

MUTAZIONI CFTR CON FUNZIONE MINIMA

Secondo la definizione data da EMA (Agenzia Europea per i Medicinali) le mutazioni del gene CFTR con funzione minima sono quelle che non fanno produrre proteina CFTR o fanno produrre una proteina CFTR non responsiva a ivacaftor (Kalydeco) o tezacaftor/ivacaftor (Symkevi) *in vitro*. EMA ha usato tale definizione per approvare nell'agosto 2020 la commercializzazione in Europa di Kaftrio (elixacaftor/tezacaftor/ivacaftor) indicato per soggetti con F508del/F508del e soggetti con F508del associata a mutazione con funzione minima. La lista sotto riportata contiene l'elenco di mutazioni con funzione minima presenti nei soggetti inclusi nei trial clinici che hanno portato all'approvazione del farmaco. **Non comprende però tutte le mutazioni considerabili con funzione minima** secondo la definizione usata da EMA, pertanto **ha solo un valore orientativo**.

Un'altra definizione di mutazioni con funzione minima usata in passato e tutt'ora valida è la seguente: mutazioni associate a una assente o scarsa (inferiore al 10%) funzione della proteina CFTR, e per lo più a insufficienza pancreatica e a un valore del cloro sudorale maggiore di 86 mmol/L.



CFTR Mutations Eligible for Phase 3 Study of Investigational VX-445 Triple Combination in People with One F508del Mutation and One Minimal Function Mutation

The below list includes currently eligible minimal function mutations for the VX-445-102 study as of April 2018 (protocol version 2.0):

CFTR Mutations Eligible for VX17-445-102

MF Mutation Category	Mutation					
Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X	
	S4X	Q220X	G542X	E822X	W1145X	
	W19X	Y275X	G550X	W882X	R1158X	
	G27X	C276X	Q552X	W846X	R1162X	
	Q39X	Q290X	R553X	Y849X	S1196X	
	W57X	G330X	E585X	R851X	W1204X	
	E60X	W401X	G673X	Q890X	L1254X	
	R75X	Q414X	Q685X	S912X	S1255X	
	L88X	S434X	R709X	Y913X	W1282X	
	E92X	S466X	K710X	Q1042X	Q1313X	
	Q98X	S489X	Q715X	W1089X	Q1330X	
	Y122X	Q493X	L732X	Y1092X	E1371X	
	E193X	W496X	R764X	W1098X	Q1382X	
	W216X	C524X	R785X	R1102X	Q1411X	
	Canonical splice mutations	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
		296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
296+1G→T		1248+1G→A	1811+1G→C	3040G→C	3600+2insT	
405+1G→A		1249-1G→A	1811+1.6kbA→G	(G970R)	3850-1G→A	
405+3A→C		1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A	
406-1G→A		1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T	
621+1G→T		1525-1G→A	1898+1G→A	3121-2A→G		
711+1G→T			1898+1G→C			
Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA	
	306insA	1119delA	1782delA	2732insA	3791delC	
	306delTAGA	1138insG	1824delA	2869insG	3821delT	
	365-366insT	1154insTC	1833delT	2896insAG	3876delA	
	394delTT	1161delC	2043delG	2942insT	3878delG	
	442delA	1213delT	2143delT	2957delT	3905insT	
	444delA	1259insA	2183AA→G ^a	3007delG	4016insT	
	457TAT→G	1288insTA	2184delA	3028delA	4021dupT	
	541delC	1343delG	2184insA	3171delC	4022insT	
	574delA	1471delA	2307insA	3171insC	4040delA	
	663delT	1497delGG	2347delG	3271delGG	4279insA	
	849delG	1548delG	2585delT	3349insT	4326delTC	
	935delA	1609del CA	2594delGT	3659delC		
Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b	1461ins4			
	CFTRdele2	CFTRdele17a,17b	1924del7			
	CFTRdele2,3	CFTRdele17a-18	2055del9→A			
	CFTRdele2-4	CFTRdele19	2105-2117del13insAGAAA			
	CFTRdele3-10,14b-16	CFTRdele19-21	2372del8			

CFTR Mutations Eligible for Phase 3 Study of Investigational VX-445 Triple Combination in People with One *F508del* Mutation and One Minimal Function Mutation

The below list includes currently eligible minimal function mutations for the VX-445-102 study as of April 2018 (protocol version 2.0):

CFTR Mutations Eligible for VX17-445-102

MF Mutation Category	Mutation		
	CFTRdele4-7	CFTRdele21	2721del11
	CFTRdele4-11	CFTRdele22-24	2991del32
	CFTR50kdel	CFTRdele22,23	3121-977_3499+248del2515
	CFTRdup6b-10	124del23bp	3667ins4
	CFTRdele11	602del14	4010del4
	CFTRdele13,14a	852del22	4209TGTT→AA
	CFTRdele14b-17b	991del5	

CFTR Mutations Eligible for Phase 3 Study of Investigational VX-445 Triple Combination in People with One *F508del* Mutation and One Minimal Function Mutation

The below list includes currently eligible minimal function mutations for the VX-445-102 study as of April 2018 (protocol version 2.0):

CFTR Mutations Eligible for VX17-445-102

MF Mutation Category	Mutation			
Missense mutations that	A46D ^b	V520F	Y569D ^b	N1303K
• Are not responsive in vitro to TEZ, IVA, or TEZ/IVA	G85E	A559T ^b	L1065P	
	R347P	R560T	R1066C	
and	L467P ^b	R560S	L1077P ^b	
• %PI >50% and SwCl >86 mmol/L	I507del	A561E	M1101K	

CFTR: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; SwCl: sweat chloride; TEZ: tezacaftor
Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: <http://www.cftr2.org/>. Accessed 15 February 2016.

Notes: %PI: percentage of *F508del*-CFTR heterozygous patients in the CFTR2 patient registry who are pancreatic insufficient; SwCl: mean sweat chloride of *F508del*-CFTR heterozygous patients in the CFTR2 patient registry.

^a Also known as 2183delAA→G.

^b Unpublished data.