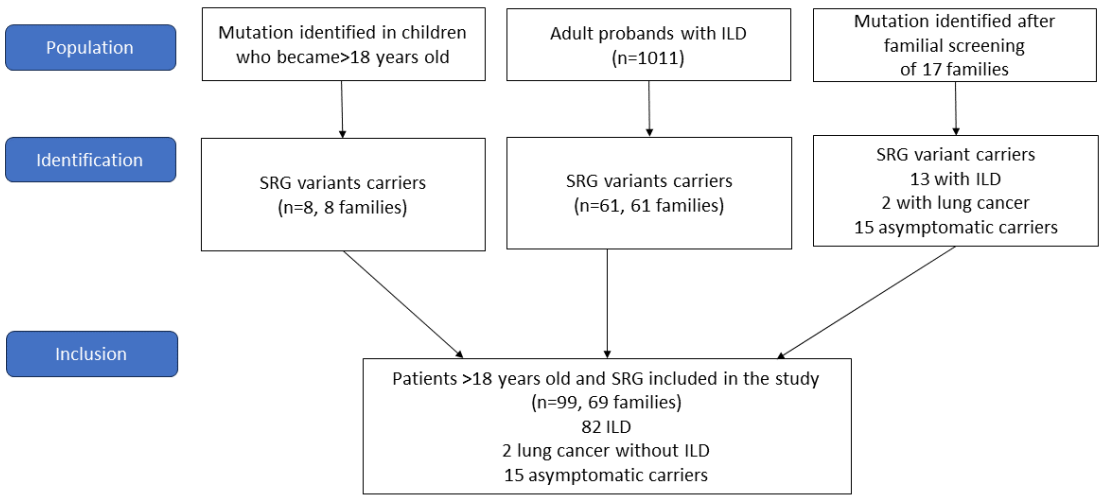
High risk of lung cancer in surfactant-related gene mutation carriers

Supplementary materials

Figure legends

Figure S1 Flow chart of the study. ILD interstitial lung disease, SRG surfactant-related gene



Methods

Each tumor underwent molecular diagnosis with one formalin-fixed parrafin-embedded sample (from 6 sections of 5 µm or 4 sections of 10 µm on slides when macrodissections were necessary) sent to the molecular laboratory to extract DNA and perform molecular analyses. DNA were extracted following standard protocol Maxwell 16 FFPE Plus LEV DNA purification kit. DNA was dosed with a Qubit 2.0 fluorometer (Thermo Fisher Scientific, Waltham, MA, USA). Next-generation sequencing (NGS) analysis was performed on a 20-ng tumor sample of DNA [Oncomine Tumor solid DNA kit (OST panel) and complementary panel (OST+V3), Thermo Fisher Scientific, San Francisco, CA, US] to detect variants on selected regions of 31 genes (*AKT1; ALK; BRAF; CTNNB1; DDR2; EGFR; ERBB2; ERBB4; FBXW7; FGFR1; FGFR2; FGFR3; HRAS; KEAP1;KIT; KRAS; MAP2K1; MET; NRAS; NOTCH1; PDGFRA; PIK3CA; POLE; POLD1; PTEN; RET; ROS1; SMAD4; STK11; TP53; TERT* (promoter). Sequences

were aligned to the hg19 human reference genome and data were analyzed by variant calling using the Torrent suit software (Thermo Fisher Scientific) and Ion reporter software for annotations of variants (Thermo Fisher Scientific). Potential mutations were retained if allelic frequency was ≥ 2% and the coverage was > 300X.

Table S1 Surfactant-related gene mutations

Patients N°	Family N°	Mutation	Mutation type (ACMG class[§])	Genotype	Genomic coordinate (GrCh37)	gnomAD v4.0 allele frequency	Conservation in 100 vertebrates (UCSC)	SpliceAI prediction	First report of the mutation	Patient previously reported
SFTPA1 (n=18) NM_005411.5)										
5	3	p.(Trp211Arg) c.631T>C	Missense (5)	Heterozygote	10:81373753T>C	0	High	No effect	[1]	[1, 2]
6	3	p.(Trp211Arg) c.631T>C	Missense (5)	Heterozygote	10:81373753T>C	0	High	No effect	[1]	[1, 2]
7	3	p.(Trp211Arg) c.631T>C	Missense (5)	Heterozygote	10:81373753T>C	0	High	No effect	[1]	[1, 2]
8‡	3	p.(Trp211Arg) c.631T>C	Missense (5)	Heterozygote	10:81373753T>C	0	High	No effect	[1]	[1, 2]
9‡	3	p.(Trp211Arg) c.631T>C	Missense (5)	Heterozygote	10:81373753T>C	0	High	No effect	[1]	[1, 2]
10‡	3	p.(Trp211Arg) c.631T>C	Missense (5)	Heterozygote	10:81373753T>C	0	High	No effect	[1]	[1–3]
11‡	3	p.(Trp211Arg) c.631T>C	Missense (5)	Heterozygote	10:81373753T>C	0	High	No effect	[1]	[1–3]
12	3	p.(Trp211Arg) c.631T>C	Missense (5)	Heterozygote	10:81373753T>C	0	High	No effect	[1]	[1–3]
13‡	4	p.(Val178Met) c.532G>A	Missense (5)	Heterozygote	10:81373654G>A	18/1461640	High	No effect	[4]#	[1, 2]
14	5	p.(Val225Met) c.673G>A	Missense (5)	Heterozygote	10:81373795G>A	0	High	No effect	[2]	[2, 3]
15	6	p.(Asn171Lys) c.513T>G	Missense (4)	Heterozygote	10:81373635T>G	0	High	No effect	[3]	[3]
16	7	p.(Tyr186Ser) c.557 A>C	Missense (4)	Heterozygote	10:81373679A>C	0	High	No effect		
17‡	7	p.(Tyr186Ser) c.557 A>C	Missense (4)	Heterozygote	10:81373679A>C	0	High	No effect		
19	9	p.(Val225Met) c.673G>A	Missense (5)	Heterozygote	10:81373795G>A	0	High	No effect	[2]	
20	9	p.(Val225Met) c.673G>A	Missense (5)	Heterozygote	10:81373795G>A	0	High	No effect	[2]	
21	10	p.(Gly231Glu) c.692G>A	Missense (4)	Heterozygote	10:81373814G>A	0	High	No effect		
23‡	12	p.(Val178Met) c.532G>A	Missense (5)	Heterozygote	10:81373654G>A	18/1461640	High	No effect	[4]#	
35	15	p.(Tyr186His)	Missense (4)	Heterozygote	10:81373678T>C	0	High	No effect		
SFTPA2 n=31 (NM_001098668.4)										

1	1	p.(Val178Met) c.532G>A	Missense (5)	Heterozygote	10:81317180C>T	45/1613790	High	No effect	[5]	[2]
2‡	1	p.(Val178Met) c.532G>A	Missense (5)	Heterozygote (de novo)	10:81317180C>T	45/1613790	High	No effect	[5]	[2]
3	2	p.(Val178Met) c.532G>A	Missense (5)	Heterozygote	10:81317180C>T	45/1613790	High	No effect	[5]	[2, 3]
4	2	p.(Val178Met) c.532G>A	Missense (5)	Heterozygote	10:81317180C>T	45/1613790	High	No effect	[5]	[2]
18	8	p.(Arg242Gln) c.725G>A	Missense (5)	Heterozygote	10:81316987C>T	8/1461878	High	No effect	[2]	[2, 3]
22‡	11	p.(Trp233Cys) c.699G>C	Missense (5)	Heterozygote	10:81317013C>G	0	High	No effect	[2]	[2]
24	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3] ##	
25	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3] ##	
26	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3] ##	[3]
27	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3]##	
28	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3] ##	
29	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3] ##	
30	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3] ##	
31	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3] ##	[3]
32	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3] ##	
33	13	p.(Tyr228Cys) c.683A>G	Missense (5)	Heterozygote	10:81317029T>C	0	High	No effect	[3] ##	
34	14	p.(Cys238Ser) c.713G>C	Missense (5)	Heterozygote	10:81316999C>G	0	High	No effect	[2]	
36‡	16	p.(Cys238Ser) c.713G>C	Missense (5)	Heterozygote	10:81316999C>G	0	High	No effect	[2]	[2, 3]
37	16	p.(Cys238Ser) c.713G>C	Missense (5)	Heterozygote	10:81316999C>G	0	High	No effect	[2]	[2]
38‡	17	p.(Val178Met) c.532G>A	Missense (5)	Heterozygote	10:81317180C>T	45/1613790	High	No effect	[5]	
39‡	17	p.(Val178Met) c.532G>A	Missense (5)	Heterozygote	10:81317180C>T	45/1613790	High	No effect	[5]	
40‡	18	p.(Trp233Arg) c.697T>A	Missense (5)	Heterozygote	10:81317015A>T	0	High	No effect	[2]	[2]

41	18	p.(Trp233Arg) c.697T>A	Missense (5)	Heterozygote	10:81316999C>G	0	High	No effect	[2]	[2]
42	19	p.(Cys238Ser) c.713G>C	Missense (5)	Heterozygote	10:81316999C>G	0	High	No effect	[2]	[2]
43	20	p.(Arg242Gln) c.725G>A	Missense (5)	Heterozygote	10:81316987C>T	8/1461878	High	No effect	[2]	[2, 3]
44	21	p.(Tyr181Cys) c.542A>G	Missense (5)	Heterozygote	10:81317170T>C	28/1461686	High	No effect	[2]	[2]
45	22	p.(Cys238Ser) c.713G>C	Missense (5)	Heterozygote	10:81316999C>G	0	High	No effect	[2]	
46	23	p.(Asn171Ile) c.512A>T	Missense (5)	Heterozygote	10:81317200T>A	0	High	No effect	[2]	[2]
47‡	24	p.(Trp233Leu) c.698G>T	Missense (5)	Heterozygote	10:81317014C>A	0	High	No effect	[2]	[2]
48	24	p.(Trp233Leu) c.698G>T	Missense (5)	Heterozygote	10:81316999C>G	0	High	No effect	[2]	[2, 3]
101	17	p.(Val178Met) c.532G>A	Missense (5)	Heterozygote	10:81317180C>T	45/1613790	High	No effect	[5]	
SFTPC n=24 (NM_001317778.2)										
57	32	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote (de novo)	8:22020609T>C	4/1461844	Partial	No effect	[6]	
58	33	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	
59	33	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	
60‡	34	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	
61	34	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[7]	
62	35	p.(Val102Met) c.304G>A	Missense (4)	Heterozygote	8:22020695G>A	4/1461868	Partial	No effect	[7]	[3]
64	37	p.(Val39Ala) c.116T>C	Missense (4)	Heterozygote	8:22020160T>C	0	Partial	No effect	[8]	[8, 9]
65‡	38	p. (Leu188Pro) c.563T>C	Missense (5)	Heterozygote	8:22021541T>C	0	Partial	No effect	[8]	[3, 9]
72‡	45	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	
77	49	p.(Ile96_Ser98del) c.287_295del	Inframe deletion (4)	Heterozygote	8:22020678_22020686del	0	High			
78	49	p.(Ile96_Ser98del) c.287_295del	Inframe deletion (4)	Heterozygote	8:22020678_22020686del	0	High			
79	51	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	[3]
80	52	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	
81	53	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	
82	54	p.(Leu188Pro) c.563T>C	Missense (5)	Heterozygote	8:22021541T>C	0	Partial (high in	No effect	[8]	[3]

							eutherians)			
83	54	p.(Leu188Pro) c.563T>C	Missense (5)	Heterozygote	8:22021541T>C	0	Partial (high in eutherians)	No effect	[8]	
84	54	p.(Leu188Pro) c.563T>C	Missense (5)	Heterozygote	8:22021541T>C	0	Partial (high in eutherians)	No effect	[8]	
85	55	p.(Tyr113Cys) c.338A>G	Missense (4)	Heterozygote	8:22020962A>G	0	High	No effect	[10]	[3]
86	55	p.(Tyr113Cys) c.338A>G	Missense (4)	Heterozygote	8:22020962A>G	0	High	No effect	[10]	[3]
87	55	p.(Tyr113Cys) c.338A>G	Missense (4)	Heterozygote	8:22020962A>G	0	High	No effect	[10]	[3]
88	56	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	[3]
89	57	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	
90	58	p.(Ile73Thr) c.218T>C	Missense (5)	Heterozygote	8:22020609T>C	4/1461844	Partial	No effect	[6]	
91	59	p.(Ser153Leufs*27) c.456del	Frameshift (4)	Heterozygote	8:22021434del	0				
ABCA3 n=14 (NM_001089.3)										
66	39	p.(Asp253His) c.757G>C	Missense (4)	Homozygote	16:2369698C>G	1/1461794	High	No effect	[11]	[11]
67	40	p.(Glu292Val) c.875A>T p.(Glu690Lys) c.2068G>A	Missense, hypomorphic (5) Missense (5)	Heterozygote[§§] Heterozygote[§§]	16:2367764T>A 16:2347525C>T	7316/1613934 4/1460336	High High	No effect No effect	[12] [12]	
68	41	p.(Gly974Asp) c.2921_2922delinsAC p.(Ala1027Pro) c.3079G>C	Missense (3) Missense (5)	Homozygote (isodisomy)	16:2338109_2338110delinsGT 16:2336894C>G	0 0	Low Low	No effect No effect	 [11]	
69	42	p.(Arg280Cys) c.838C>T p.? c.4984-2A>C	Missense (5) Splice (4)	Heterozygote[§§] Heterozygote[§§]	16:2369617G>A 16:2326808T>G	364/1613144 0	High NR	No effect Acceptor loss (0.99)	[13]	
70	43	p.(Val1495Cysfs*21) c.4483_4507del p.(Glu292Val) c.875A>T	Frameshift (5) Missense, hypomorphic (5)	Heterozygote[§§] Heterozygote[§§]	16:2328984_2329008del 16:2367764T>A	9/1613482 7316/1613934	NR High	No effect No effect	[14] [12]	
71	44	p.(Gly1413Ser) c.4237G>A p.(Arg1482Trp)	Missense (4) Missense (5)	Heterozygote[§§] Heterozygote[§§]	16:2331150C>T 16:2329047G>A	26/1613714 8/1461044	High High	No effect No effect	 [12]	

		c.4444C>T								
92	61	p.(Glu1625*) c.4873G>T p.(Glu292Val) c.875A>T	Nonsense (4) Missense, hypomorphic (5)	Heterozygote Heterozygote	16:2327916C>A 16:2367764T>A	0 7316/1613934	NR High	No effect No effect	 [12]	
93	62	p.(Arg20Trp) c.58C>T p.(Ile1569del) c.4706_4708del	Missense (4) Inframe deletion (5)	Heterozygote[§§] Heterozygote[§§]	16:2376272G>A 16:2328299_2328301del	178/1612822 2/1456192	High Partial	No effect No effect	 [15]	
94	63	p.? c.2414+1G>C p.(Glu292Val) c.875A>T	Splice (4) Missense, hypomorphic (5)	Heterozygote[§§] Heterozygote[§§]	16:2345584G>C 16:2367764T>A	0 7316/1613934	NR High	No effect No effect	 [12]	
95	64	p.(Glu292Val) c.875A>T p.(Ser1028Valfs*103) c.3081_3092delinsCG	Missense, hypomorphic (5) Frameshift (4)	Heterozygote Heterozygote	16:2367764T>A 16:2336881_2336892delinsCG	7316/1613934 0	High NR	No effect No effect	[12] [16]	[16]
96	65	p.(Arg43Cys) c.127C>T p.(Gly1002Ser) c.3004G>A	Missense (4) Missense/Splice (4)	Heterozygote[§§] Heterozygote[§§]	16:2376203G>A 16:2338027C>T	7/1613992 4/1452718	High High	No effect Creation of a weak donor site	[17] [18]	[18]
97	66	p.(Phe116Ser) c.347T>C p.(Arg280Cys) c.838C>T	Missense (4) Missense (5)	Heterozygote[§§] Heterozygote[§§]	16:2374505A>G 16:2369617G>A	0 364/1613144	High High	No effect No effect	[17] [12]	[18]
98	67	p.(Thr1173Arg) c.3518C>G	Missense (4)	Homozygote[§§]	16:2334965G>C	0	Partial	No effect	[11]	[11]
99	68	p.(Gly964Ser) c.2890G>A p.(Arg1482Trp) c.4444C>T	Missense (5) Missense (5)	Heterozygote[§§] Heterozygote[§§]	16:2338141C>T 16:2329047G>A	7/1612054 8/1461044	High High	No effect No effect	[11] [13]	[18–20]
NKX2-1 (n=12) (NM_001079668)										
49	25	p.? c.463+2T>C	Splice (4)	Heterozygote (de novo)	14:36988188A>G	0	NR	Donor loss	[21]	[22]
50	26	p.(Trp238*) c.714G>A	Nonsense (5)	Heterozygote	14:36986975C>T	0	NR		[22]	[22]
51	69	p.(Arg191Leu) c.572G>T	Missense (4)	Heterozygote	14:36987117C>A	0	High	Creation of a weak acceptor site	[23]	[22]
52	69	p.(Arg191Leu) c.572G>T	Missense (4)	Heterozygote	14:36987117C>A	2/1608866	High	Creation of a weak acceptor site	[23]	[22]

53	27	p.(Gln317*) c.949C>T	Nonsense (4)	Heterozygote	14:36986740G>A	0	NR		[24]	[24]
54‡	28	p.(His90Alafs*349) c.267dup	Frameshift (4)	Heterozygote (de novo)	14:36988386dup	0	NR		[22]	[22, 25]
55	29	p.(Met59Glyfs*379) c.175_176del	Frameshift (4)	Heterozygote	14:36988477_36988478del	0	NR		[22]	[22]
56	30	p.(Gln317Alafs*121) c.948_954delinsAGCAC	Frameshift (4)	Heterozygote	14:36986735_36986741delinsGTGCT	0	NR			[22]
73	46	p.(Val374Tyrfs*7) c.1120del	Frameshift (4)	Heterozygote	14:36986569del	0	NR			
74	47	p.(Ser163Argfs*3) c.489del	Frameshift (4)	Heterozygote	14:3698200del	0	NR		[26]	
75‡	48	p.(Gly171Glufs*276) c.512_576del	Frameshift (4)	Heterozygote	14:36987115_36987179del	0	NR			
76	48	p.(Gly171Glufs*276) c.512_576del	Frameshift (4)	Heterozygote	14:36987115_36987179del	0	NR			

§: 4: likely pathogenic, 5: pathogenic; §§: homozygosity or compound heterozygosity was checked in parents; #: same variant reported in *SFTPA2* [5]; ##: personal data; NR: not relevant. ‡ and highlighted in grey patients with lung cancer

Table S2 Factors associated with lung cancer in surfactant-related gene (SRG) variant carriers

	No lung cancer	Lung cancer	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*p*	OR (95% CI)	*p*
Patients	79	20				
Age at diagnosis	37.5 (28.9-47.9)	48.70 (42.5- 53.3)	1.04 (1.01-1.08)	**0.029**	0.98 (0.91-1.05)	0.59
Male sex	41 (51.9)	11 (55)	1.13 (0.42-3.10)	0.80	ND	-
Mutated SRG gene						
SFTPA2	23(29.1)	8 (40.0)	Ref	Ref	Ref	Ref
SFTPA1	11 (13.9)	7 (35.0)	1.83 (0.52-6.44)		0.78 (0.06-8.72)	0.84
NKX2-1	10 (12.6)	2 (10.0)	0.57 (0.08-2.83)		0.43 (0.01-9.92)	0.61
ABCA3	14 (17.7)	0	ND		ND	
SFTPC	21 (26.6)	3 (15.0)	0.41 (0.08-1.63)		0.10 (0.01-0.94)	0.05
Smoking	10 (12.7)	15 (75)	20.7 (6.60-76.2)	**<0.001**	60.7 (9.23-834)	**<0.001**
Environmental exposure	6 (7.6)	2 (10)	1.35 (0.19-6.45)	0.72	-	-
Antifibrotic treatment, n (%)	4 (5.1)	7 (35)	10.1 (2.68-43.4)	**<0.001**	ND	
Lung transplantation, n(%)	22 (27.8)	4 (20)	0.65 (0.17-2.00)	0.48	ND	
FVC (%)	62 [51.5-77]	65 (53-84)	1.01 [0.99-1.04]	0.31	0.98 (0.92-1.04)	0.42
DLCO (%)	37.0 (28-57.5)	44.5 (32.2-64)	1.01 [0.98-1.04]	0.45	1.03 (0.97-1.11)	0.91

FVC forced viral capacity, DLCO diffusing capacity of the lungs for carbon monoxide

Table S3 Oncogenic driver molecular alteration (18 patients analyzed)

	KRAS	*TP53*	*ERBB2*	*MAPK21*	*PIK3CA*
Patient 2	*Exon 2 p.(Gly12Val)*	*Exon 8 p.(Lys305*)*			
Patient 8	*Exon 2 p.(Gly13Asp)*	*Exon 8 p.(Ala276Pro)*	*Exon 21 p.(Asp880Glu)*		
Patient 9				*Exon 2 p.(Lys57Asn)*	
Patient 13		*Exon 8 p.(Arg273Leu)*			
Patient 17	*Exon 2 p.(Gly12Val)*				
Patient 39	*Exon 2 p.(Gly12Val)*				
Patient 60	*Exon 2 p.(Gly12Asp);*				*Exon 10 p.(Glu542Lys)*
Patient 75	*Exon 2 p.(Gly12Asp);*				

Table S4 Univariable analysis of factors associated survival in lung cancer patients

	Univariate analysis	
	HR (95% CI)	*p*
Age at diagnosis	0.93 (0.85-1.03)	0.16
SRG mutation		
SFTPC/NKX2.1/ABCA3	Ref	
SFTPA1/SFTPA2	0.96 (0.29-3.21)	0.94
Tobacco exposure	5.22 (0.67-40.9)	0.11
Stage at diagnosis		
Stage I and II	Ref	
Stage III	6.4 (0.83-51.8)	0.07
Stage IV	6.96 (1.43-34.0)	0.023

Hazard ratios (HR) are calculated by a univariable Cox proportional hazard model, using time of lung cancer as time 0 and death as the outcome of interest. CI confidence interval, Ref referenc**References**

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