

Supplementary Table 1. Demographics and clinical characteristics of AIS patients

	AIS trios (n=40)	Sporadic AIS (n=183)	In-house controls (n=153)
Sex, n (%)			
Male	3 (7.5%)	21 (11.48%)	14 (9.15%)
Female	37 (92.5%)	162 (88.52%)	139 (90.85%)
Age of curve onset ^a , yrs, mean ± SD	12.48 ± 1.77	12.50 ± 1.74	12.76 ± 1.86
Age at menarche, yrs, mean ± SD	13.60 ± 0.50	13.18 ± 1.34	13.46 ± 1.52
Lenke classification, n (%)			
1	2 (5%)	21 (11.48%)	
2	20 (50%)	90 (49.18%)	
3	5 (12.5%)	23 (12.57%)	
4	5 (12.5%)	22 (12.02%)	
5	5 (12.5%)	24 (13.11%)	
6	3 (7.5%)	3 (1.64%)	
Spinal curve at first presentation, °, mean ± SD	18.18 ± 4.07	18.14 ± 4.06	
Body mass index, Kg/m ² , mean ± SD	21.88 ± 2.62	21.97 ± 2.52	22.53 ± 3.70

^aIn case of In-house controls, it means the age of individuals when enrolled.

Supplementary Table 2. Summary data and technical characters of exome sequencing data

Average Raw bases (Mb)	Average QC rates (%)	Average Target average read length	Average Total reads mapping rate (%)	Average Total bases mapping rate (%)	Average Target bases capture rate (%)	Average Target mean depth	Average Target covered mean depth	Average TC 10%X coverage rate (%)	Average Ti/Tv
11729.02	96.03	147	99.58	98.84	76.78	130.28	130.54	99.47	2.30

Supplementary Table 3. AIS-Associated genes

Gene Name	References	Animal model studies
Genes implicated in human idiopathic scoliosis		
<i>ABO</i>	PMID:30395268	NA
<i>AKAP2</i>	PMCID: PMC4941158	NA
<i>CALM1</i>	PMID:3914287	NA
<i>CDH13</i>	PMID:30395268	NA
<i>CHL1</i>	PMID:21216876	NA
<i>CNTNAP2</i>	PMID:21216876	NA
<i>COL11A2</i>	PMCID: PMC4690498	NA
<i>DSCAM</i>	PMID:21216876	NA
<i>ESR1</i>	PMIDs:12438984,16648749	NA
<i>ESR2</i>	PMID:19337134	NA
<i>FBN1</i>	PMID:24833718	NA
<i>FBN2</i>	PMID:24833718	NA
<i>GPER</i>	PMID:22002330	NA
<i>GPR126</i>	PMIDs:23666238 , 28198779	Spinal curvature in KO mouse
<i>IGF1</i>	PMID:23364988	NA
<i>IL6</i>	PMIDs:18007247,20675750	NA
<i>LBX1</i>	PMIDs:28334814 ,22019779	NA
<i>LBX1AS1</i>	PMCID: PMC4595747	NA
<i>MAPK7</i>	PMID:28714182	Curved body axis in MO zebrafish
<i>MATN1</i>	PMIDs:22193623,2986210, 24469715	NA
<i>PAX1</i>	PMID:25784220	NA
<i>POC5</i>	PMID:25642776	Curved body axis in MO zebrafish
<i>SLC39A8</i>	PMID:30301978	Curved body axis in MO zebrafish
<i>SOX6</i>	PMID:30395268	NA

<i>TIMP2</i>	PMID:21228746	NA
<i>TNFRSF11B(OPG)</i>	PMID:19705167	NA
<i>TPH1</i>	PMID:18794762	NA
<i>VDR</i>	PMID:2989276	NA
genes whose inactivation or mutation results in IS phenotype in mice or zebrafish		
<i>CCDC103</i>	PMIDs:22581229, 23796196	Curved body axis in MO zebrafish larvae
<i>CCDC151</i>	PMIDs: 27284198, 25192045	Curved body axis in MO zebrafish
<i>CCDC28B</i>	PMIDs: 23015189, 14676542	Curved and shortened body axis in MO zebrafish
<i>CCDC40</i>	PMIDs: 27284198, 21131974	Curved body axis in MO zebrafish
<i>C21ORF59</i>	PMID:27284198	Curved body axis in MO zebrafish
<i>CLUAP1</i>	PMID: 25348401	Kyphosis phenotype in KO mouse model
<i>DCDC2</i>	PMIDs: 25557784, 19066617	Curved body axis and kinky tail in MO zebrafish
<i>DNAAF3</i>	PMIDs:22387996, 23796196, 17449765, 8414746	Curved body axis in MO zebrafish
<i>DYX1C1</i>	PMIDs: 23650548, 23796196, 17449765, 8414746	Curved body axis in MO zebrafish larvae
<i>FLNB</i>	PMIDs:17360453,17635842,23979929, 24760772	Spinal curvature in KO mouse
<i>HSPB11</i>	PMID: 22205996	Curved body axis in MO zebrafish larvae
<i>IFT122</i>	PMID:20493458	Curved body axis in MO zebrafish larvae
<i>IFT172</i>	PMIDs: 19517571, 12637423, 23456818, 19361615	Curved body axis in MO zebrafish larvae
<i>IFT27</i>	PMID: 25446516	Spinal curvature in KO mouse
<i>IFT57</i>	PMID: 19517571	Curved body axis in MO zebrafish larvae
<i>IFT80</i>	PMID: 17468754	Curved body axis in MO zebrafish larvae
<i>IFT88</i>	PMID: 19517571	Curved body axis in MO zebrafish larvae
<i>KIF3B</i>	PMIDs: 22308397, 19384852	Curved body axis in MO zebrafish larvae
<i>KIF6</i>	PMID:25283277	Curved body axis in MO zebrafish

<i>OFD1</i>	PMID:18971206	Curved body axis in MO zebrafish larvae
<i>PCMI</i>	PMID: 22767577	urved body axis in MO zebrafish larvae
<i>PTK7</i>	PMIDs: 27284198, 25182715	Curved body axis in MO zebrafish
<i>RP2</i>	PMIDs: 16770799, 21282572	Slight to sever curved tail in MO zebrafish larvae
<i>RPGR</i>	PMIDs: 16770799, 22927466	Curved body axis in MO zebrafish larvae
<i>RPGRIP1L</i>	PMIDs: 20301500, 15473174, 22927466, 19955120	Curved tail in MO zebrafish larvae
<i>SDCCAG8</i>	PMIDs: 20835237, 14676542	Curved and shortened body axis in MO zebrafish larvae
<i>TTC26</i>	PMID: 22718903	Curved body axis in MO zebrafish larvae
<i>TLL3</i>	PMID: 21262966	Curved body axis in MO zebrafish larvae
<i>TLL6</i>	PMID: 25446516	Curved body axis in MO zebrafish larvae
<i>ZMYND10</i>	PMID:30420648	Curved body axis in MO zebrafish larvae

Supplementary Table 4. Rare-damaging variants identified in AIS trios

Gene	Chr: position (hg 19)	Variant	Consequence	Max freq ^a	Case
<i>FLNB</i>	3:58090892	c.C1696T	p.R566W	N	Trio 25
	3:58090893	c.G1697T	p.R566L	N	Trio 22
	3:58090941	c.T1745C	p.L582P	N	Trio 31
	3:58109123	c.G3430C	p.E1144Q	7.21E-03	Trio 32
	3:58141758	c.G6844A	p.A2282T	N	Trio 27
<i>CNTNAP2</i>	7:146536932	c.A338G	p.Y113C	7.42E-04	Trio 3
	7:146829467	c.A1214G	p.N405S	N	Trio 5
	7:147092836	c.C1634T	p.A545V	3.18E-04	Trio 12
	7:147259289	c.T1837C	p.W613R	N	Trio 20
<i>COL11A2</i>	6:33156921	c.C277T	p.R93C	N	Trio 32
<i>DSCAM</i>	21:42080556	c.C185T	p.T62M	N	Trio 36
<i>FBN2</i>	5:127610373	c.C7597T	p.L2533F	N	Trio 20
	5:127613686	c.T7357A	p.C2453S	N	Trio 4
	5:127674703	c.G3394A	p.V1132I	3.71E-04	Trio 6
	5:127685149	c.A2879G	p.E960G	N	Trio 10
<i>FBN1</i>	15:48779517	c.C3455T	p.A1152V	N	Trio 38
	15:48826346	c.A793G	p.T265A	N	Trio 15
<i>MAPK7</i>	17:19284408	c.G469A	p.A157T	6.90E-03	Trio 3
<i>VDR</i>	12:48258951	c.G156T	p.M52I	1.00E-03	Trio 14
<i>IFT122</i>	3:129159200	c.T27G	p.D9E	4.88E-04	Trio 1
	3:129202460	c.G1453A	p.G485S	1.00E-03	Trio 31
	3:129233378	c.A2804C	p.K935T	N	Trio 40
	3:129238472	c.G3203A	p.R1068H	8.38E-03	Trio 29
<i>IFT88</i>	13:21173662	c.G713A	p.R238Q	2.68E-03	Trio 26
<i>PTK7</i>	6:43109815	c.C1525T	p.P509S	3.18E-04	Trio 32
	6:43111200	c.C1703G	p.P568R	6.00E-03	Trio 25
	6:43112233	c.G1906C	p.E636Q	3.00E-03	Trio 35
	6:43112285	c.A1958G	p.H653R	2.00E-03	Trio 7
<i>RPGRIP1L</i>	16:53683024	c.C2156G	p.T719R	N	Trio 4

	16:53706849	c.G962A	p.R321H	1.53E-03	Trio 11
<i>SDCCAG8</i>	1:243507569	c.A1115G	p.E372G	9.43E-03	Trio 17
<i>TTC26</i>	7:138822599	c.C148T	p.R50C	8.76E-03	Trio 27
	7:138849974	c.C889T	p.R297C	6.09E-03	Trio 22
	7:138862965	c.A1075G	p.I359V	2.12E-04	Trio 9
	7:138865921	c.C1396T	p.L466F	N	Trio 24
<i>TTL3</i>	3:9868810	c.T1433G	p.F478C	N	Trio 36
<i>SLC39A8</i>	4:103189063	c.A813G	p.I271M	1.00E-03	Trio 38
<i>SOX6</i>	11:16208472	c.C565T	p.R189W	5.80E-05	Trio 34
<i>KIF6</i>	6:39311541	c.C725T	p.T242M	3.00E-04	Trio 2
<i>KIF6</i>	6:39602700	c.A434G	p.Y145C	N	Trio 8

^aMaximum frequency across public databases: 1000 Genomes Project phase 3; GnomAD, Genome Aggregation Database; and NHLBI Exome Sequencing Project databases; N: absence in any database

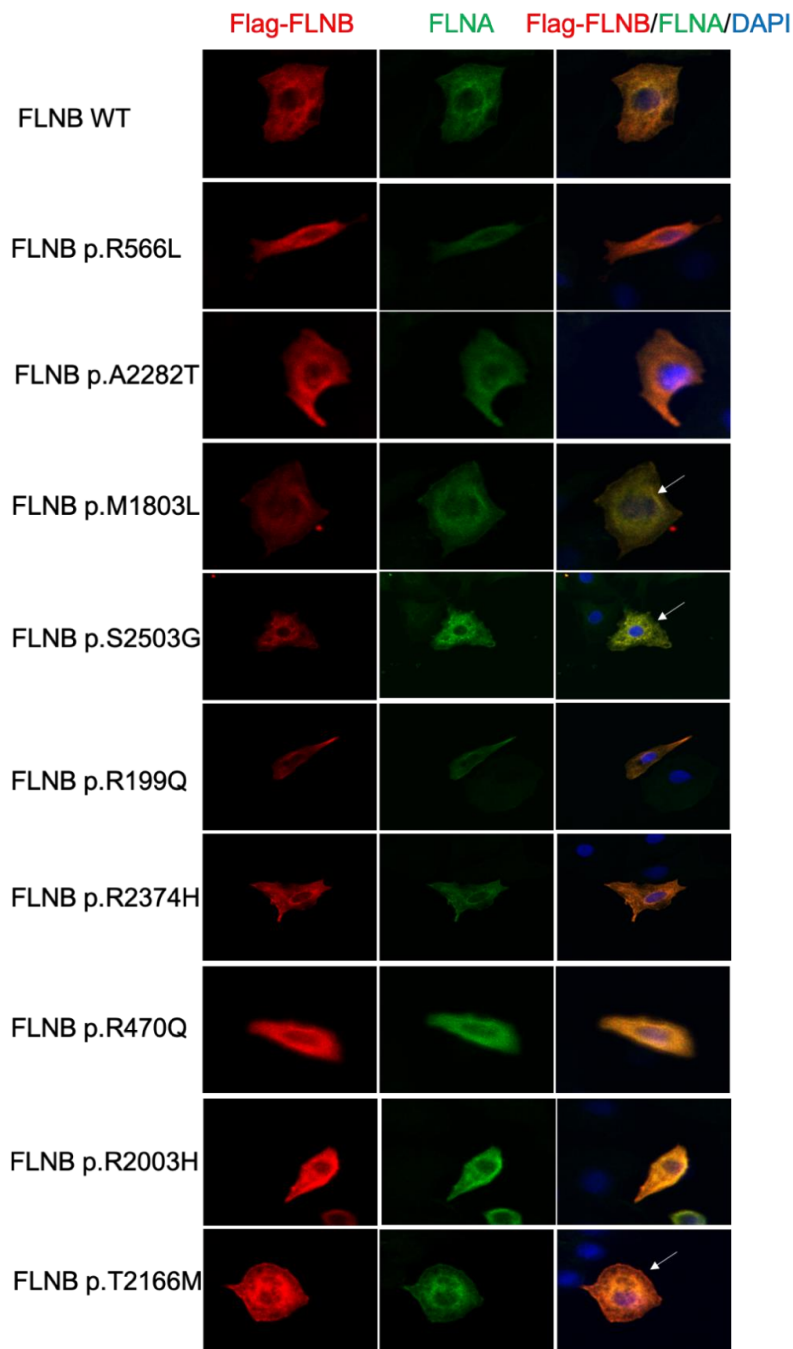
Supplementary Table 5. Rare damaging variant profile for AIS patients with two or more mutations of AIS-Associated genes

Sample ID	AIS-Associated genes	Sex	Spinal curve at first presentation, °	Body mass index (Kg/m ²)	Age at menarche (yrs)	Age of curve onset (yrs)
Trio-3	<i>CNTNAP2, MAPK7</i>	F	20	24.73	14	13
Trio-4	<i>FBN2, RPGRIPL</i>	F	30	20.90	14	14
Trio-22	<i>FLNB, TTC26</i>	F	26	19.99	11	11
Trio-25	<i>FLNB, PTK7</i>	M	23	22.71	10	12
Trio-27	<i>FLNB, TTC26</i>	F	28	19.56	12	13
Trio-31	<i>FLNB, IFT122</i>	F	25	24.67	15	15
Trio-32	<i>FLNB, COL11A2, PTK7</i>	F	28	27.78	15	12
Trio-38	<i>FBN1, SLC39A8</i>	F	31	22.68	13	11
24-11	<i>PCMI, PTK7</i>	F	18	20.02	13	12
59-1	<i>IFT88, CHL1, FLNB, PTK7</i>	F	24	18.20	14	11
59-2	<i>FLNB, TTLL3</i>	F	22	20.09	15	14
59-9	<i>IFT88, CHL1</i>	F	32	19.89	13	11
59-10	<i>FLNB, TTC26</i>	F	26	20.44	10	12
59-13	<i>IFT88, FBN1, IFT172</i>	F	34	19.52	15	12
59-15	<i>TTC26, ZMYND10</i>	F	30	25.62	14	12
59-16	<i>DSCAM, TTC26</i>	M	17	17.27	11	12
59-17	<i>MAPK7, FBN2</i>	F	29	21.43	12	10
59-19	<i>TPHI, CNTNAP2</i>	F	28	22.67	12	12
59-21	<i>HSPB11, FBN1, CHL1</i>	F	31	23.67	13	13
98-1	<i>ESR2, POC5, FLNB</i>	F	28	20.93	13	11
98-3	<i>POC5, IFT80</i>	F	24	23.56	15	12
98-4	<i>FLNB, IFT27</i>	M	22	18.86	10	12
98-7	<i>FBN1, FLNB, TTLL3</i>	F	30	17.12	10	11
98-9	<i>IFT172, PCMI</i>	F	27	17.10	13	12

98-10	<i>TLL3, TLL6</i>	F	24	24.04	12	11
98-13	<i>FLNB, PTK7</i>	F	22	19.27	13	10
98-16	<i>CLUAP1, FLNB</i>	F	30	17.71	11	12
98-20	<i>FBN2, IFT88</i>	F	27	17.45	14	10
98-21	<i>TLL3, TLL6</i>	F	25	18.29	14	14
98-24	<i>TTC26, SOX6</i>	F	13	23.81	14	14
98-36	<i>CNTNAP2, TTC26</i>	F	30	23.13	10	12
98-46	<i>CNTNAP2, DSCAM</i>	F	24	19.54	14	13
98-73	<i>FLNB, OFD1</i>	F	21	17.32	12	13
43-5	<i>SOX6, CLUPI</i>	F	27	20.13	12	12
43-13	<i>AKAP2, CHL1</i>	M	22	18.86	13	11
43-29	<i>FBN2, IFT88</i>	F	30	22.13	10	10
43-36	<i>SOX6, FLNB, TTC26</i>	F	31	19.07	10	11

Supplementary Table 6. *FLNB*-interacting partners with significant burden of rare-damaging variants

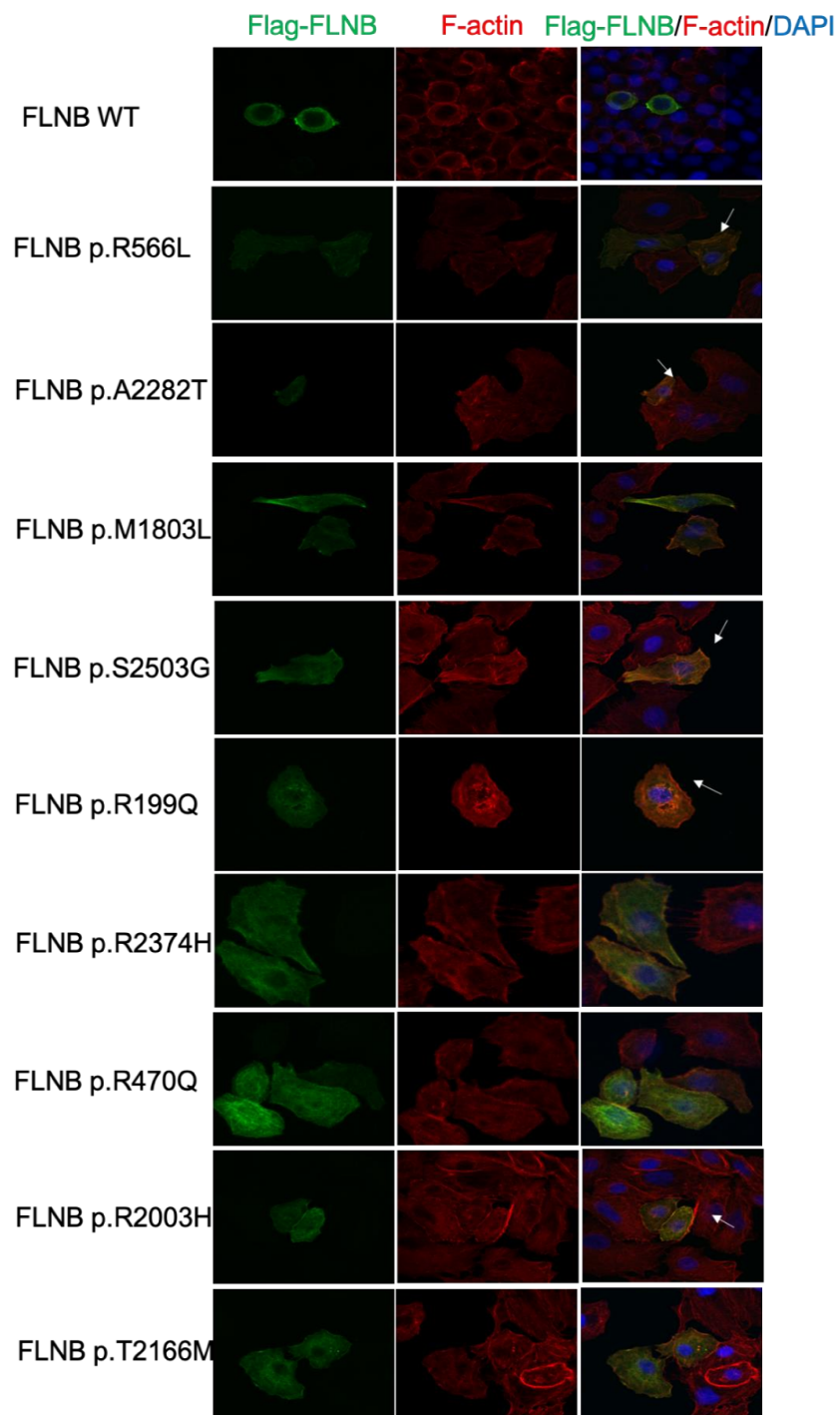
Gene	Other <i>FLNB</i> -interacting partners	Count		OR (95% CI)	<i>p</i>
		Cases	Controls		
<i>FLNA</i>	<i>ASB2, KCNJ2, PDLIM2, FBLIM1, HACE1, GPIBA, IFGB6</i>	6	0	12.073(1.476-98.783)	2.58E-03
<i>ITGB6</i>	<i>FLNA</i>	6	1	10.341(1.237-86.463)	1.24E-02



Supplementary Figure 1. Subcellular localization and expression is affected in some

FLNB variants

293T cells were transfected with Flag-tagged *FLNB* expression vector (wildtype or mutant). Protein expression of each variant and wild-type *FLNB* was assessed with a Flag antibody (red). Nuclear counter-staining was performed with DAPI (blue) and protein expression of *FLNA* was stained with a FLNA antibody (green).



Supplementary Figure 2. Actin stress fiber formation is affected in some *FLNB* variants

293T cells were transfected with Flag-tagged *FLNB* expression vector (wildtype or mutant). Protein expression of each variant and wild-type *FLNB* was assessed with a Flag antibody (green). Nuclear counter-staining was performed with DAPI (blue) and stress fiber was stained with DyLight™ 554 Phalloidin (red).

Supplementary Table 7. Rare-damaging variants Gene-Based Burden Tests for AIS-Related Genes (In-house controls only)

Rank	Gene	Count of Rare-damaging Variants		Frequency of Rare-damaging Variants in AIS subjects	Frequency of Rare-damaging Variants in controls subjects	OR (95% CI) (AIS versus controls)	p Value (AIS versus controls)
		AIS (n=223)	Controls ^a (n=153)				
1	<i>FLNB</i>	25	3	11.21%	1.96%	6.313 (1.871-21.303)	5.15E-04
2	<i>TTC26</i>	16	2	7.17%	1.31%	5.836 (1.322-25.761)	1.18E-02
3	<i>CNTNAP2</i>	8	0	3.59%	0	6.417 (0.805-51.172)	2.34E-02
4	<i>FBN1</i>	8	0	3.59%	0	6.417 (0.805-51.172)	2.34E-02
5	<i>TLL3</i>	8	0	3.59%	0	6.417 (0.805-51.172)	2.34E-02
6	<i>PTK7</i>	11	1	4.93%	0.65%	7.887 (1.008-61.737)	3.20E-02
7	<i>IFT122</i>	6	0	2.69%	0	4.945 (0.602-40.601)	8.50E-02
8	<i>FBN2</i>	8	4	3.59%	2.61%	1.386 (0.410-4.687)	7.68E-01

^aonly in-house controls (n=153) was included in gene-based burden tests here

p value is calculated using Fisher's exact test. CI, confidence interval, OR, odds ratio

