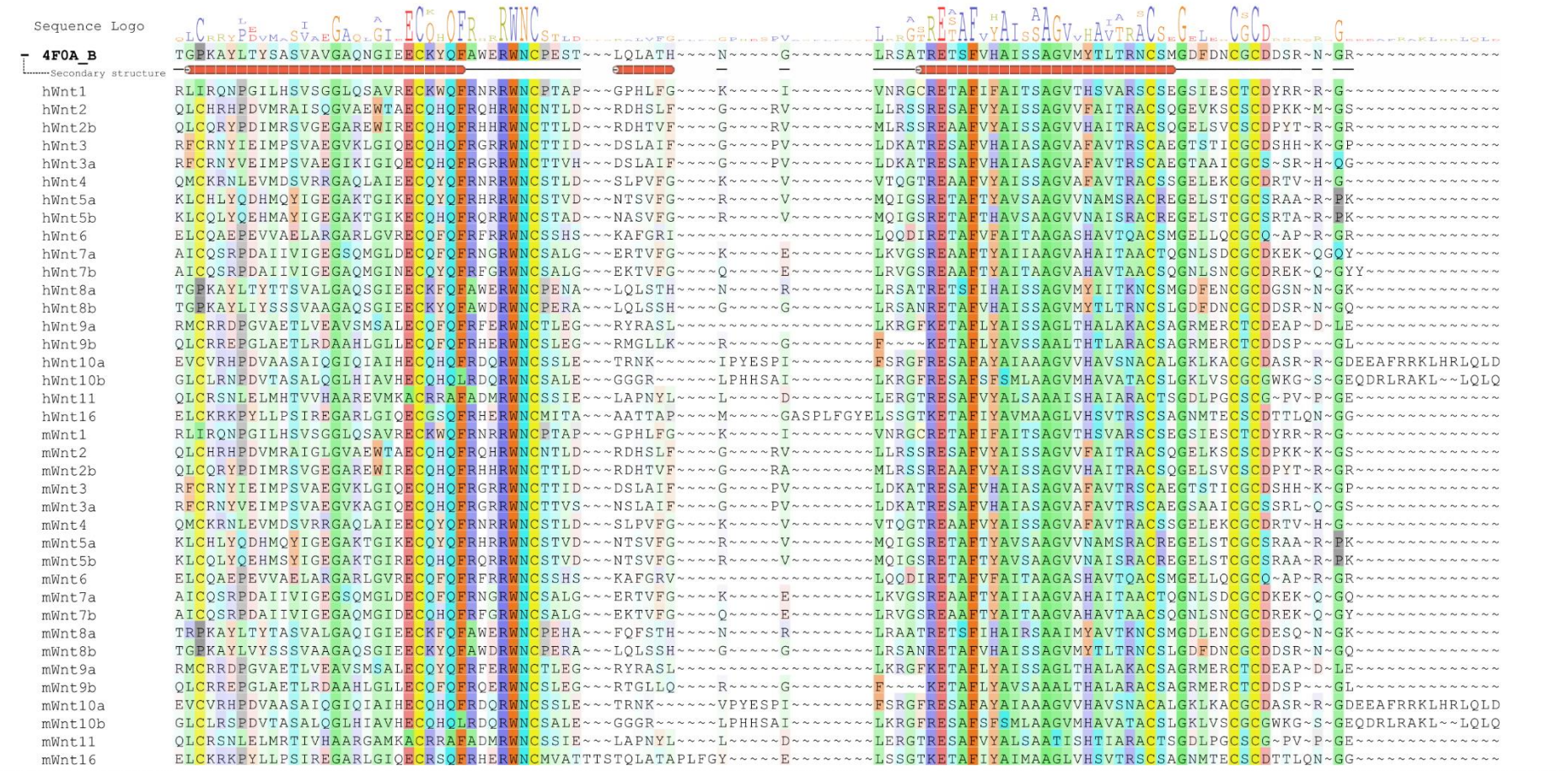
Table S1. UniProt accession numbers, sequence ranges and lengths used in model building.

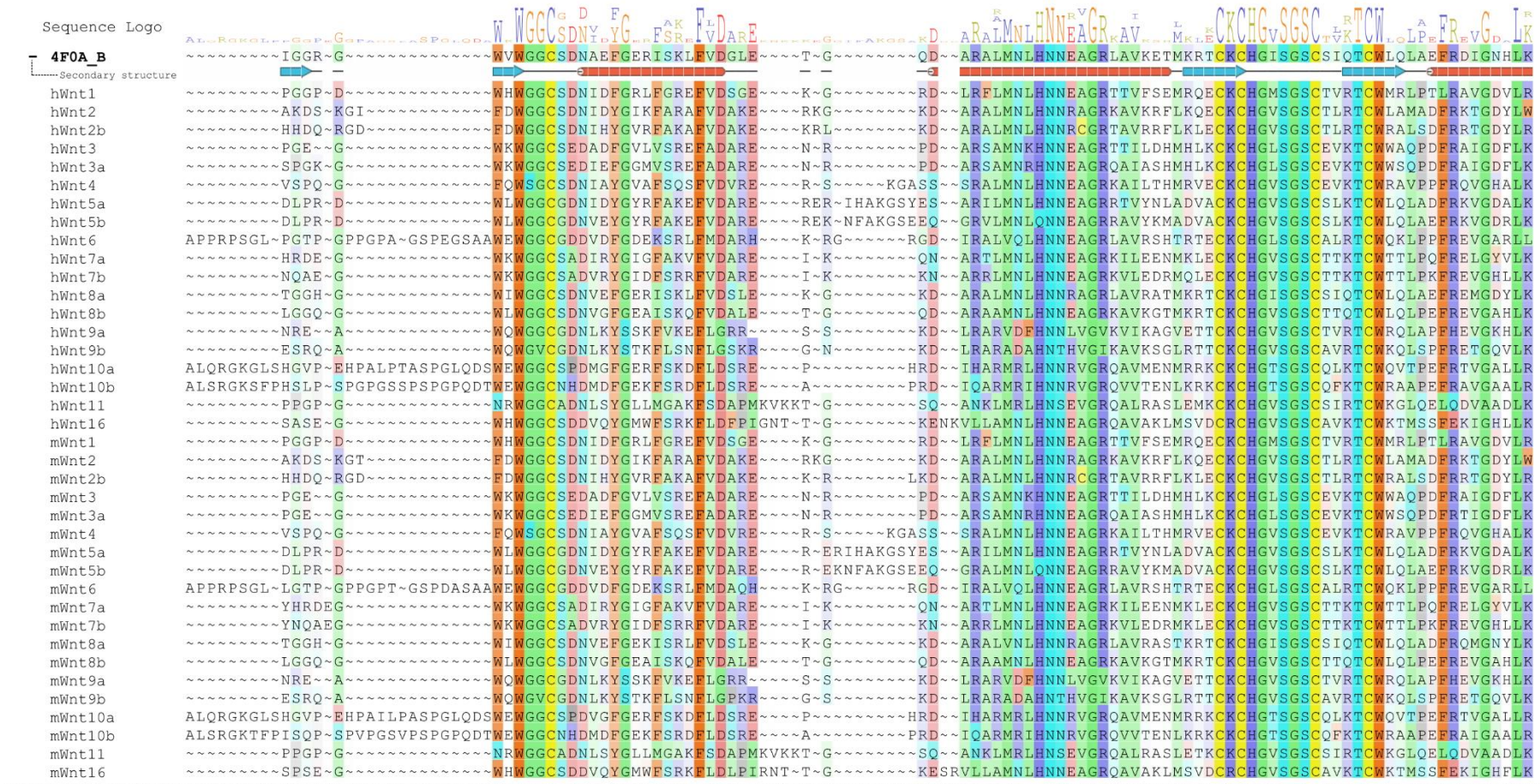
UniProt accession	Protein	Sequence range used	Length
P28026	XWnt8[a]	32-338	307
P04628	hWnt1	70-370	301
P09544	hWnt2	53-349	297
Q93097	hWnt2b	84-380	297
P56703	hWnt3	57-355	299
P56704	hWnt3a	54-352	299
P56705	hWnt4	55-351	297
P41221	hWnt5a	81-380	300
Q9H1J7	hWnt5b	62-359	298
Q9Y6F9	hWnt6	53-365	313
O00755	hWnt7a	50-349	300
P56706	hWnt7b	50-349	300
Q9H1J5	hWnt8a	31-337	307
Q93098	hWnt8b	31-334	304
O14904	hWnt9a	70-364	295
O14905	hWnt9b	66-356	291
Q9GZT5	hWnt10a	73-417	345
O00744	hWnt10b	60-389	330
O96014	hWnt11	57-354	298
Q9UBV4	hWnt16	58-365	308
P04426	mWnt1	70-370	301
P21552	mWnt2	53-349	297
O70283	mWnt2b	82-378	297
P17553	mWnt3	57-355	299
P27467	mWnt3a	54-352	299
P22724	mWnt4	55-351	297
P22725	mWnt5a	81-380	300
P22726	mWnt5b	60-358	299
P22727	mWnt6	52-364	313
P24383	mWnt7a	50-349	300
P28047	mWnt7b	50-349	300
Q64527	mWnt8a	31-337	307
Q9WUD6	mWnt8b	30-333	304
Q8R5M2	mWnt9a	70-364	295
O35468	mWnt9b	68-358	291
P70701	mWnt10a	73-417	345
P48614	mWnt10b	60-389	330
P48615	mWnt11	57-354	298
Q9QYS1	mWnt16	60-364	305
Q9UP38	hFzd1	116-230	115
Q14332	hFzd2	39-153	115
Q9NPG1	hFzd3	28-136	109
Q9ULV1	hFzd4	45-161	117
Q13467	hFzd5	33-150	118
O60353	hFzd6	24-132	109
O75084	hFzd7	49-163	115
Q9H461	hFzd8	35-151	117

O00144	hFzd9	39-155	117
Q9ULW2	hFzd10	34-150	117
Q8N474	hSFRP1	58-169	112
Q96HF1	hSFRP2	40-155	116
Q92765	hSFRP3	35-150	116
Q6FHJ7	hSFRP4	24-139	116
Q5T4F7	hSFRP5	53-165	113
O70421	mFzd1	111-225	115
Q9JIP6	mFzd2	44-158	115
Q61086	mFzd3	28-136	109
Q61088	mFzd4	45-161	117
Q9EQD0	mFzd5	33-150	118
Q61089	mFzd6	24-132	109
Q61090	mFzd7	49-163	115
Q61091	mFzd8[b]	35-151	117
Q9R216	mFzd9	40-156	117
Q8BKG4	mFzd10	35-151	117
Q8C4U3	mSFRP1	58-169	112
P97299	mSFRP2	40-155	116
P97401	mSFRP3	35-150	116
Q9Z1N6	mSFRP4	24-139	116
Q9WU66	mSFRP5	50-162	113

[a]Template for all Wnt structures; sequence range corresponds to N- and C-terminal limits available in PDB 4F0A chain B. [b]Template for all Fzd CRD structures; sequence range corresponds to N- and C-terminal limits available in PDB 4F0A chain A.

Figure S2. Sequence alignments of Wnts to XWnt8 (PDB 4F0A chain B) (NOTE: continues over multiple pages).[a]




Sequence Logo
4F0A_B
Secondary structure
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hWnt2
hWnt2b
hWnt3
hWnt3a
hWnt4
hWnt5a
hWnt5b
hWnt6
hWnt7a
hWnt7b
hWnt8a
hWnt8b
hWnt9a
hWnt9b
hWnt10a
hWnt10b
hWnt11
hWnt16
mWnt1
mWnt2
mWnt2b
mWnt3
mWnt3a
mWnt4
mWnt5a
mWnt5b
mWnt6
mWnt7a
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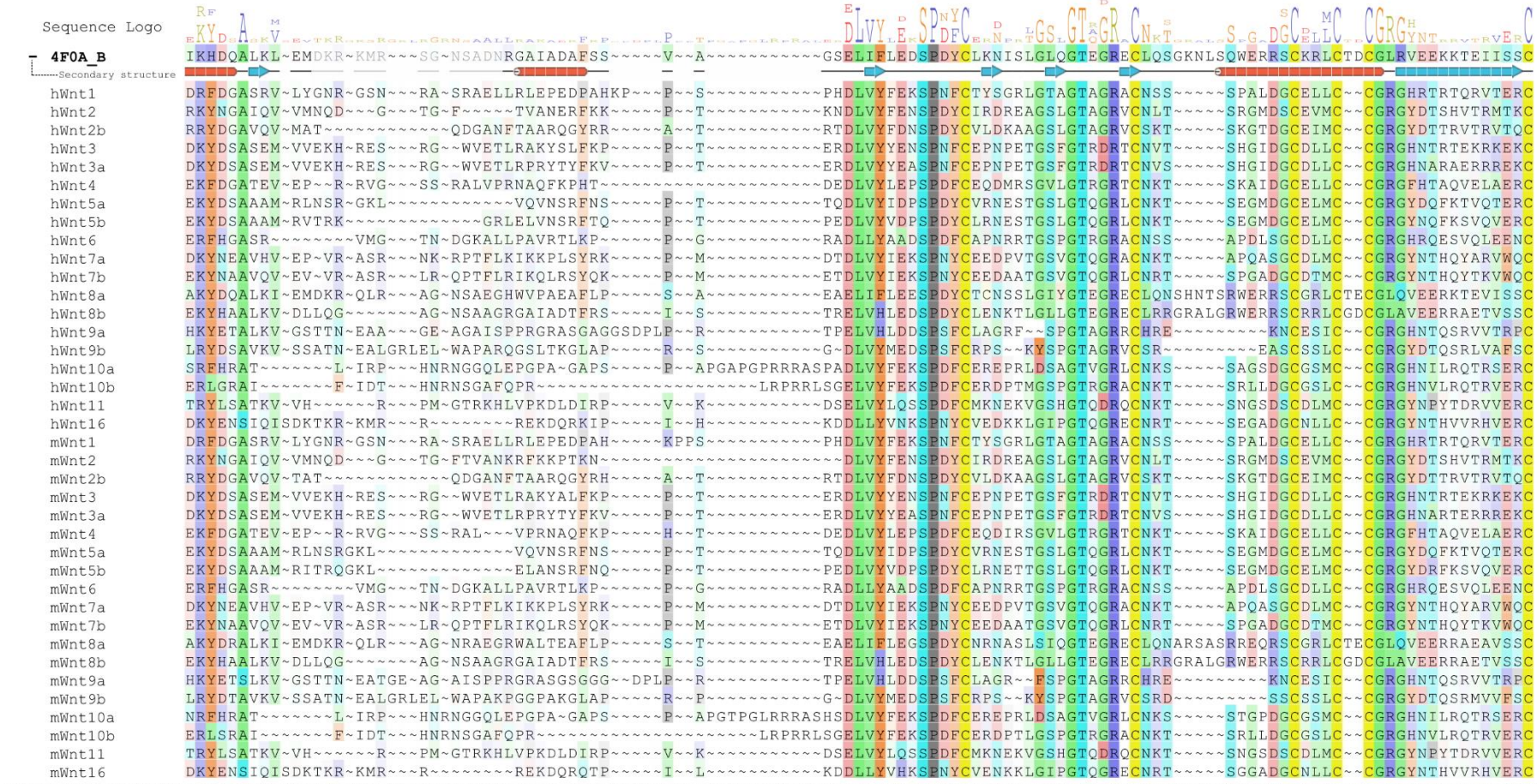
mWnt10a
mWnt10b
mWnt11
mWnt16


Sequence Logo
4F0A_B
Secondary structure
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hWnt2
hWnt2b
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hWnt6
hWnt7a
hWnt7b
hWnt8a
hWnt8b
hWnt9a
hWnt9b
hWnt10a
hWnt10b
hWnt11
hWnt16
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mWnt2
mWnt2b
mWnt3
mWnt3a
mWnt4
mWnt5a
mWnt5b
mWnt6
mWnt7a
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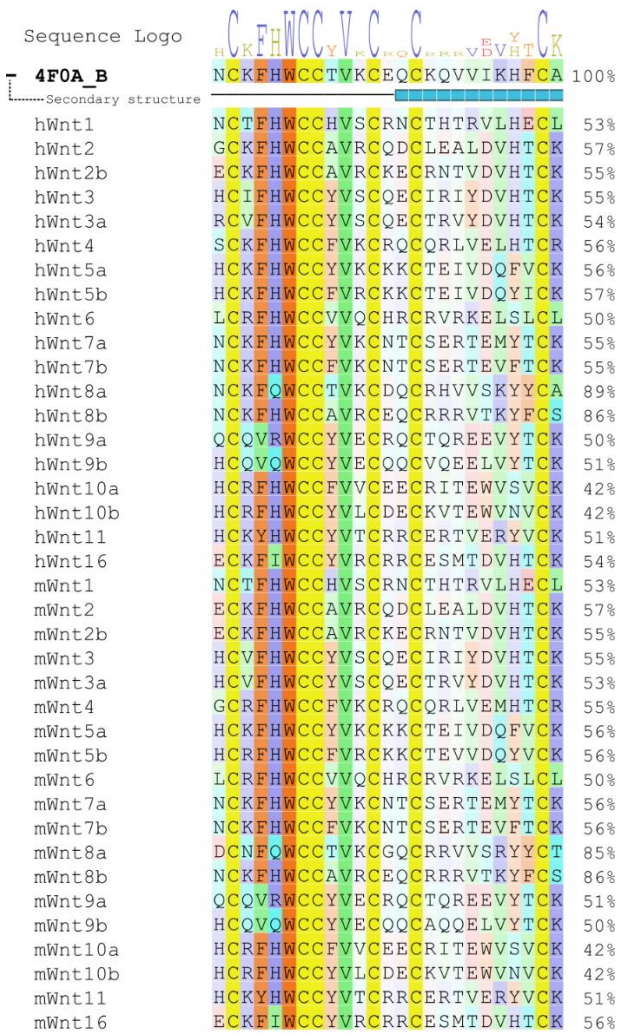
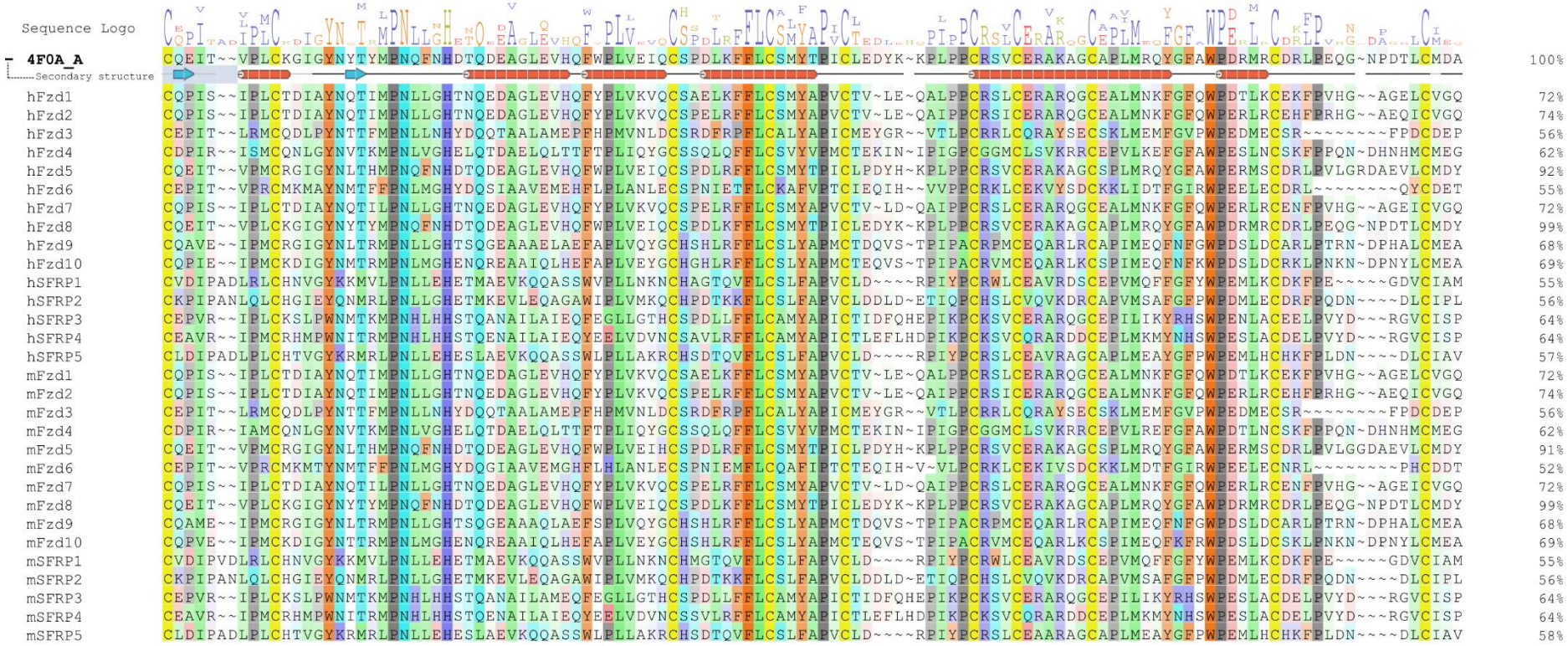
mWnt10a
mWnt10b
mWnt11
mWnt16



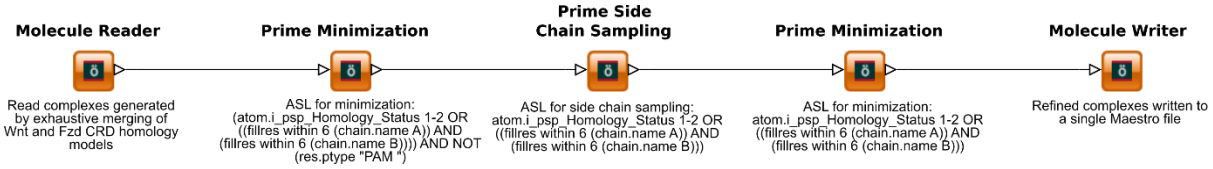
[a]Sequence logo and intensity of position colouring indicates level of conservation. Percentage similarity to mFzd8 sequence contained in PDB 4F0A chain A shown at end of sequences.

Figure S3. Sequence alignments of Fzd and SFRP CRDS to mFzd8 (PDB 4F0A chain A).[a]



[a]Sequence logo and intensity of position colouring indicates level of conservation. Percentage similarity to mFzd8 sequence contained in PDB 4F0A chain A shown at end of sequences.

Figure S4. KNIME workflow of complex refinement process.[a]



[a]Complex refinement achieved using Prime (Schrodinger) and automated by KNIME. ASL refers to Atom Specification Language used by Schrodinger software to define chemical selections. ASL selections for each of the Prime steps are specified under each node. In all complexes, chain A is a Fzd CRD and chain B is a Wnt. The residue name PAM is ascribed to the lipid portion of *O*-palmitoleylserine.

Table S5. MolProbity Scores for mouse complexes.

		mWnt																	
		1	2	2b	3	3a	4	5	5b	6	7a	7b	8a	8b	9a	9b	10a	10b	11	16
mFzd	1	2.00	2.09	2.49	1.90	1.88	1.97	2.14	1.84	2.03	2.03	2.03	2.08	1.94	2.14	1.92	2.34	2.11	1.78	2.64
	2	2.13	2.20	2.52	1.94	1.87	1.97	1.93	1.92	2.08	1.91	2.01	2.10	1.78	2.33	2.14	2.28	1.99	1.80	2.64
	3	2.12	2.20	2.63	1.98	2.02	1.99	1.89	2.09	1.89	1.95	2.03	2.28	2.08	2.44	2.14	2.14	2.13	1.91	2.64
	4	2.12	2.16	2.49	2.06	2.04	1.99	1.77	1.84	2.03	2.09	2.24	2.33	2.17	2.36	2.14	2.36	2.16	1.87	2.59
	5	2.07	2.18	2.49	2.16	2.02	1.78	2.13	1.81	2.01	1.90	2.05	2.07	1.89	2.28	2.04	2.27	1.93	1.90	2.63
	6	2.27	2.39	2.44	2.44	2.12	2.08	2.29	2.26	2.11	2.19	2.27	2.46	2.30	2.43	2.26	2.30	2.27	1.96	2.75
	7	2.00	2.21	2.53	2.24	1.89	1.79	2.08	2.04	1.88	1.69	1.92	2.23	1.91	2.34	2.01	2.29	2.03	1.95	2.64
	8	2.05	2.03	2.44	2.02	2.00	1.73	1.94	1.63	1.81	1.81	1.91	1.99	1.85	2.17	2.06	2.33	2.01	1.77	2.53
	9	2.11	1.91	2.54	2.14	1.99	1.94	1.90	1.80	1.95	1.88	2.10	2.27	1.96	2.10	2.10	2.39	2.13	1.99	2.63
	10	2.00	2.28	2.54	1.99	1.96	1.85	1.88	1.82	2.08	1.93	1.98	2.25	2.04	2.26	2.07	2.08	2.17	1.87	2.68
mSFRP	1	2.14	2.22	2.78	2.28	1.98	1.89	1.88	1.96	2.02	2.08	2.10	2.36	2.19	2.42	2.19	2.25	2.25	1.95	2.64
	2	2.11	2.26	2.77	2.19	2.08	2.14	2.15	2.13	2.30	2.08	2.15	2.24	2.11	2.32	2.28	2.31	2.25	2.09	2.73
	3	1.84	2.46	2.46	1.97	1.89	2.02	1.98	1.94	1.83	1.92	2.08	2.27	1.97	2.35	2.24	2.25	2.13	1.97	2.75
	4	2.05	1.97	2.62	2.02	1.98	1.98	2.01	2.01	2.06	1.89	1.96	2.15	1.89	2.29	2.15	2.22	2.28	1.71	2.62
	5	2.13	2.30	2.74	1.94	2.01	1.84	1.99	1.90	2.08	2.07	2.09	2.16	2.05	2.38	2.28	2.23	2.13	2.22	2.75

Table S6. MolProbity Scores for human complexes.

		hWnt																	
		1	2	2b	3	3a	4	5a	5b	6	7a	7b	8a	8b	9a	9b	10a	10b	11	16
hFzd	1	2.13	1.88	2.45	1.91	2.00	1.75	2.14	1.69	2.12	2.03	1.96	2.06	2.01	2.28	2.06	2.30	2.20	1.72	2.11
	2	1.92	2.02	2.24	1.81	2.01	1.73	1.93	1.60	2.03	1.91	1.94	2.08	1.74	2.31	2.18	2.20	2.15	1.75	2.20
	3	2.14	1.98	2.69	2.22	2.11	2.01	1.89	1.94	2.29	1.95	1.95	2.14	2.01	2.42	2.22	2.27	2.31	2.03	2.21
	4	2.09	1.95	2.75	1.82	2.04	1.96	1.86	1.92	2.05	2.12	2.05	2.23	2.15	2.33	2.06	2.36	2.13	1.96	2.19
	5	2.02	1.88	2.52	1.84	1.94	1.82	1.77	1.72	2.05	1.90	1.88	2.01	1.98	2.25	2.06	2.39	2.23	1.99	2.13
	6	2.04	2.01	2.62	2.11	2.22	1.85	1.73	2.07	2.16	1.99	1.97	2.00	2.10	2.41	2.17	2.19	2.16	1.89	2.16
	7	1.95	1.80	2.44	1.88	2.01	1.78	2.08	1.97	2.22	1.69	1.90	2.11	1.87	2.25	2.21	2.15	2.18	1.78	2.17
	8	1.74	1.74	2.43	1.74	1.97	1.52	1.94	1.70	2.00	1.81	1.82	1.92	1.92	2.27	2.03	2.11	2.14	1.49	2.21
	9	1.98	1.99	2.26	1.88	2.22	1.78	1.67	1.86	1.99	1.93	2.03	2.04	2.05	2.27	1.97	2.25	2.03	1.79	2.32
	10	2.07	1.75	2.54	2.02	2.03	1.60	1.92	1.80	1.98	2.03	2.05	2.16	2.02	2.31	1.99	2.05	2.26	1.79	2.20
hSFRP	1	2.18	1.97	2.69	2.29	2.20	1.94	1.94	1.96	2.17	1.99	2.15	2.26	2.17	2.28	2.24	2.26	2.18	2.05	2.26
	2	2.11	2.08	2.65	2.20	2.16	1.93	2.15	2.02	2.30	2.08	2.13	2.37	2.26	2.48	2.23	2.32	2.27	2.18	2.49
	3	2.09	1.97	2.52	2.11	2.13	1.92	1.87	2.08	2.18	2.02	2.07	2.26	2.13	2.49	2.21	2.22	2.27	1.92	2.29
	4	2.02	2.06	2.62	1.90	1.99	1.77	2.04	1.76	2.11	1.77	2.08	2.14	2.04	2.24	2.22	2.18	2.10	1.88	2.17
	5	2.28	1.91	2.66	1.86	1.96	1.87	2.13	2.02	2.17	2.11	2.17	2.35	2.17	2.26	2.14	2.23	2.17	2.08	2.33

Table S7. TM-Scores for mouse complexes with respect to the XWnt8-mFzd8 CRD complex (PDB 4F0A).

		mWnt																	
		1	2	2b	3	3a	4	5	5b	6	7a	7b	8a	8b	9a	9b	10a	10b	11	16
mFzd	1	0.91	0.90	0.93	0.92	0.92	0.92	0.89	0.92	0.90	0.90	0.92	0.92	0.95	0.89	0.88	0.93	0.91	0.92	0.91
	2	0.92	0.90	0.93	0.92	0.92	0.92	0.90	0.92	0.90	0.90	0.92	0.87	0.95	0.89	0.88	0.92	0.92	0.93	0.91
	3	0.89	0.89	0.91	0.88	0.91	0.91	0.88	0.91	0.88	0.87	0.91	0.89	0.93	0.87	0.86	0.91	0.91	0.90	0.90
	4	0.92	0.91	0.93	0.92	0.93	0.92	0.90	0.93	0.90	0.90	0.93	0.92	0.96	0.89	0.89	0.92	0.92	0.93	0.93
	5	0.91	0.91	0.93	0.93	0.90	0.93	0.90	0.91	0.88	0.91	0.93	0.92	0.95	0.89	0.88	0.93	0.93	0.93	0.92
	6	0.87	0.89	0.92	0.91	0.91	0.91	0.88	0.91	0.88	0.88	0.91	0.89	0.94	0.87	0.87	0.91	0.91	0.90	0.90
	7	0.91	0.91	0.92	0.93	0.92	0.89	0.89	0.90	0.90	0.90	0.92	0.91	0.96	0.87	0.88	0.92	0.91	0.91	0.91
	8	0.92	0.91	0.94	0.93	0.93	0.93	0.91	0.93	0.91	0.91	0.93	0.91	0.96	0.89	0.88	0.93	0.93	0.93	0.92
	9	0.91	0.89	0.93	0.93	0.94	0.92	0.90	0.93	0.90	0.91	0.93	0.91	0.95	0.90	0.88	0.93	0.93	0.92	0.92
	10	0.92	0.91	0.93	0.93	0.93	0.92	0.90	0.93	0.91	0.90	0.93	0.91	0.95	0.90	0.88	0.93	0.92	0.92	0.92
mSFRP	1	0.89	0.89	0.91	0.91	0.91	0.90	0.88	0.89	0.89	0.89	0.90	0.89	0.92	0.85	0.83	0.89	0.91	0.88	0.87
	2	0.91	0.91	0.93	0.92	0.93	0.92	0.87	0.92	0.87	0.88	0.91	0.91	0.95	0.89	0.88	0.90	0.93	0.92	0.89
	3	0.89	0.87	0.90	0.90	0.90	0.90	0.86	0.91	0.89	0.87	0.90	0.90	0.92	0.85	0.84	0.91	0.89	0.90	0.90
	4	0.90	0.90	0.92	0.92	0.92	0.91	0.89	0.93	0.90	0.87	0.89	0.91	0.94	0.88	0.85	0.89	0.91	0.92	0.91
	5	0.90	0.87	0.91	0.90	0.88	0.88	0.89	0.91	0.89	0.87	0.91	0.89	0.91	0.85	0.83	0.89	0.88	0.90	0.90

Table S8. TM-Scores for human complexes with respect to the XWnt8-mFzd8 CRD complex (PDB 4F0A).

		hWnt																	
		1	2	2b	3	3a	4	5a	5b	6	7a	7b	8a	8b	9a	9b	10a	10b	11	16
hFzd	1	0.91	0.92	0.93	0.92	0.92	0.91	0.89	0.89	0.90	0.90	0.93	0.95	0.95	0.89	0.87	0.92	0.92	0.92	0.91
	2	0.92	0.92	0.93	0.92	0.92	0.91	0.90	0.89	0.91	0.90	0.91	0.96	0.95	0.89	0.88	0.93	0.91	0.92	0.91
	3	0.88	0.90	0.91	0.88	0.91	0.90	0.88	0.88	0.88	0.87	0.91	0.93	0.94	0.88	0.85	0.91	0.91	0.90	0.90
	4	0.92	0.92	0.94	0.94	0.93	0.92	0.89	0.91	0.91	0.89	0.93	0.96	0.96	0.89	0.88	0.93	0.93	0.93	0.92
	5	0.92	0.92	0.93	0.93	0.93	0.92	0.90	0.90	0.91	0.91	0.91	0.96	0.96	0.90	0.88	0.93	0.93	0.90	0.89
	6	0.87	0.90	0.92	0.91	0.91	0.90	0.88	0.88	0.89	0.88	0.90	0.92	0.94	0.87	0.86	0.91	0.91	0.90	0.90
	7	0.91	0.92	0.92	0.92	0.91	0.89	0.89	0.89	0.91	0.90	0.92	0.96	0.95	0.88	0.85	0.92	0.92	0.92	0.91
	8	0.91	0.93	0.94	0.93	0.93	0.92	0.91	0.90	0.91	0.91	0.93	0.95	0.95	0.90	0.88	0.94	0.94	0.94	0.92
	9	0.91	0.90	0.92	0.93	0.92	0.92	0.90	0.89	0.91	0.91	0.93	0.96	0.93	0.90	0.88	0.93	0.93	0.92	0.92
	10	0.91	0.89	0.93	0.93	0.93	0.92	0.90	0.90	0.91	0.91	0.93	0.96	0.93	0.89	0.88	0.93	0.93	0.92	0.90
hSFRP	1	0.89	0.89	0.90	0.88	0.91	0.90	0.88	0.89	0.86	0.89	0.91	0.94	0.93	0.86	0.85	0.89	0.89	0.90	0.90
	2	0.91	0.89	0.92	0.92	0.92	0.90	0.87	0.89	0.87	0.88	0.92	0.95	0.93	0.89	0.85	0.89	0.93	0.88	0.90
	3	0.89	0.89	0.92	0.92	0.86	0.90	0.86	0.87	0.88	0.87	0.90	0.94	0.94	0.85	0.86	0.89	0.91	0.90	0.86
	4	0.91	0.92	0.92	0.92	0.91	0.91	0.89	0.89	0.88	0.88	0.90	0.95	0.94	0.86	0.87	0.92	0.91	0.92	0.91
	5	0.89	0.88	0.91	0.89	0.88	0.91	0.87	0.88	0.89	0.89	0.91	0.94	0.91	0.85	0.85	0.88	0.88	0.88	0.87

Table S9. Cα RMSDs for mouse complexes with respect to the XWnt8-mFzd8 CRD complex (PDB 4F0A).

		mWnt																	
		1	2	2b	3	3a	4	5	5b	6	7a	7b	8a	8b	9a	9b	10a	10b	11	16
mFzd	1	1.61	1.48	1.29	1.29	1.30	1.34	1.27	1.43	1.69	1.55	1.31	1.03	1.16	1.75	1.54	1.36	1.44	1.42	1.55
	2	1.49	1.52	1.32	1.34	1.37	1.22	1.26	1.46	1.62	1.58	1.37	1.27	1.17	1.77	1.53	1.45	1.31	1.31	1.58
	3	1.89	1.51	1.26	1.37	1.26	1.33	1.44	1.37	1.67	1.56	1.26	1.27	1.12	1.66	1.47	1.43	1.38	1.45	1.60
	4	1.54	1.48	1.28	1.28	1.18	1.34	1.19	1.26	1.63	1.42	1.27	0.98	1.02	1.61	1.38	1.40	1.17	1.24	1.39
	5	1.58	1.42	1.13	1.19	1.21	1.24	1.20	1.28	1.58	1.49	1.23	1.04	0.98	1.58	1.45	1.25	1.32	1.25	1.43
	6	1.69	1.44	1.23	1.29	1.31	1.30	1.35	1.33	1.73	1.54	1.36	1.13	1.05	1.82	1.58	1.37	1.38	1.39	1.41
	7	1.63	1.44	1.36	1.22	1.24	1.44	1.42	1.34	1.65	1.59	1.39	1.13	1.05	2.08	1.53	1.39	1.41	1.28	1.51
	8	1.54	1.33	1.14	1.11	1.20	1.24	1.14	1.33	1.54	1.49	1.21	1.06	0.99	1.30	1.47	1.23	1.29	1.22	1.42
	9	1.60	1.45	1.20	1.20	1.11	1.34	1.25	1.36	1.62	1.53	1.27	1.09	1.07	1.56	1.50	1.32	1.37	1.38	1.48
	10	1.50	1.39	1.22	1.22	1.23	1.35	1.19	1.32	1.61	1.53	1.23	1.06	1.10	1.67	1.46	1.34	1.38	1.34	1.41
mSFRP	1	1.69	1.59	1.49	1.48	1.41	1.53	1.36	1.56	1.65	1.80	1.52	1.25	1.25	1.77	1.56	1.46	1.47	1.52	1.67
	2	1.62	1.39	1.20	1.23	1.19	1.31	1.33	1.48	1.78	1.60	1.44	0.85	1.09	1.70	1.44	1.35	1.22	1.25	1.51
	3	1.52	1.25	1.13	1.58	1.19	1.19	1.04	1.43	1.70	1.36	1.63	1.03	1.04	1.82	1.47	1.35	1.34	1.24	1.37
	4	1.75	1.45	1.34	1.29	1.38	1.48	1.25	1.30	1.65	1.52	1.30	1.03	1.07	1.49	1.47	1.47	1.40	1.21	1.51
	5	1.58	1.61	1.34	1.82	1.33	1.33	1.59	1.48	1.63	1.70	1.36	1.09	1.26	1.77	1.70	1.48	1.42	1.37	1.54

Table S10. Cα RMSDs for human complexes with respect to the XWnt8-mFzd8 CRD complex (PDB 4F0A).

		hWnt																	
		1	2	2b	3	3a	4	5a	5b	6	7a	7b	8a	8b	9a	9b	10a	10b	11	16
hFzd	1	1.62	1.39	1.30	1.27	1.38	1.38	1.27	1.54	1.64	1.55	1.31	1.13	1.13	1.66	1.52	1.38	1.37	1.42	1.52
	2	1.52	1.49	1.37	1.32	1.25	1.38	1.26	1.57	1.56	1.58	1.45	0.99	1.16	1.74	1.58	1.25	1.40	1.39	1.54
	3	2.05	1.36	1.25	1.20	1.30	1.26	1.44	1.63	1.81	1.56	1.30	1.24	1.03	1.56	1.70	1.36	1.32	1.41	1.54
	4	1.35	1.41	1.12	1.13	1.24	1.28	1.05	1.43	1.72	1.50	1.22	0.62	0.93	1.61	1.54	1.37	1.38	1.24	1.44
	5	1.53	1.36	1.17	1.18	1.18	1.21	1.18	1.46	1.66	1.47	1.21	0.98	1.03	1.55	1.47	1.29	1.28	1.29	1.53
	6	1.74	1.45	1.21	1.21	1.16	1.37	1.23	1.59	1.74	1.49	1.37	1.70	1.08	1.70	1.50	1.37	1.31	1.43	1.40
	7	1.64	1.46	1.36	1.23	1.74	1.33	1.42	1.56	1.68	1.59	1.42	1.00	1.25	1.63	1.58	1.37	1.41	1.38	1.60
	8	1.58	1.32	1.15	1.17	1.15	1.21	1.14	1.41	1.54	1.49	1.17	1.02	0.92	1.46	1.46	1.15	1.16	1.13	1.43
	9	1.61	1.41	1.32	1.23	1.35	1.27	1.26	1.53	1.73	1.55	1.22	1.02	1.11	1.55	1.51	1.30	1.30	1.37	1.51
	10	1.51	1.48	1.23	1.20	1.21	1.27	1.29	1.46	1.65	1.52	1.23	1.00	1.08	1.60	1.52	1.29	1.38	1.31	1.44
hSFRP	1	1.67	1.95	1.90	1.38	1.32	1.40	1.35	1.50	1.75	1.62	1.43	1.01	1.23	1.70	2.15	1.46	1.45	1.34	1.51
	2	1.52	1.52	1.25	1.24	1.26	1.34	1.33	1.59	1.80	1.60	1.37	0.84	1.09	1.51	1.52	1.46	1.20	1.54	1.88
	3	1.33	1.40	1.02	1.23	1.24	1.37	1.10	1.32	1.61	1.44	1.11	0.81	0.85	1.34	1.36	1.20	1.18	1.07	1.36
	4	1.54	1.37	1.26	1.27	1.39	1.29	1.21	1.50	1.73	1.49	1.24	0.90	1.10	1.49	1.52	1.37	1.34	1.21	1.51
	5	1.70	2.25	1.38	2.09	1.31	1.27	1.32	1.56	1.70	1.66	1.40	1.09	1.26	1.64	1.64	1.42	1.39	1.51	1.57

Table S11. Descriptors considered during model building.

Name	Source
MMGBSA dG Bind	Prime MM-GB/SA
MMGBSA dG Bind Coulomb	Prime MM-GB/SA
MMGBSA dG Bind Covalent	Prime MM-GB/SA
MMGBSA dG Bind Lipo	Prime MM-GB/SA
MMGBSA dG Bind Solv GB	Prime MM-GB/SA
MMGBSA dG Bind Solv SA	Prime MM-GB/SA
MMGBSA dG Bind vdW	Prime MM-GB/SA
CP_BFKV	CCharPPI
CP_BL	CCharPPI
CP_BT	CCharPPI
CP_HLPL	CCharPPI
CP_MJPL	CCharPPI
CP_MJ3h	CCharPPI
CP_MJ2h	CCharPPI
CP_MJ1	CCharPPI
CP_Qa	CCharPPI
CP_Qm	CCharPPI
CP_Qp	CCharPPI
CP_RO	CCharPPI
CP_SKOb	CCharPPI
CP_TD	CCharPPI
CP_TEl	CCharPPI
CP_TEs	CCharPPI
CP_TS	CCharPPI
CP_SKOIP	CCharPPI
AP_DCOMPLEX	CCharPPI
AP_dDFIRE	CCharPPI
AP_DFIRE2	CCharPPI
CP_RMFCEN1	CCharPPI
CP_RMFCEN2	CCharPPI
CP_RMFCA	CCharPPI
CP_TB	CCharPPI
CP_TSC	CCharPPI
AP_T1	CCharPPI
AP_DOPE	CCharPPI
AP_DOPE_HR	CCharPPI
AP_ACE	CCharPPI
INSIDE	CCharPPI
HBOND	CCharPPI
ALIPH	CCharPPI
FA_ATR	CCharPPI
FA_REP	CCharPPI
LK_SOLV	CCharPPI
FA_PP	CCharPPI
CG_ENV	CCharPPI
CG_BETA	CCharPPI
HBOND2	CCharPPI
ROSETTA	CCharPPI
ROSETTADOCK	CCharPPI

NHB	CCharPPI
ELE	CCharPPI
DESOLV	CCharPPI
VDW	CCharPPI
PYDOCK_TOT	CCharPPI
ODA	CCharPPI
SIPPER	CCharPPI
AP_OPUS_PSP	CCharPPI
AP_GEOMETRIC	CCharPPI
AP_DARS	CCharPPI
AP_URS	CCharPPI
AP_WENG	CCharPPI
CP_DECK	CCharPPI
CP_ZPAIR_CB	CCharPPI
CP_ZLOCAL_CB	CCharPPI
CP_ELOCAL_CB	CCharPPI
CP_E3DC_CB	CCharPPI
CP_E3D_CB	CCharPPI
CP_ZPAIR_MIN	CCharPPI
CP_ZLOCAL_MIN	CCharPPI
CP_ZS3DC_MIN	CCharPPI
CP_Z3DC_MIN	CCharPPI
CP_ELOCAL_MIN	CCharPPI
CP_E3D_MIN	CCharPPI
AP_calRW	CCharPPI
AP_calRWp	CCharPPI
AP_GOAP_DF	CCharPPI
AP_GOAP_G	CCharPPI
AP_PISA	CCharPPI
FIREDOCK	CCharPPI
FIREDOCK_AB	CCharPPI
FIREDOCK_EI	CCharPPI

Table S12. Best performing three-descriptor models (RMSEtrain, RMSEtest < 0.40 kcal/mol).

Model (ΔG (kcal/mol) = ...)	**$RMSE_{train}$**	**$RMSE_{test}$**	**$InExp_{train}$**	**$InExp_{test}$**
0.21816 × AP_dDFIRE – 0.18648 × MMGBSA dG Bind – 0.00055766 × CP_RMFCA – 17.716	0.39	0.33	60%	50%
0.18371 × AP_DFIRE2 – 0.15660 × MMGBSA dG Bind – 0.00055871 × CP_RMFCA – 16.395	0.34	0.33	60%	50%
0.15502 × AP_DFIRE2 – 0.14163 × MMGBSA dG Bind – 0.24627 × HBOND2 – 13.557	0.34	0.38	53%	75%
0.0028131 × AP_GOAP_DF – 0.15928 × MMGBSA dG Bind – 0.00052876 × CP_RMFCA – 17.520	0.36	0.35	60%	50%
0.0016543 × AP_calRW – 0.15889 × MMGBSA dG Bind – 0.00059240 × CP_RMFCA – 14.146	0.34	0.32	60%	50%
0.0016602 × AP_calRWp – 0.15897 × MMGBSA dG Bind – 0.00058860 × CP_RMFCA – 13.968	0.34	0.32	60%	50%
0.0031082 × AP_GOAP_DF – 0.23987 × MMGBSA dG Bind vdW – 0.18455 × HBOND2 – 13.711	0.32	0.28	53%	63%
0.0015763 × CP_E3D_CB – 0.24556 × MMGBSA dG Bind vdW – 0.22431 × HBOND2 – 15.176	0.36	0.36	53%	50%
0.0017757 × AP_calRWp – 0.24096 × MMGBSA dG Bind vdW – 0.20469 × HBOND2 – 9.7535	0.30	0.30	67%	75%
0.065874 × NHB + 0.0034340 × AP_GOAP_DF – 0.24326 × MMGBSA dG Bind vdW – 12.833	0.36	0.38	53%	50%
0.0087303 × AP_DARS – 0.29292 × MMGBSA dG Bind vdW – 0.00026790 × CP_RMFCA – 20.681	0.38	0.39	60%	50%
0.26323 × AP_dDFIRE – 0.29244 × MMGBSA dG Bind vdW – 0.00042005 × CP_RMFCA – 15.570	0.39	0.38	60%	63%
0.23059 × AP_DFIRE2 – 0.25405 × MMGBSA dG Bind vdW – 0.00044639 × CP_RMFCA – 14.388	0.30	0.35	60%	50%
0.17165 × AP_DFIRE2 + 0.023350 × CP_TEl – 0.30444 × MMGBSA dG Bind vdW – 14.211	0.36	0.38	53%	63%
0.20365 × AP_DFIRE2 – 0.23701 × MMGBSA dG Bind vdW – 0.20039 × HBOND2 – 12.319	0.30	0.30	67%	50%
0.0017891 × AP_calRW – 0.23994 × MMGBSA dG Bind vdW – 0.21047 × HBOND2 – 9.8024	0.31	0.29	67%	75%

Table S13. Descriptor values, predicted binding energy and predicted dissociation constants for all mouse Wnt-Fzd CRD interactions using Model 1.

PROTEINS		DESCRIPTORS				BINDING AFFINITY[a]		
Wnt	**Fzd CRD**	**AP_calRW**	**MMGBSA dG Bind vdW**	**HBOND2**	**FIREDOCK_AB**	**ΔG**	**K_d**	**Approximate strength**
mWnt1	mFzd1	-5074.68	-31.00	-5.22	-104.70	-9.23	169.69	+
	mFzd2	-5281.12	-31.22	-4.30	-94.61	-10.70	14.26	+++
	mFzd3	-5233.08	-30.34	-2.57	-76.70	-12.03	1.50	++++
	mFzd4	-5608.64	-32.46	-4.70	-104.01	-11.10	7.21	++++
	mFzd5	-5858.39	-34.32	-5.43	-115.46	-10.88	10.40	+++
	mFzd6	-4890.46	-34.58	-3.09	-96.38	-8.66	444.20	-
	mFzd7	-5265.44	-30.98	-5.67	-104.64	-9.85	59.23	++
	mFzd8	-5676.61	-33.87	-3.26	-119.27	-10.64	15.74	+++
	mFzd9	-5438.60	-33.16	-1.93	-109.80	-10.69	14.48	+++
	mFzd10	-5212.25	-32.73	-4.35	-110.92	-9.27	158.73	+
	mSFRP1	-5254.01	-34.47	-6.96	-133.28	-7.28	4570.72	-
	mSFRP2	-5013.35	-34.50	-3.73	-99.03	-8.86	318.46	+
	mSFRP3	-5440.90	-29.35	-2.69	-109.32	-11.39	4.41	++++
	mSFRP4	-5620.02	-32.42	-2.59	-104.06	-11.67	2.76	++++
	mSFRP5	-5233.30	-30.05	-4.91	-129.43	-8.89	300.24	+
mWnt2	mFzd1	-5179.33	-34.33	-5.79	-89.19	-9.51	105.34	+
	mFzd2	-5381.39	-35.32	-4.78	-102.77	-9.64	85.78	++
	mFzd3	-5135.41	-36.13	-2.50	-72.28	-10.60	16.93	+++
	mFzd4	-5646.48	-34.38	-5.61	-110.43	-10.27	29.34	+++
	mFzd5	-5540.93	-33.55	-5.70	-104.57	-10.33	26.75	+++
	mFzd6	-4784.78	-33.62	-3.19	-75.79	-9.48	112.19	+
	mFzd7	-5282.69	-35.07	-5.76	-89.54	-9.73	72.86	++
	mFzd8	-5351.56	-31.42	-3.84	-100.10	-10.76	12.78	+++
	mFzd9	-5323.28	-31.93	-3.83	-105.81	-10.26	30.04	+++
	mFzd10	-5364.06	-34.59	-7.35	-122.88	-8.10	1154.35	-
	mSFRP1	-5059.93	-34.72	-4.06	-98.85	-8.91	290.14	+
	mSFRP2	-5058.23	-37.11	-3.20	-92.88	-8.88	306.99	+
	mSFRP3	-5312.23	-30.54	-5.39	-107.72	-10.05	42.65	++
	mSFRP4	-5472.46	-35.46	-4.07	-109.04	-9.81	63.64	++

	mSFRP5	-5314.40	-32.81	-5.87	-105.99	-9.51	105.24	+
mWnt2b	mFzd1	-4883.44	-32.65	-3.37	-63.31	-10.65	15.47	+++
	mFzd2	-5172.91	-33.78	-5.39	-85.82	-9.88	56.73	++
	mFzd3	-4945.07	-28.33	-1.81	-55.87	-12.61	0.56	++++
	mFzd4	-5563.40	-35.51	-4.65	-103.42	-10.28	28.67	+++
	mFzd5	-5352.37	-32.59	-4.25	-76.07	-11.60	3.11	++++
	mFzd6	-4933.70	-34.03	-4.05	-95.49	-8.76	376.87	+
	mFzd7	-5274.48	-34.26	-6.73	-91.42	-9.55	98.82	++
	mFzd8	-5119.72	-31.98	-4.41	-96.86	-9.77	67.91	++
	mFzd9	-5152.70	-30.65	-3.70	-95.01	-10.46	21.17	+++
	mFzd10	-5209.10	-30.24	-3.50	-99.55	-10.60	16.94	+++
	mSFRP1	-5016.89	-34.63	-3.77	-95.97	-8.99	257.15	+
	mSFRP2	-5076.22	-31.66	-4.25	-82.56	-10.43	22.35	+++
	mSFRP3	-5085.88	-30.84	-3.83	-72.18	-11.27	5.39	++++
	mSFRP4	-5585.45	-35.65	-3.33	-98.64	-10.90	10.12	+++
	mSFRP5	-5141.99	-32.66	-2.02	-93.42	-10.46	21.14	+++
mWnt3	mFzd1	-5496.48	-32.80	-5.30	-107.45	-10.28	28.91	+++
	mFzd2	-5488.11	-31.94	-6.02	-107.74	-10.25	30.47	+++
	mFzd3	-5353.88	-36.05	-2.30	-82.36	-10.99	8.65	++++
	mFzd4	-5763.95	-35.55	-5.50	-115.13	-10.25	30.47	+++
	mFzd5	-5995.00	-28.57	-4.83	-127.21	-12.26	1.01	++++
	mFzd6	-5319.01	-34.12	-2.13	-91.40	-10.89	10.38	+++
	mFzd7	-5539.45	-33.92	-6.23	-103.63	-10.15	35.85	+++
	mFzd8	-5528.45	-30.52	-3.55	-93.42	-12.04	1.47	++++
	mFzd9	-5432.32	-30.99	-4.37	-105.64	-10.76	12.81	+++
	mFzd10	-5776.75	-30.45	-7.02	-124.77	-10.59	17.13	+++
	mSFRP1	-5378.32	-36.75	-5.47	-111.74	-8.68	428.52	-
	mSFRP2	-5309.58	-37.69	-4.58	-110.58	-8.49	595.96	-
	mSFRP3	-5838.86	-33.28	-3.66	-97.64	-12.37	0.85	++++
	mSFRP4	-5985.22	-35.87	-3.42	-112.88	-11.65	2.88	++++
	mSFRP5	-5624.69	-31.28	-5.80	-129.62	-9.88	56.76	++
mWnt3a	mFzd1	-5410.88	-32.06	-4.55	-101.29	-10.61	16.51	+++
	mFzd2	-5524.88	-29.90	-5.95	-101.89	-11.16	6.55	++++

	mFzd3	-5413.67	-35.21	-2.81	-105.25	-10.14	36.36	+++
	mFzd4	-5836.26	-34.68	-3.90	-113.24	-11.21	6.02	++++
	mFzd5	-5946.28	-31.28	-6.77	-113.92	-11.65	2.83	++++
	mFzd6	-5264.13	-34.71	-2.81	-91.98	-10.35	25.78	+++
	mFzd7	-5567.30	-30.44	-5.50	-111.14	-10.85	11.06	+++
	mFzd8	-5554.38	-30.42	-2.78	-103.30	-11.86	1.99	++++
	mFzd9	-5411.50	-34.55	-2.20	-109.74	-10.21	32.44	+++
	mFzd10	-5625.81	-32.00	-4.77	-119.72	-10.47	20.89	+++
	mSFRP1	-5320.10	-33.18	-6.11	-110.66	-9.16	191.53	+
	mSFRP2	-5251.53	-31.51	-3.66	-103.64	-10.23	31.55	+++
	mSFRP3	-5854.30	-29.20	-3.38	-105.63	-13.02	0.28	++++
	mSFRP4	-5975.20	-35.07	-4.03	-129.43	-10.81	11.74	+++
	mSFRP5	-5432.51	-36.93	-3.65	-127.18	-8.53	556.23	-
mWnt4	mFzd1	-5356.66	-34.34	-6.92	-98.99	-9.42	122.94	+
	mFzd2	-5450.41	-35.53	-7.19	-97.22	-9.53	101.79	+
	mFzd3	-5360.32	-35.69	-3.98	-95.00	-10.05	42.26	++
	mFzd4	-5547.18	-34.96	-5.38	-112.40	-9.72	74.24	++
	mFzd5	-5852.27	-32.63	-6.78	-108.69	-11.25	5.62	++++
	mFzd6	-5271.93	-36.79	-2.40	-82.27	-10.49	20.08	+++
	mFzd7	-5515.36	-33.84	-8.67	-96.66	-9.83	62.25	++
	mFzd8	-5354.13	-32.46	-3.73	-97.34	-10.70	14.11	+++
	mFzd9	-5318.58	-33.24	-3.34	-98.09	-10.45	21.64	+++
	mFzd10	-5421.85	-35.48	-4.96	-116.03	-9.05	231.84	+
	mSFRP1	-5180.93	-35.13	-4.25	-103.37	-9.01	244.91	+
	mSFRP2	-5272.26	-37.52	-4.85	-115.48	-8.07	1203.08	-
	mSFRP3	-5667.58	-32.58	-3.21	-108.23	-11.46	3.96	++++
	mSFRP4	-6049.46	-34.07	-4.80	-107.71	-12.21	1.10	++++
	mSFRP5	-5326.17	-34.82	-6.01	-114.12	-8.67	440.31	-
mWnt5a	mFzd1	-5108.67	-33.73	-4.41	-77.28	-10.31	27.26	+++
	mFzd2	-5414.58	-34.57	-5.82	-89.57	-10.33	26.45	+++
	mFzd3	-5423.76	-33.30	-4.21	-95.50	-10.75	13.00	+++
	mFzd4	-5679.15	-35.51	-4.85	-111.87	-10.26	30.05	+++
	mFzd5	-5675.78	-32.28	-6.05	-101.57	-11.19	6.23	++++

	mFzd6	-4867.59	-34.94	-1.40	-71.62	-10.14	36.38	+++
	mFzd7	-5334.05	-33.94	-5.90	-92.99	-9.98	48.18	++
	mFzd8	-5472.42	-31.60	-4.08	-93.94	-11.43	4.13	++++
	mFzd9	-5253.23	-32.68	-3.86	-91.01	-10.55	18.23	+++
	mFzd10	-5338.52	-33.01	-3.65	-103.32	-10.24	30.82	+++
	mSFRP1	-5328.48	-36.22	-8.11	-114.70	-7.81	1859.63	-
	mSFRP2	-5416.60	-35.15	-4.90	-111.49	-9.34	140.71	+
	mSFRP3	-5367.23	-30.42	-4.99	-104.27	-10.56	18.07	+++
	mSFRP4	-5700.57	-35.02	-2.46	-95.79	-11.84	2.07	++++
	mSFRP5	-5088.20	-37.00	-4.66	-107.10	-7.95	1480.95	-
mWnt5b	mFzd1	-5321.63	-33.87	-4.96	-99.43	-9.85	59.19	++
	mFzd2	-5361.69	-34.37	-7.98	-93.10	-9.47	113.93	+
	mFzd3	-5415.63	-35.14	-2.44	-83.09	-11.36	4.63	++++
	mFzd4	-5692.32	-35.41	-4.85	-112.63	-10.29	28.35	+++
	mFzd5	-5735.24	-35.16	-6.00	-110.16	-10.35	25.57	+++
	mFzd6	-5049.95	-36.82	-4.03	-77.60	-9.47	113.18	+
	mFzd7	-5505.25	-34.82	-5.39	-106.37	-9.89	55.81	++
	mFzd8	-5461.02	-31.83	-3.67	-98.85	-11.19	6.17	++++
	mFzd9	-5408.02	-33.40	-3.30	-105.80	-10.38	24.34	+++
	mFzd10	-5582.17	-36.07	-6.01	-129.16	-8.61	482.31	-
	mSFRP1	-5242.36	-35.78	-4.87	-102.10	-9.01	246.18	+
	mSFRP2	-5381.10	-34.60	-4.55	-121.88	-8.90	297.91	+
	mSFRP3	-5563.89	-30.88	-2.86	-87.59	-12.56	0.61	++++
	mSFRP4	-5623.82	-35.16	-3.55	-105.65	-10.75	12.98	+++
	mSFRP5	-5693.14	-30.75	-6.49	-126.05	-10.27	29.33	+++
mWnt6	mFzd1	-5335.95	-31.30	-4.74	-90.25	-11.00	8.57	++++
	mFzd2	-5089.54	-31.98	-3.44	-84.64	-10.51	19.74	+++
	mFzd3	-5307.54	-34.99	-2.47	-80.73	-11.09	7.31	++++
	mFzd4	-5639.72	-33.72	-4.16	-103.37	-11.10	7.19	++++
	mFzd5	-5679.96	-30.45	-5.26	-108.52	-11.46	3.90	++++
	mFzd6	-5097.94	-33.91	-4.23	-91.82	-9.55	98.61	++
	mFzd7	-5426.29	-33.78	-5.52	-111.49	-9.53	101.78	+
	mFzd8	-5246.91	-31.62	-4.44	-101.93	-10.08	40.53	++

	mFzd9	-5380.60	-31.39	-4.10	-109.39	-10.35	25.60	+++
	mFzd10	-5494.12	-32.42	-5.47	-109.49	-10.21	32.44	+++
	mSFRP1	-5274.01	-34.01	-2.72	-107.42	-9.79	65.68	++
	mSFRP2	-5241.87	-35.52	-3.59	-103.76	-9.30	151.35	+
	mSFRP3	-5569.92	-32.63	-3.48	-88.52	-11.99	1.61	++++
	mSFRP4	-5980.49	-34.91	-5.41	-121.57	-10.92	9.82	++++
	mSFRP5	-5457.22	-34.38	-3.47	-106.23	-10.28	28.65	+++
mWnt7a	mFzd1	-5284.87	-33.97	-3.83	-87.68	-10.56	18.09	+++
	mFzd2	-5413.95	-37.39	-4.86	-94.87	-9.67	81.25	++
	mFzd3	-5272.43	-32.75	-3.45	-82.99	-11.11	7.11	++++
	mFzd4	-5704.50	-35.21	-5.77	-116.02	-9.99	47.50	++
	mFzd5	-5787.96	-32.50	-5.35	-109.20	-11.36	4.66	++++
	mFzd6	-5095.50	-39.11	-3.05	-103.08	-8.10	1146.21	-
	mFzd7	-5504.88	-37.30	-4.54	-97.80	-9.96	49.16	++
	mFzd8	-5361.35	-33.37	-4.45	-101.54	-10.14	36.56	+++
	mFzd9	-5378.68	-32.06	-2.85	-100.60	-10.94	9.45	++++
	mFzd10	-5474.29	-33.03	-3.88	-117.00	-10.02	45.01	++
	mSFRP1	-5262.63	-33.80	-4.02	-94.22	-10.14	36.88	+++
	mSFRP2	-5180.46	-37.63	-2.86	-97.34	-9.09	214.92	+
	mSFRP3	-5595.52	-30.68	-2.22	-99.88	-12.27	1.00	++++
	mSFRP4	-5783.44	-35.32	-4.11	-102.90	-11.33	4.94	++++
	mSFRP5	-5133.57	-34.78	-2.78	-96.47	-9.62	88.54	++
mWnt7b	mFzd1	-5059.18	-34.31	-5.34	-77.28	-9.77	68.89	++
	mFzd2	-5402.23	-34.11	-3.83	-85.12	-11.10	7.24	++++
	mFzd3	-5271.19	-30.78	-3.13	-81.61	-11.70	2.64	++++
	mFzd4	-5717.79	-38.97	-4.05	-101.44	-10.34	25.99	+++
	mFzd5	-5537.05	-31.68	-5.39	-102.32	-10.92	9.79	++++
	mFzd6	-5032.26	-33.36	-2.51	-74.63	-10.70	14.12	+++
	mFzd7	-5415.75	-34.46	-4.75	-99.86	-10.11	38.43	+++
	mFzd8	-5452.76	-32.53	-3.98	-96.83	-11.03	8.19	++++
	mFzd9	-5305.49	-31.83	-3.68	-104.19	-10.33	26.61	+++
	mFzd10	-5265.58	-33.05	-2.45	-109.36	-9.95	50.62	++
	mSFRP1	-5051.85	-34.48	-3.88	-96.69	-9.09	215.35	+

	mSFRP2	-5309.31	-31.28	-4.76	-116.09	-9.61	89.44	++
	mSFRP3	-5547.94	-32.15	-2.68	-99.94	-11.64	2.89	++++
	mSFRP4	-5757.34	-34.79	-4.05	-92.03	-11.90	1.87	++++
	mSFRP5	-5181.09	-36.87	-3.04	-94.48	-9.36	136.24	+
mWnt8a	mFzd1	-4966.17	-33.01	-3.11	-75.39	-10.35	25.76	+++
	mFzd2	-5161.48	-32.09	-3.08	-88.61	-10.65	15.53	+++
	mFzd3	-5065.63	-35.87	-3.98	-78.13	-9.73	73.04	++
	mFzd4	-5450.66	-34.02	-4.65	-102.24	-10.25	30.42	+++
	mFzd5	-5280.15	-31.41	-3.63	-93.71	-10.86	10.79	+++
	mFzd6	-4682.42	-35.10	-2.36	-73.39	-9.08	220.30	+
	mFzd7	-5193.03	-32.31	-2.76	-92.02	-10.63	16.11	+++
	mFzd8	-5335.82	-31.78	-3.04	-104.20	-10.61	16.44	+++
	mFzd9	-5105.40	-33.82	-2.94	-95.32	-9.74	71.52	++
	mFzd10	-5143.39	-33.31	-4.77	-98.23	-9.41	126.02	+
	mSFRP1	-4911.86	-32.30	-3.64	-97.19	-9.08	218.44	+
	mSFRP2	-4810.55	-33.71	-2.26	-79.07	-9.62	87.79	++
	mSFRP3	-5305.82	-29.80	-2.69	-81.44	-12.16	1.20	++++
	mSFRP4	-5236.84	-35.04	-2.17	-80.36	-10.90	10.05	+++
	mSFRP5	-4778.75	-30.99	-2.41	-85.18	-9.77	68.24	++
mWnt8b	mFzd1	-5099.76	-33.87	-3.98	-98.12	-9.31	147.71	+
	mFzd2	-5179.11	-34.95	-4.40	-87.41	-9.81	64.39	++
	mFzd3	-4985.54	-31.33	-1.55	-74.57	-11.22	5.86	++++
	mFzd4	-5378.44	-34.98	-4.10	-104.00	-9.81	64.26	++
	mFzd5	-5389.40	-33.40	-5.92	-94.32	-10.24	31.04	+++
	mFzd6	-4902.07	-34.66	-2.25	-94.06	-9.01	246.38	+
	mFzd7	-5194.16	-34.36	-8.27	-91.74	-8.83	336.83	+
	mFzd8	-5112.71	-32.41	-2.85	-94.85	-10.13	36.93	+++
	mFzd9	-5105.60	-35.82	-2.83	-94.96	-9.34	141.79	+
	mFzd10	-5043.80	-32.83	-5.01	-101.66	-8.90	294.41	+
	mSFRP1	-4908.99	-34.92	-1.97	-81.26	-9.69	78.65	++
	mSFRP2	-4893.00	-36.29	-2.80	-79.23	-9.21	174.58	+
	mSFRP3	-5091.44	-31.35	-4.60	-79.83	-10.61	16.56	+++
	mSFRP4	-5315.15	-35.22	-2.25	-91.70	-10.58	17.49	+++

	mSFRP5	-4950.91	-36.93	-4.13	-89.44	-8.45	630.95	-
mWnt9a	mFzd1	-5134.93	-31.66	-4.01	-109.42	-9.37	133.34	+
	mFzd2	-5315.47	-34.29	-5.53	-113.94	-8.87	310.93	+
	mFzd3	-5386.30	-37.30	-6.15	-105.91	-8.71	406.85	-
	mFzd4	-5512.33	-34.97	-5.91	-112.81	-9.43	120.70	+
	mFzd5	-5429.76	-31.97	-6.40	-119.88	-9.32	146.44	+
	mFzd6	-5109.24	-34.20	-2.06	-82.75	-10.51	19.43	+++
	mFzd7	-5312.98	-34.44	-5.83	-116.19	-8.64	459.06	-
	mFzd8	-5316.60	-32.30	-3.65	-104.32	-10.27	29.43	+++
	mFzd9	-5240.73	-33.10	-4.04	-115.64	-9.14	199.17	+
	mFzd10	-5204.03	-35.41	-5.38	-104.57	-8.70	417.80	-
	mSFRP1	-4988.57	-34.89	-4.22	-105.71	-8.22	932.42	-
	mSFRP2	-4783.35	-35.24	-5.85	-92.91	-7.60	2671.56	-
	mSFRP3	-5532.61	-30.56	-2.57	-111.41	-11.40	4.39	++++
	mSFRP4	-5407.21	-35.09	-4.15	-95.91	-10.28	28.76	+++
	mSFRP5	-4924.67	-36.22	-4.09	-109.97	-7.50	3167.05	-
mWnt9b	mFzd1	-4967.83	-34.21	-4.62	-97.22	-8.62	475.61	-
	mFzd2	-5148.77	-34.86	-3.95	-105.15	-8.93	280.20	+
	mFzd3	-5083.35	-35.35	-2.45	-78.14	-10.29	28.37	+++
	mFzd4	-5488.12	-35.27	-6.86	-115.40	-8.91	292.04	+
	mFzd5	-5429.80	-32.38	-4.98	-113.76	-9.88	56.36	++
	mFzd6	-5161.81	-34.41	-3.78	-92.79	-9.75	71.26	++
	mFzd7	-5067.43	-34.40	-5.13	-106.64	-8.36	734.45	-
	mFzd8	-5403.72	-31.31	-4.34	-110.35	-10.35	25.57	+++
	mFzd9	-5204.47	-34.05	-4.57	-103.44	-9.26	161.03	+
	mFzd10	-5147.63	-32.53	-3.84	-119.97	-8.74	386.34	+
	mSFRP1	-4867.94	-36.53	-2.95	-100.68	-7.96	1460.79	-
	mSFRP2	-4954.24	-37.22	-4.80	-91.59	-8.13	1089.96	-
	mSFRP3	-5096.51	-32.55	-2.85	-84.24	-10.57	17.65	+++
	mSFRP4	-5589.40	-34.90	-3.67	-111.82	-10.34	25.97	+++
	mSFRP5	-5103.49	-32.43	-1.56	-118.67	-9.22	172.11	+
mWnt10a	mFzd1	-5227.43	-31.87	-6.07	-86.06	-10.34	26.24	+++
	mFzd2	-5643.63	-31.40	-7.10	-101.95	-10.99	8.75	++++

	mFzd3	-5266.38	-30.92	-3.49	-61.59	-12.56	0.62	++++
	mFzd4	-5824.01	-35.75	-6.45	-103.65	-10.77	12.57	+++
	mFzd5	-5870.02	-31.79	-6.96	-106.68	-11.56	3.31	++++
	mFzd6	-5135.94	-36.28	-3.29	-89.36	-9.52	104.93	+
	mFzd7	-5630.07	-31.76	-5.66	-103.88	-11.11	7.07	++++
	mFzd8	-5561.72	-32.12	-3.74	-95.98	-11.64	2.92	++++
	mFzd9	-5480.95	-33.77	-2.42	-105.92	-10.79	12.28	+++
	mFzd10	-5606.99	-35.38	-4.56	-114.85	-9.93	51.95	++
	mSFRP1	-5305.18	-32.77	-5.89	-98.68	-9.85	59.87	++
	mSFRP2	-5372.57	-33.13	-5.13	-112.03	-9.55	99.66	++
	mSFRP3	-5961.36	-34.27	-6.45	-111.91	-11.22	5.92	++++
	mSFRP4	-6238.36	-35.04	-4.00	-129.29	-11.84	2.09	++++
	mSFRP5	-5298.27	-32.44	-5.90	-104.00	-9.63	87.04	++
mWnt10b	mFzd1	-5199.88	-31.48	-6.30	-86.87	-10.22	31.74	+++
	mFzd2	-5442.90	-33.78	-8.00	-96.67	-9.73	73.48	++
	mFzd3	-5386.46	-34.80	-2.42	-75.16	-11.73	2.50	++++
	mFzd4	-5699.57	-31.03	-3.85	-110.62	-11.65	2.85	++++
	mFzd5	-5734.11	-31.71	-6.16	-118.75	-10.66	15.31	+++
	mFzd6	-5197.61	-35.29	-2.81	-80.92	-10.51	19.48	+++
	mFzd7	-5610.95	-34.12	-6.67	-106.55	-10.13	37.41	+++
	mFzd8	-5613.33	-32.19	-6.04	-104.98	-10.80	11.91	+++
	mFzd9	-5508.10	-31.92	-4.55	-108.14	-10.67	14.87	+++
	mFzd10	-5550.26	-33.07	-6.20	-109.88	-10.08	40.40	++
	mSFRP1	-5182.66	-35.84	-3.66	-92.88	-9.53	102.89	+
	mSFRP2	-5241.36	-33.01	-6.35	-102.82	-9.23	170.59	+
	mSFRP3	-5764.47	-30.77	-4.64	-99.02	-12.34	0.89	++++
	mSFRP4	-5807.81	-35.38	-4.58	-104.65	-11.20	6.06	++++
	mSFRP5	-5383.10	-36.71	-5.27	-117.14	-8.49	592.77	-
mWnt11	mFzd1	-5040.37	-33.31	-6.54	-85.90	-9.19	180.86	+
	mFzd2	-5400.23	-34.46	-6.47	-102.82	-9.48	111.32	+
	mFzd3	-5309.48	-33.90	-2.38	-79.65	-11.42	4.18	++++
	mFzd4	-5573.00	-34.75	-5.79	-105.92	-10.09	39.97	+++
	mFzd5	-5353.63	-32.10	-4.71	-88.66	-10.97	8.94	++++

	mFzd6	-5040.50	-38.87	-3.68	-94.82	-8.20	963.89	-
	mFzd7	-5222.60	-33.65	-6.39	-85.21	-9.88	56.33	++
	mFzd8	-5472.48	-31.63	-4.38	-99.20	-11.09	7.38	++++
	mFzd9	-5200.17	-31.63	-5.61	-102.47	-9.58	93.46	++
	mFzd10	-5271.72	-33.52	-3.87	-109.84	-9.49	109.34	+
	mSFRP1	-5200.50	-35.02	-5.50	-102.95	-8.82	337.05	+
	mSFRP2	-5162.47	-34.88	-5.15	-106.54	-8.62	477.87	-
	mSFRP3	-5403.72	-30.66	-4.92	-84.68	-11.64	2.92	++++
	mSFRP4	-5614.32	-35.68	-3.95	-112.96	-10.14	36.63	+++
	mSFRP5	-5181.64	-31.09	-4.02	-107.26	-9.79	66.41	++
mWnt16	mFzd1	-5466.87	-32.37	-5.85	-100.56	-10.47	20.90	+++
	mFzd2	-5719.15	-34.79	-9.16	-111.55	-9.52	103.39	+
	mFzd3	-5624.22	-30.22	-3.75	-98.69	-12.17	1.19	++++
	mFzd4	-5713.11	-33.92	-6.05	-117.83	-10.15	36.03	+++
	mFzd5	-5868.00	-32.30	-6.17	-107.42	-11.60	3.13	++++
	mFzd6	-4852.22	-34.87	-4.29	-75.18	-9.21	175.18	+
	mFzd7	-5647.84	-34.39	-5.34	-111.35	-10.29	28.17	+++
	mFzd8	-5614.44	-32.39	-4.83	-119.71	-10.33	26.76	+++
	mFzd9	-5528.19	-31.98	-2.62	-101.54	-11.54	3.44	++++
	mFzd10	-5328.45	-32.58	-5.24	-110.80	-9.53	101.94	+
	mSFRP1	-5262.37	-38.28	-7.64	-103.07	-7.80	1916.49	-
	mSFRP2	-5422.17	-32.59	-4.68	-125.72	-9.29	154.95	+
	mSFRP3	-5710.29	-30.27	-5.11	-115.18	-11.33	4.94	++++
	mSFRP4	-6140.70	-35.54	-4.61	-118.58	-11.74	2.47	++++
	mSFRP5	-5307.54	-31.90	-5.55	-107.68	-9.69	78.29	++

[a]ΔG is in kcal/mol and calculated according to Model 1: ΔG = 0.0038165 × AP_calRW – 0.22506 × MMGBSA dG Bind vdW – 0.24626 × HBOND2 – 0.049875 × FIREDOCK_AB – 3.3475. K_d is in nM and calculated according to the following equation: $K_d = e^{\frac{\Delta G}{RT}} \times 10^9$, where ΔG is the binding energy predicted by Model 1, R is the gas constant (1.987×10^{-3} kcal/(K mol)) and T is standard ambient temperature (298K). Approximate strength based on ranges defined by Dijksterhuis et al. (1): ++++, <10nM; +++, 10-40nM; ++, 40-100nM; +, 100-400nM; -, >400nM.

Table S14. Descriptor values, predicted binding energy and predicted dissociation constants for all human Wnt-Fzd CRD interactions using Model 1.

PROTEINS		DESCRIPTORS				BINDING AFFINITY[a]		
Wnt	**Fzd CRD**	**AP_calRW**	**MMGBSA dG Bind vdW**	**HBOND2**	**FIREDOCK_AB**	**ΔG**	**K_d**	**Approximate strength**
hWnt1	hFzd1	-5125.51	-32.26	-4.94	-105.98	-9.15	196.29	+
	hFzd2	-5220.44	-30.91	-5.34	-86.54	-10.68	14.61	+++
	hFzd3	-5207.67	-32.02	-3.82	-69.88	-11.59	3.16	++++
	hFzd4	-5605.74	-34.45	-8.33	-126.10	-8.65	453.24	-
	hFzd5	-5665.03	-32.21	-5.95	-111.05	-10.72	13.80	+++
	hFzd6	-4661.20	-33.24	-1.60	-91.60	-8.69	421.09	-
	hFzd7	-5419.01	-30.58	-6.38	-111.68	-10.01	45.87	++
	hFzd8	-5498.09	-32.31	-4.25	-114.96	-10.28	28.91	+++
	hFzd9	-5473.54	-32.67	-3.25	-113.41	-10.43	22.44	+++
	hFzd10	-5287.00	-32.74	-4.99	-110.12	-9.44	120.10	+
	hSFRP1	-5116.15	-35.16	-3.56	-96.94	-9.25	165.10	+
	hSFRP2	-5046.52	-34.83	-4.52	-95.01	-8.92	288.74	+
	hSFRP3	-5314.86	-29.72	-3.91	-85.69	-11.71	2.60	++++
	hSFRP4	-5679.62	-35.09	-4.67	-113.09	-10.34	26.22	+++
	hSFRP5	-5308.18	-34.82	-6.26	-126.58	-7.92	1562.14	-
hWnt2	hFzd1	-5081.27	-34.12	-3.46	-84.17	-10.01	45.32	++
	hFzd2	-5411.40	-37.07	-4.96	-93.00	-9.80	65.05	++
	hFzd3	-5248.10	-35.32	-2.73	-76.34	-10.95	9.34	++++
	hFzd4	-5429.61	-34.01	-3.72	-104.17	-10.30	27.74	+++
	hFzd5	-5714.09	-30.99	-6.59	-117.78	-10.68	14.62	+++
	hFzd6	-4620.71	-33.93	-1.27	-67.94	-9.64	84.44	++
	hFzd7	-5308.35	-35.07	-5.74	-97.52	-9.44	119.59	+
	hFzd8	-5097.49	-32.30	-3.76	-79.47	-10.64	15.64	+++
	hFzd9	-5067.32	-32.92	-3.16	-95.23	-9.75	70.41	++
	hFzd10	-5163.29	-31.91	-4.52	-93.92	-10.07	40.87	++
	hSFRP1	-5031.23	-35.39	-4.89	-102.99	-8.24	901.29	-
	hSFRP2	-5080.01	-33.85	-4.47	-98.09	-9.12	203.37	+
	hSFRP3	-5208.18	-30.68	-2.78	-81.06	-11.59	3.15	++++
	hSFRP4	-5558.17	-35.78	-4.01	-104.49	-10.31	27.50	+++

	hSFRP5	-5141.65	-36.06	-2.27	-97.86	-9.41	124.82	+
hWnt2b	hFzd1	-5117.82	-33.40	-4.87	-88.13	-9.77	68.63	++
	hFzd2	-5183.22	-34.28	-4.17	-87.10	-10.04	43.16	++
	hFzd3	-5151.61	-36.42	-1.99	-78.64	-10.40	23.61	+++
	hFzd4	-5384.81	-33.87	-7.01	-99.17	-9.61	90.27	++
	hFzd5	-5388.93	-31.80	-5.57	-103.91	-10.20	32.86	+++
	hFzd6	-4753.32	-32.99	-2.56	-80.33	-9.43	122.15	+
	hFzd7	-5239.07	-34.63	-5.52	-85.67	-9.92	53.44	++
	hFzd8	-5236.14	-31.56	-4.53	-98.22	-10.21	32.27	+++
	hFzd9	-5276.05	-31.45	-4.87	-102.59	-10.09	39.92	+++
	hFzd10	-5320.50	-32.22	-5.42	-114.86	-9.34	141.76	+
	hSFRP1	-5058.39	-34.88	-4.97	-98.83	-8.65	454.31	-
	hSFRP2	-4888.40	-32.37	-3.44	-86.73	-9.55	99.69	++
	hSFRP3	-5425.42	-29.00	-3.61	-88.16	-12.24	1.05	++++
	hSFRP4	-5787.17	-33.67	-3.84	-99.34	-11.96	1.70	++++
	hSFRP5	-5181.91	-34.95	-2.75	-94.91	-9.85	60.01	++
hWnt3	hFzd1	-5381.52	-31.36	-4.66	-98.55	-10.77	12.69	+++
	hFzd2	-5490.48	-31.88	-8.32	-102.73	-9.95	50.09	++
	hFzd3	-5325.29	-32.29	-2.39	-78.51	-11.90	1.87	++++
	hFzd4	-5779.86	-34.38	-8.11	-110.90	-10.14	36.54	+++
	hFzd5	-6019.14	-28.42	-6.14	-124.95	-12.18	1.17	++++
	hFzd6	-5166.62	-35.78	-2.88	-92.12	-9.71	75.79	++
	hFzd7	-5602.13	-33.92	-4.08	-106.64	-10.77	12.60	+++
	hFzd8	-5828.74	-30.33	-4.78	-115.00	-11.85	2.02	++++
	hFzd9	-5632.10	-31.00	-2.79	-117.73	-11.31	5.10	++++
	hFzd10	-5640.69	-34.07	-4.47	-115.56	-10.34	25.99	+++
	hSFRP1	-5417.17	-36.28	-5.97	-121.86	-8.31	806.28	-
	hSFRP2	-5329.85	-35.12	-3.40	-108.57	-9.53	102.17	+
	hSFRP3	-5793.83	-29.12	-5.37	-90.65	-13.06	0.26	++++
	hSFRP4	-6004.77	-34.32	-4.37	-109.55	-12.00	1.58	++++
	hSFRP5	-5502.07	-36.72	-6.35	-126.59	-8.20	961.38	-
hWnt3a	hFzd1	-5316.97	-31.38	-3.51	-100.62	-10.69	14.34	+++
	hFzd2	-5417.95	-29.94	-5.66	-88.41	-11.48	3.78	++++

	hFzd3	-5319.63	-32.69	-3.59	-76.27	-11.60	3.08	++++
	hFzd4	-5725.13	-35.84	-6.03	-111.14	-10.10	38.89	+++
	hFzd5	-5608.71	-30.47	-6.67	-95.60	-11.49	3.77	++++
	hFzd6	-5076.58	-33.72	-3.14	-90.87	-9.83	61.84	++
	hFzd7	-5721.14	-30.22	-6.15	-122.10	-10.78	12.50	+++
	hFzd8	-5414.12	-30.54	-4.69	-93.80	-11.30	5.13	++++
	hFzd9	-5374.24	-31.98	-1.80	-103.77	-11.04	7.98	++++
	hFzd10	-5401.16	-34.21	-4.36	-110.91	-9.66	82.72	++
	hSFRP1	-5373.17	-31.75	-4.01	-114.16	-10.03	44.28	++
	hSFRP2	-5337.45	-34.06	-1.73	-96.72	-10.80	11.95	+++
	hSFRP3	-5668.07	-32.80	-4.88	-94.32	-11.69	2.67	++++
	hSFRP4	-5900.28	-33.08	-3.95	-118.48	-11.54	3.43	++++
	hSFRP5	-5355.19	-35.66	-4.88	-113.22	-8.91	291.29	+
hWnt4	hFzd1	-5334.08	-35.25	-4.77	-92.86	-9.96	49.21	++
	hFzd2	-5456.69	-35.27	-6.47	-116.35	-8.84	328.99	+
	hFzd3	-5315.37	-34.81	-3.79	-95.65	-10.09	39.48	+++
	hFzd4	-5374.34	-34.41	-3.85	-108.43	-9.76	69.64	++
	hFzd5	-5503.62	-31.15	-5.30	-92.36	-11.43	4.14	++++
	hFzd6	-4958.20	-33.15	-2.53	-97.39	-9.33	143.80	+
	hFzd7	-5391.49	-34.87	-5.81	-93.40	-9.99	47.25	++
	hFzd8	-5510.28	-32.83	-4.16	-103.75	-10.79	12.19	+++
	hFzd9	-5140.31	-33.29	-3.30	-99.67	-9.69	78.49	++
	hFzd10	-5334.68	-31.83	-4.09	-106.89	-10.20	32.78	+++
	hSFRP1	-5047.47	-36.16	-3.22	-89.72	-9.21	177.26	+
	hSFRP2	-5268.29	-31.89	-5.17	-99.93	-10.02	44.81	++
	hSFRP3	-5629.70	-31.69	-5.91	-99.18	-11.30	5.17	++++
	hSFRP4	-5738.76	-34.72	-4.23	-102.31	-11.29	5.23	++++
	hSFRP5	-5222.05	-36.48	-5.02	-103.29	-8.68	431.05	-
hWnt5a	hFzd1	-5108.67	-33.73	-4.41	-77.28	-10.31	27.26	+++
	hFzd2	-5414.58	-34.57	-5.82	-89.57	-10.33	26.45	+++
	hFzd3	-5423.76	-33.30	-4.21	-95.50	-10.75	13.00	+++
	hFzd4	-5683.63	-34.26	-8.89	-116.45	-9.33	143.63	+
	hFzd5	-5811.29	-32.06	-6.48	-110.18	-11.22	5.89	++++

	hFzd6	-5306.77	-36.24	-3.20	-106.19	-9.36	136.83	+
	hFzd7	-5334.05	-33.94	-5.90	-92.99	-9.98	48.18	++
	hFzd8	-5472.42	-31.60	-4.08	-93.94	-11.43	4.13	++++
	hFzd9	-5283.82	-31.70	-3.54	-96.51	-10.69	14.33	+++
	hFzd10	-5310.19	-33.08	-5.91	-120.99	-8.68	430.12	-
	hSFRP1	-5268.67	-33.99	-4.20	-95.49	-10.01	45.49	++
	hSFRP2	-5416.60	-35.15	-4.90	-111.49	-9.34	140.71	+
	hSFRP3	-5529.29	-33.27	-5.08	-96.69	-10.89	10.31	+++
	hSFRP4	-5606.86	-34.85	-3.89	-90.82	-11.41	4.25	++++
	hSFRP5	-5310.86	-36.03	-4.44	-111.26	-8.87	314.74	+
hWnt5b	hFzd1	-5168.76	-33.84	-5.42	-86.57	-9.81	64.33	++
	hFzd2	-5513.26	-34.49	-6.00	-96.14	-10.35	25.50	+++
	hFzd3	-5239.02	-34.22	-3.81	-93.97	-10.01	45.21	++
	hFzd4	-5833.57	-35.51	-7.90	-115.29	-9.92	52.65	++
	hFzd5	-5957.00	-31.77	-5.48	-129.73	-11.11	7.08	++++
	hFzd6	-5227.81	-37.10	-3.06	-107.35	-8.84	328.03	+
	hFzd7	-5500.76	-35.05	-4.90	-109.72	-9.77	67.85	++
	hFzd8	-5539.38	-31.33	-4.44	-106.51	-11.03	8.10	++++
	hFzd9	-5414.55	-35.81	-3.87	-114.43	-9.29	152.87	+
	hFzd10	-5380.64	-34.73	-3.85	-120.63	-9.10	210.82	+
	hSFRP1	-5158.20	-33.88	-2.54	-90.13	-10.29	28.52	+++
	hSFRP2	-5168.00	-35.23	-2.69	-117.44	-8.62	474.39	-
	hSFRP3	-5702.86	-33.06	-5.48	-106.57	-11.01	8.47	++++
	hSFRP4	-5661.96	-35.06	-3.07	-93.76	-11.63	2.94	++++
	hSFRP5	-5432.88	-37.16	-5.24	-117.59	-8.56	524.50	-
hWnt6	hFzd1	-5232.23	-31.08	-4.15	-78.98	-11.36	4.66	++++
	hFzd2	-5263.66	-32.38	-6.97	-88.42	-10.02	44.49	++
	hFzd3	-5290.62	-35.48	-2.22	-75.02	-11.26	5.48	++++
	hFzd4	-5668.22	-34.97	-5.17	-98.02	-10.95	9.34	++++
	hFzd5	-5680.62	-29.47	-5.04	-107.47	-11.80	2.23	++++
	hFzd6	-5021.35	-32.42	-2.10	-95.04	-9.96	49.76	++
	hFzd7	-5321.62	-32.53	-3.89	-100.01	-10.39	23.91	+++
	hFzd8	-5558.65	-31.65	-4.47	-116.51	-10.53	19.01	+++

	hFzd9	-5504.66	-30.74	-4.61	-108.52	-10.89	10.31	+++
	hFzd10	-5357.12	-32.21	-4.41	-115.12	-9.72	74.85	++
	hSFRP1	-5230.01	-34.67	-4.53	-110.74	-8.87	314.23	+
	hSFRP2	-5488.81	-34.64	-3.25	-119.13	-9.76	69.74	++
	hSFRP3	-5674.66	-30.51	-6.75	-86.22	-12.18	1.17	++++
	hSFRP4	-5853.01	-34.99	-3.67	-102.65	-11.79	2.27	++++
	hSFRP5	-5444.94	-30.74	-3.51	-112.26	-10.75	13.12	+++
hWnt7a	hFzd1	-5284.87	-33.97	-3.83	-87.68	-10.56	18.09	+++
	hFzd2	-5413.95	-37.39	-4.86	-94.87	-9.67	81.25	++
	hFzd3	-5272.43	-32.75	-3.45	-82.99	-11.11	7.11	++++
	hFzd4	-5605.57	-35.20	-4.64	-108.28	-10.28	29.10	+++
	hFzd5	-5497.67	-31.68	-5.32	-91.58	-11.32	4.96	++++
	hFzd6	-4748.48	-32.77	-2.12	-80.55	-9.56	98.20	++
	hFzd7	-5504.88	-37.30	-4.54	-97.80	-9.96	49.16	++
	hFzd8	-5361.35	-33.37	-4.45	-101.54	-10.14	36.56	+++
	hFzd9	-5371.27	-34.79	-3.74	-103.69	-9.92	52.63	++
	hFzd10	-5433.52	-32.94	-3.16	-114.90	-10.16	35.29	+++
	hSFRP1	-5050.47	-36.10	-5.38	-98.32	-8.27	861.04	-
	hSFRP2	-5180.46	-37.63	-2.86	-97.34	-9.09	214.92	+
	hSFRP3	-5604.03	-31.44	-4.85	-87.24	-12.11	1.31	++++
	hSFRP4	-5456.61	-35.41	-3.28	-97.62	-10.53	19.06	+++
	hSFRP5	-5155.36	-36.42	-3.01	-99.23	-9.14	199.02	+
hWnt7b	hFzd1	-5069.82	-34.66	-4.43	-78.89	-9.87	57.62	++
	hFzd2	-5374.43	-34.64	-4.54	-86.32	-10.64	15.73	+++
	hFzd3	-5172.57	-30.94	-2.73	-72.30	-11.85	2.05	++++
	hFzd4	-5545.77	-35.24	-4.09	-97.53	-10.71	13.95	+++
	hFzd5	-5683.73	-31.88	-5.53	-101.28	-11.45	4.00	++++
	hFzd6	-5013.44	-34.07	-3.05	-100.19	-9.06	224.77	+
	hFzd7	-5418.94	-34.49	-4.85	-99.71	-10.10	39.22	+++
	hFzd8	-5431.66	-32.34	-3.76	-95.49	-11.11	7.10	++++
	hFzd9	-5205.43	-34.01	-2.97	-96.14	-10.03	43.79	++
	hFzd10	-5369.38	-34.66	-2.16	-108.45	-10.10	39.25	+++
	hSFRP1	-5135.65	-35.34	-3.11	-95.37	-9.47	113.01	+

	hSFRP2	-5188.94	-33.87	-2.76	-83.53	-10.68	14.62	+++
	hSFRP3	-5493.66	-29.07	-5.29	-81.23	-12.42	0.78	++++
	hSFRP4	-5603.82	-35.00	-3.80	-105.59	-10.65	15.36	+++
	hSFRP5	-5164.84	-34.00	-5.18	-93.43	-9.47	113.01	+
hWnt8a	hFzd1	-4995.38	-31.48	-3.76	-83.99	-10.21	32.42	+++
	hFzd2	-5132.74	-32.56	-3.80	-83.43	-10.51	19.49	+++
	hFzd3	-5058.66	-33.55	-2.75	-70.37	-10.92	9.85	++++
	hFzd4	-5289.35	-34.52	-5.28	-95.99	-9.68	79.86	++
	hFzd5	-5281.44	-30.95	-3.43	-96.51	-10.88	10.46	+++
	hFzd6	-4673.64	-32.47	-2.90	-78.44	-9.25	163.93	+
	hFzd7	-5112.61	-32.80	-4.72	-91.47	-9.75	70.19	++
	hFzd8	-5144.71	-31.59	-3.18	-95.06	-10.35	25.78	+++
	hFzd9	-5058.07	-34.33	-4.58	-90.96	-9.26	161.19	+
	hFzd10	-5113.55	-31.46	-4.63	-98.03	-9.75	70.11	++
	hSFRP1	-4865.37	-31.93	-3.79	-94.16	-9.10	211.68	+
	hSFRP2	-4832.60	-32.84	-4.16	-86.54	-9.06	226.71	+
	hSFRP3	-5275.94	-29.13	-3.37	-82.47	-11.99	1.62	++++
	hSFRP4	-5269.13	-34.83	-2.02	-88.27	-10.72	13.79	+++
	hSFRP5	-4961.98	-30.64	-2.61	-91.85	-10.17	35.05	+++
hWnt8b	hFzd1	-5077.41	-33.80	-4.74	-88.53	-9.54	101.21	+
	hFzd2	-5154.30	-34.99	-3.99	-85.09	-9.92	53.12	++
	hFzd3	-5021.89	-35.07	-2.06	-74.96	-10.37	24.63	+++
	hFzd4	-5287.95	-34.02	-4.68	-100.90	-9.69	78.54	++
	hFzd5	-5637.89	-32.05	-4.54	-107.82	-11.15	6.59	++++
	hFzd6	-4593.74	-33.19	-3.10	-66.61	-9.32	145.18	+
	hFzd7	-5068.34	-34.29	-5.35	-93.93	-8.97	264.18	+
	hFzd8	-5143.70	-32.40	-3.71	-92.70	-10.15	36.04	+++
	hFzd9	-5092.38	-33.03	-2.78	-98.47	-9.75	70.19	++
	hFzd10	-5146.40	-33.08	-3.29	-101.38	-9.68	79.82	++
	hSFRP1	-4971.95	-35.85	-3.26	-94.15	-8.75	379.54	+
	hSFRP2	-4821.20	-33.04	-3.35	-90.54	-8.97	262.97	+
	hSFRP3	-5130.11	-29.64	-3.52	-85.93	-11.10	7.18	++++
	hSFRP4	-5343.75	-35.44	-3.34	-90.16	-10.45	21.77	+++

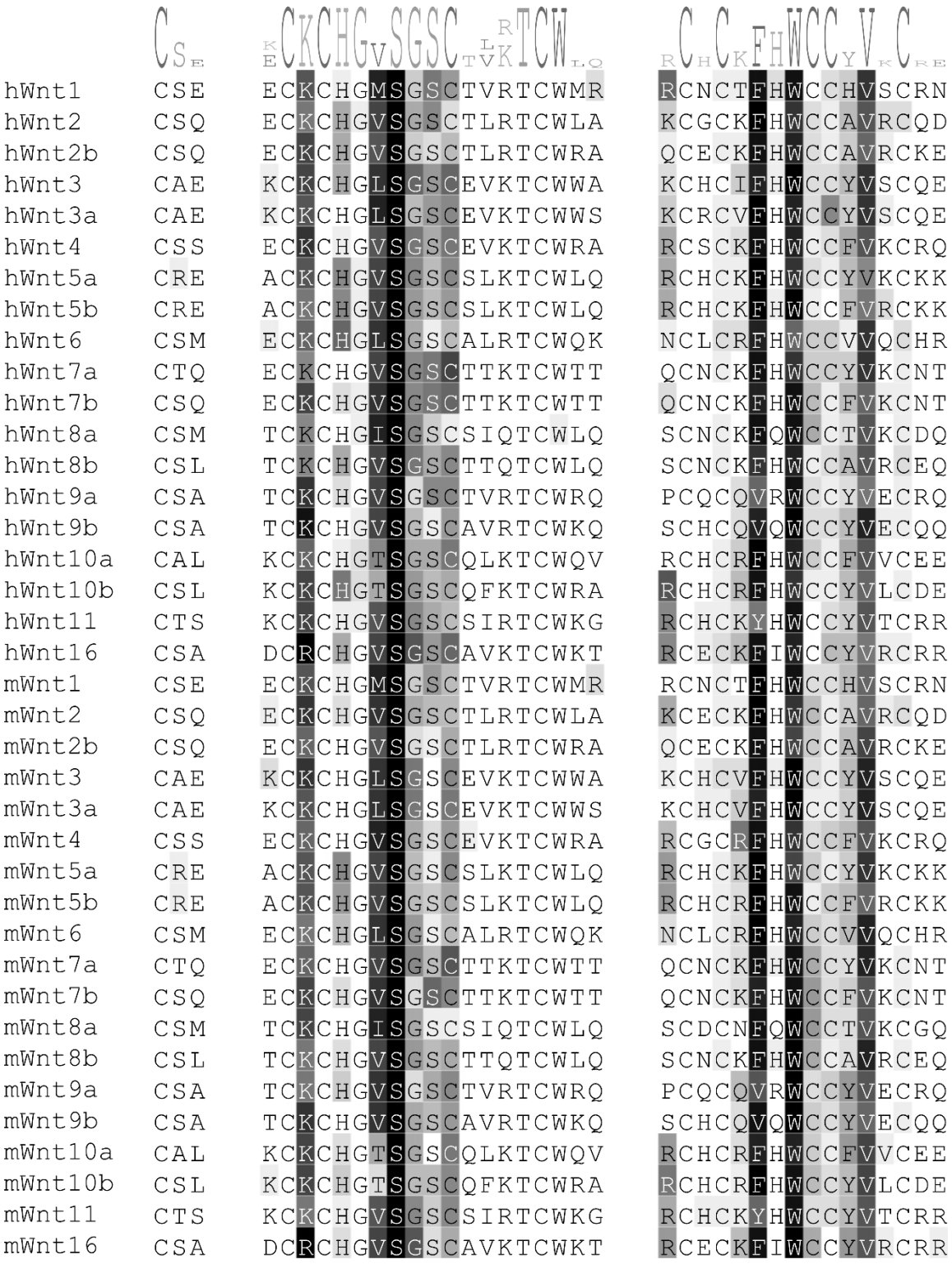
	hSFRP5	-5079.79	-32.47	-2.62	-100.10	-9.79	66.01	++
hWnt9a	hFzd1	-5226.24	-32.08	-4.96	-106.87	-9.52	104.12	+
	hFzd2	-5266.17	-34.35	-5.21	-109.00	-9.00	252.49	+
	hFzd3	-5345.14	-36.33	-3.53	-93.20	-10.05	42.26	++
	hFzd4	-5276.22	-35.40	-5.70	-110.43	-8.61	488.20	-
	hFzd5	-5463.04	-32.27	-6.48	-118.06	-9.45	117.22	+
	hFzd6	-5096.52	-32.76	-2.30	-98.23	-9.96	49.58	++
	hFzd7	-5207.88	-34.39	-6.49	-114.22	-8.19	989.57	-
	hFzd8	-5403.63	-32.28	-4.27	-109.33	-10.20	32.97	+++
	hFzd9	-5122.08	-32.37	-3.91	-107.44	-9.29	154.18	+
	hFzd10	-5141.55	-32.76	-3.44	-103.09	-9.61	89.81	++
	hSFRP1	-4940.84	-35.38	-2.63	-99.83	-8.62	479.93	-
	hSFRP2	-4763.78	-34.83	-3.46	-91.33	-8.28	841.16	-
	hSFRP3	-5144.42	-30.28	-4.75	-90.06	-10.51	19.74	+++
	hSFRP4	-5418.18	-35.43	-4.76	-112.75	-9.26	162.56	+
	hSFRP5	-4932.60	-33.90	-3.06	-102.32	-8.69	425.36	-
hWnt9b	hFzd1	-5032.20	-33.86	-4.06	-97.80	-9.05	229.10	+
	hFzd2	-5277.71	-34.65	-3.61	-104.98	-9.57	96.54	++
	hFzd3	-5089.16	-34.81	-0.98	-76.76	-10.87	10.73	+++
	hFzd4	-5322.72	-35.25	-5.15	-109.91	-8.98	259.62	+
	hFzd5	-5602.89	-30.54	-6.14	-116.11	-10.55	18.20	+++
	hFzd6	-4906.76	-34.68	-1.94	-81.51	-9.73	73.59	++
	hFzd7	-5075.64	-34.62	-5.29	-102.53	-8.51	575.01	-
	hFzd8	-5389.01	-31.76	-3.35	-101.29	-10.89	10.33	+++
	hFzd9	-5135.63	-32.52	-4.51	-108.10	-9.13	202.19	+
	hFzd10	-5222.85	-31.85	-3.32	-110.58	-9.78	67.09	++
	hSFRP1	-4822.03	-35.08	-4.88	-103.73	-7.48	3262.66	-
	hSFRP2	-5007.94	-35.19	-3.20	-103.17	-8.61	485.62	-
	hSFRP3	-5360.23	-32.51	-3.96	-90.27	-11.01	8.40	++++
	hSFRP4	-5462.27	-33.57	-2.13	-108.12	-10.72	13.68	+++
	hSFRP5	-4981.14	-36.20	-4.29	-116.35	-7.35	4054.56	-
hWnt10a	hFzd1	-5350.00	-34.35	-6.00	-87.29	-10.20	32.84	+++
	hFzd2	-5488.62	-32.08	-10.08	-98.81	-9.66	81.83	++

	hFzd3	-5316.43	-33.24	-2.58	-66.77	-12.19	1.14	++++
	hFzd4	-5751.67	-34.94	-4.41	-107.81	-10.97	8.97	++++
	hFzd5	-5622.01	-31.87	-5.93	-88.04	-11.78	2.29	++++
	hFzd6	-4926.90	-34.03	-2.92	-86.76	-9.45	118.23	+
	hFzd7	-5539.19	-33.57	-6.44	-96.58	-10.53	18.96	+++
	hFzd8	-5611.36	-31.94	-3.47	-102.76	-11.60	3.13	++++
	hFzd9	-5472.15	-32.84	-3.32	-107.26	-10.67	14.86	+++
	hFzd10	-5495.75	-32.60	-3.58	-100.63	-11.08	7.42	++++
	hSFRP1	-5293.27	-34.48	-4.61	-104.78	-9.43	121.59	+
	hSFRP2	-5280.93	-35.97	-4.70	-102.32	-9.15	196.10	+
	hSFRP3	-5773.46	-29.84	-6.06	-97.39	-12.32	0.93	++++
	hSFRP4	-5938.36	-35.00	-4.35	-114.18	-11.37	4.59	++++
	hSFRP5	-5455.90	-35.24	-3.64	-110.71	-9.82	62.86	++
hWnt10b	hFzd1	-5156.09	-31.78	-4.18	-78.20	-10.94	9.42	++++
	hFzd2	-5432.02	-33.40	-6.42	-93.09	-10.34	26.20	+++
	hFzd3	-5478.15	-36.71	-3.04	-77.63	-11.37	4.57	++++
	hFzd4	-5917.85	-34.48	-5.28	-120.27	-10.87	10.60	+++
	hFzd5	-5676.75	-31.71	-6.09	-101.07	-11.33	4.87	++++
	hFzd6	-5232.82	-32.98	-2.83	-95.10	-10.46	21.41	+++
	hFzd7	-5504.24	-33.04	-5.32	-94.52	-10.89	10.25	+++
	hFzd8	-5382.41	-32.36	-4.18	-99.98	-10.59	17.05	+++
	hFzd9	-5456.54	-32.73	-3.15	-101.70	-10.96	9.20	++++
	hFzd10	-5602.70	-32.92	-5.44	-111.51	-10.42	22.79	+++
	hSFRP1	-5093.64	-34.76	-5.55	-103.33	-8.44	640.96	-
	hSFRP2	-5376.60	-33.03	-5.89	-90.87	-10.45	21.58	+++
	hSFRP3	-5824.58	-29.93	-7.19	-104.13	-11.88	1.95	++++
	hSFRP4	-5725.59	-34.69	-3.76	-109.81	-10.99	8.71	++++
	hSFRP5	-5269.80	-36.90	-5.43	-105.92	-8.53	551.06	-
hWnt11	hFzd1	-5038.42	-33.32	-6.25	-86.02	-9.25	164.77	+
	hFzd2	-5277.48	-34.07	-6.51	-96.35	-9.41	124.77	+
	hFzd3	-5199.77	-34.20	-2.20	-70.39	-11.44	4.05	++++
	hFzd4	-5561.39	-34.84	-6.63	-112.28	-9.50	107.79	+
	hFzd5	-5602.22	-31.06	-4.55	-100.04	-11.63	2.97	++++

	hFzd6	-4661.44	-31.53	-1.28	-80.21	-9.72	73.79	++
	hFzd7	-5264.77	-34.64	-6.64	-89.54	-9.54	100.04	+
	hFzd8	-5317.07	-31.69	-3.94	-97.56	-10.67	14.92	+++
	hFzd9	-5182.88	-32.47	-4.55	-93.42	-10.04	43.35	++
	hFzd10	-5370.64	-32.92	-3.78	-128.57	-9.09	215.09	+
	hSFRP1	-5172.05	-34.62	-2.26	-95.80	-9.96	49.60	++
	hSFRP2	-5156.51	-33.11	-4.60	-115.43	-8.68	427.70	-
	hSFRP3	-5207.56	-31.70	-4.74	-80.97	-10.88	10.45	+++
	hSFRP4	-5541.09	-35.35	-2.66	-94.03	-11.19	6.17	++++
	hSFRP5	-5219.82	-32.66	-4.74	-107.78	-9.38	132.46	+
hWnt16	hFzd1	-5722.76	-34.52	-7.31	-110.03	-10.13	37.11	+++
	hFzd2	-5526.44	-35.27	-7.60	-109.87	-9.15	195.05	+
	hFzd3	-5794.42	-35.88	-3.62	-109.89	-11.01	8.35	++++
	hFzd4	-5600.05	-35.93	-5.84	-112.07	-9.61	90.16	++
	hFzd5	-5807.22	-33.05	-6.82	-97.45	-11.53	3.48	++++
	hFzd6	-5163.84	-35.34	-2.46	-97.02	-9.66	82.83	++
	hFzd7	-5548.70	-34.91	-10.33	-99.55	-9.16	191.75	+
	hFzd8	-5829.12	-32.14	-5.01	-114.55	-11.41	4.25	++++
	hFzd9	-5459.92	-31.16	-4.96	-110.29	-10.45	21.73	+++
	hFzd10	-5617.41	-35.51	-7.48	-116.93	-9.12	204.64	+
	hSFRP1	-5466.31	-35.94	-3.50	-119.39	-9.30	149.97	+
	hSFRP2	-5604.14	-33.89	-3.77	-122.98	-10.05	42.83	++
	hSFRP3	-5676.68	-31.49	-7.53	-97.87	-11.19	6.22	++++
	hSFRP4	-6026.34	-35.24	-5.29	-120.12	-11.12	6.97	++++
	hSFRP5	-5399.92	-33.03	-7.76	-117.60	-8.75	385.05	+

[a]ΔG is in kcal/mol and calculated according to Model 1: ΔG = 0.0038165 × AP_calRW – 0.22506 × MMGBSA dG Bind vdW – 0.24626 × HBOND2 – 0.049875 × FIREDOCK_AB – 3.3475. K_d is in nM and calculated according to the following equation: $K_d = e^{\frac{\Delta G}{RT}} \times 10^9$, where ΔG is the binding energy predicted by Model 1, R is the gas constant (1.987×10^{-3} kcal/(K mol)) and T is standard ambient temperature (298K). Approximate strength based on ranges defined by Dijksterhuis et al. (1): ++++, <10nM; +++, 10-40nM; ++, 40-100nM; +, 100-400nM; -, >400nM.

Figure S15. Involvement of Wnt residues in recognizing Fzd-type CRDs.[a]



[a]Wnt sequences abridged to the following three locations: cysteine 8 and its two immediately following residues, the Wnt thumb region and the Wnt index finger region. Intensity of shading indicates number of Wnt-Fzd CRD complexes involving the specified Wnt in which that residue is a significant contributor to the binding energy.

Figure S16. Involvement of Fzd-type CRD residues in recognizing Wnts.[a]

[a]Due to the involvement of selected residues approximately evenly distributed over the sequences, the entire Fzd CRD sequences are shown. Intensity of shading indicates number of Wnt-Fzd CRD complexes involving the specified Fzd CRD in which that residue is a significant contributor to the binding energy.

Reference

1. Dijksterhuis, J. P., Baljinnyam, B., Stanger, K., Sercan, H. O., Ji, Y., Andres, O., Rubin, J. S., Hannoush, R. N., and Schulte, G. (2015) Systematic mapping of WNT-FZD protein interactions reveals functional selectivity by distinct WNT-FZD pairs. *J. Biol. Chem.* **290**, 6789-6798