ABCMdb reloaded: updates on mutations in ATP Binding Cassette proteins

Hedvig Tordai, Kristóf Jakab, Gergely Gyimesi, Kinga András, Anna Brózik,

Balázs Sarkadi, Tamás Hegedűs

Supporting Information

Table S1. Variations queried from ClinVar. Genetic alterations were filtered and categorized as missense, nonsense, and synonymous mutations. Genes were ordered by the number of variations. D: deleterious, N: neutral, ?: unspecified.

gene	all	coding	unique	synonymous	missense				nonsense			
				total	D	N	?	total	D	N	?	total
CFTR	901	747	**731**	**38**	100	10	440	**550**	52	0	91	**143**
ABCA4	476	372	**370**	**52**	28	10	234	**272**	7	0	39	**46**
ABCC9	115	91	**91**	**33**	14	2	38	**54**	1	1	2	**4**
ABCC8	66	49	**49**	**16**	24	3	2	**29**	4	0	0	**4**
ABCD1	50	43	**43**	**4**	28	0	5	**33**	6	0	0	**6**
ABCA3	27	26	**26**	**7**	6	1	11	**18**	1	0	0	**1**
ABCC2	25	20	**20**	**5**	4	6	3	**13**	2	0	0	**2**
ABCC6	23	21	**21**	**1**	13	3	1	**17**	3	0	0	**3**
ABCB4	21	19	**19**	**2**	6	2	7	**15**	2	0	0	**2**
ABCC1	21	5	**5**	**2**	0	0	3	**3**	0	0	0	**0**
ABCA1	15	14	**14**	**0**	12	0	1	**13**	1	0	0	**1**
ABCB11	15	14	**14**	**4**	2	3	3	**8**	2	0	0	**2**
ABCG8	13	12	**12**	**1**	3	1	3	**7**	4	0	0	**4**
ABCB7	11	9	**9**	**2**	5	2	0	**7**	0	0	0	**0**
ABCG5	10	9	**9**	**1**	2	0	2	**4**	4	0	0	**4**
ABCB6	9	9	**9**	**0**	6	0	2	**8**	1	0	0	**1**
ABCA12	8	8	**8**	**0**	7	0	0	**7**	1	0	0	**1**
ABCB1	5	5	**5**	**1**	1	3	0	**4**	0	0	0	**0**
ABCG2	5	5	**5**	**0**	0	0	2	**2**	1	0	2	**3**
TAP1	3	3	**3**	**0**	1	2	0	**3**	0	0	0	**0**
TAP2	3	3	**3**	**0**	0	2	0	**2**	0	1	0	**1**
ABCC4	1	1	**1**	**0**	0	0	1	**1**	0	0	0	**0**
ABCC5	1	1	**1**	**0**	0	0	1	**1**	0	0	0	**0**
ABCD3	1	1	**1**	**0**	0	0	1	**1**	0	0	0	**0**
ABCD4	1	1	**1**	**0**	1	0	0	**1**	0	0	0	**0**
ABCG4	1	1	**1**	**0**	0	0	1	**1**	0	0	0	**0**
ABCA5	1	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCA10	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCA13	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCA2	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCA6	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCA7	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCA8	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCA9	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCB10	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCB5	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCB8	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCB9	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCC10	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCC11	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCC12	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCC3	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCD2	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**
ABCG1	0	0	**0**	**0**	0	0	0	**0**	0	0	0	**0**

Table S2. Performance of SNAP2 and PROVEAN does not increase largely and consequently for the conserved nucleotide binding domains as compared to curated mutations from databases.

NBD:

gene	effect	curated	SNAP2		PROVEAN	
ABCB11/BSEP	deleterious	*75*	*52*	*(69%)**	*54*	*(72%)*
	neutral	*18*	*7*	*(39%)*	*6*	*(33%)*
	unspecified	*5*				
ABCC6/MRP6	deleterious	*79*	*55*	*(70%)*	*56*	*(71%)*
	neutral	*0*				
	unspecified	*0*				
ABCC7/**CFTR**	deleterious	*121*	*63*	*(52%)*	*70*	*(58%)*
	neutral	*14*	*4*	*(29%)*	*6*	*(43%)*
	unspecified	*213*				

TMD:

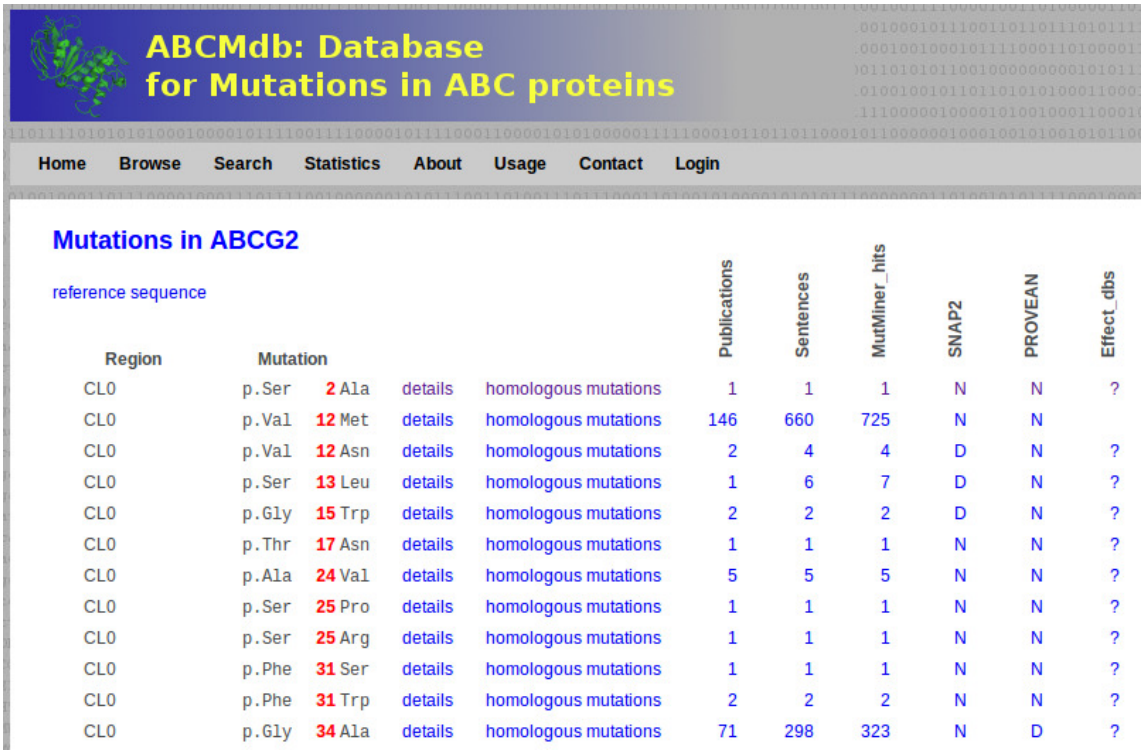
gene	effect	curated	SNAP2		PROVEAN	
ABCB11/BSEP	deleterious	57	37	*(65%)*	36	*(63%)*
	neutral	26	17	*(65%)*	10	*(38%)*
	unspecified	8				
ABCC6/MRP6	deleterious	71	50	*(70%)*	49	*(69%)*
	neutral	1	0	*(0%)*	0	*(0%)*
	unspecified	0				
ABCC7/**CFTR**	deleterious	151	91	*(60%)*	68	*(45%)*
	neutral	7	1	*(14%)*	4	*(57%)*
	unspecified	279				

** The number of correctly predicted mutation effects (true positive hits)*

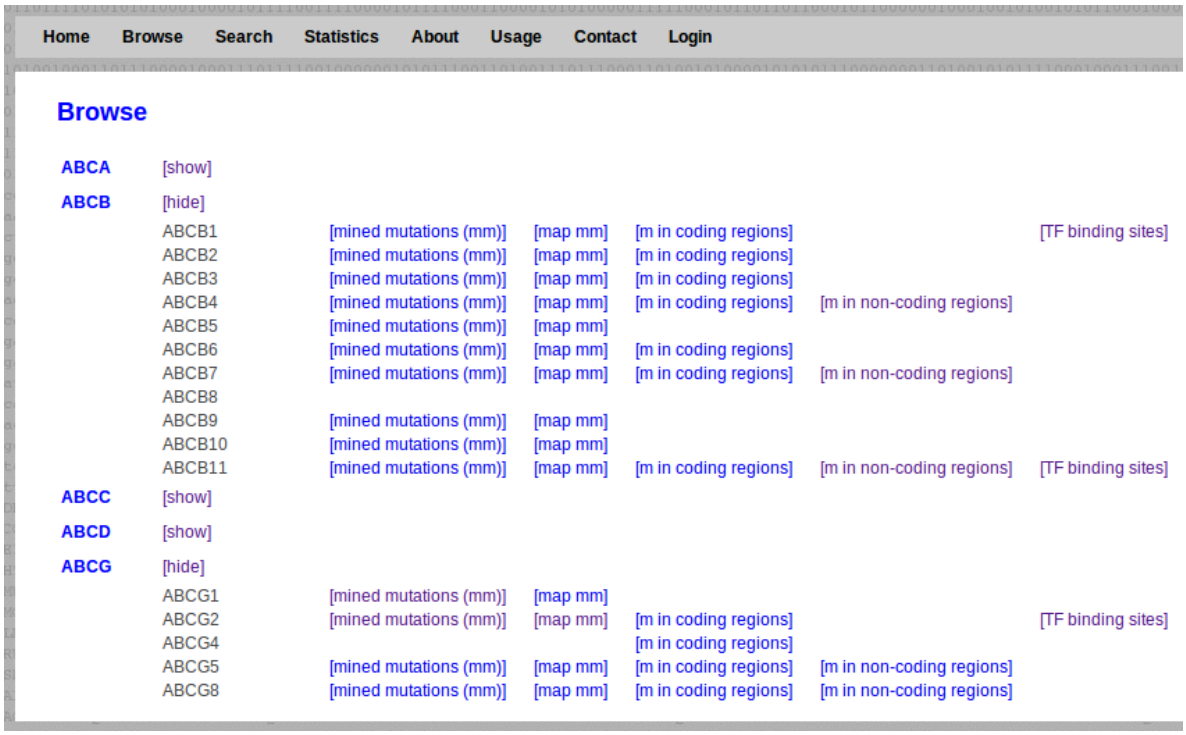
Table S3. Significant portion of conservative and non-conservative amino acid replacements can lead to deleterious and neutral changes, respectively. Variants with premature stop and silent amino acid changes were not counted.

a.a. change:	conservative				non-conservative			
effect:	deleterious		neutral		deleterious		neutral	
ABCB11/BSEP	51%	(25/49)	49%	(24/49)	80%	(105/131)	20%	(26/131)
ABCC6/MRP6	100%	(39/39)	0%	(0/39)	98%	(117/120)	3%	(3/120)
ABCC7/CFTR	87%	(48/55)	13%	(7/55)	94%	(206/218)	6%	(12/218)

Figure S1. The major changes in the web interface associated with novel data, such as predicted effect of mutations by SNAP2 and PROVEAN, effect of mutations collected from databases (top panel), and mutations in non-coding regions (bottom panel).



Region	Mutation			Publications	Sentences	MutMiner_hits	SNAP2	PROVEAN	Effect_dbs
CL0	p.Ser 2 Ala	details	homologous mutations	1	1	1	N	N	?
CL0	p.Val 12 Met	details	homologous mutations	146	660	725	N	N	
CL0	p.Val 12 Asn	details	homologous mutations	2	4	4	D	N	?
CL0	p.Ser 13 Leu	details	homologous mutations	1	6	7	D	N	?
CL0	p.Gly 15 Trp	details	homologous mutations	2	2	2	D	N	?
CL0	p.Thr 17 Asn	details	homologous mutations	1	1	1	N	N	?
CL0	p.Ala 24 Val	details	homologous mutations	5	5	5	N	N	?
CL0	p.Ser 25 Pro	details	homologous mutations	1	1	1	N	N	?
CL0	p.Ser 25 Arg	details	homologous mutations	1	1	1	N	N	?
CL0	p.Phe 31 Ser	details	homologous mutations	1	1	1	N	N	?
CL0	p.Phe 31 Trp	details	homologous mutations	2	2	2	N	N	?
CL0	p.Gly 34 Ala	details	homologous mutations	71	298	323	N	D	?



ABCA	[show]					
ABCB	[hide]					
	ABCB1	[mined mutations (mm)]	[map mm]	[m in coding regions]		[TF binding sites]
	ABCB2	[mined mutations (mm)]	[map mm]	[m in coding regions]		
	ABCB3	[mined mutations (mm)]	[map mm]	[m in coding regions]		
	ABCB4	[mined mutations (mm)]	[map mm]	[m in coding regions]	[m in non-coding regions]	
	ABCB5	[mined mutations (mm)]	[map mm]			
	ABCB6	[mined mutations (mm)]	[map mm]	[m in coding regions]		
	ABCB7	[mined mutations (mm)]	[map mm]	[m in coding regions]	[m in non-coding regions]	
	ABCB8					
	ABCB9	[mined mutations (mm)]	[map mm]			
	ABCB10	[mined mutations (mm)]	[map mm]			
	ABCB11	[mined mutations (mm)]	[map mm]	[m in coding regions]	[m in non-coding regions]	[TF binding sites]
ABCC	[show]					
ABCD	[show]					
ABCG	[hide]					
	ABCG1	[mined mutations (mm)]	[map mm]			
	ABCG2	[mined mutations (mm)]	[map mm]	[m in coding regions]		[TF binding sites]
	ABCG4			[m in coding regions]		
	ABCG5	[mined mutations (mm)]	[map mm]	[m in coding regions]	[m in non-coding regions]	
	ABCG8	[mined mutations (mm)]	[map mm]	[m in coding regions]	[m in non-coding regions]	

Figure S2. Mutations identified in an automatic way in full text papers are connected to entries in other data sources such as ClinVar and LSDBs and to *in silico* predictions by SNAP2 and PROVEAN to deliver as much information on phenotype as possible.

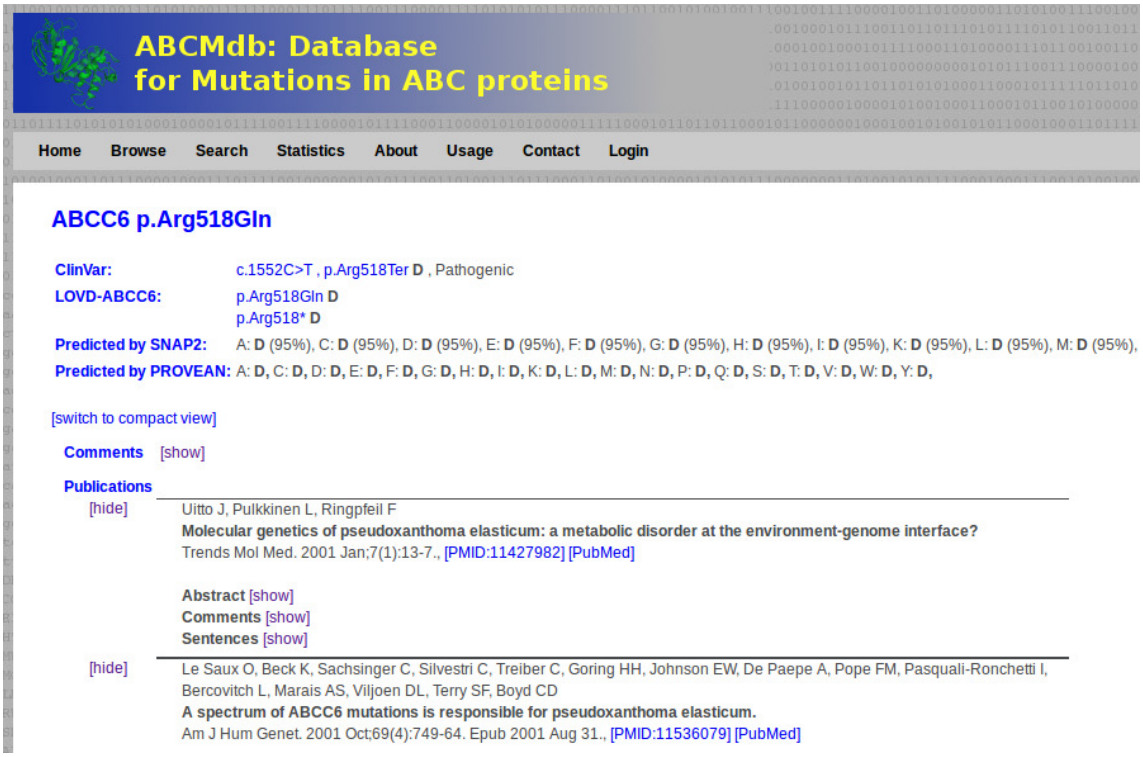


Figure S3. Querying variations at the DNA level and batch queries are also novel additional changes in the web interface.