III Congresso Nacional Ciências Biomédicas Laboratoriais

ESCOLA SUPERIOR DE TECNOLOGIA DA SAÚDE DE LISBOA
INSTITUTO POLITÉCNICO DE LISBOA

H&TRC
Health and Technology Research Center

MUTAÇÕES SINÓNIMAS NA PATOGÉNESE

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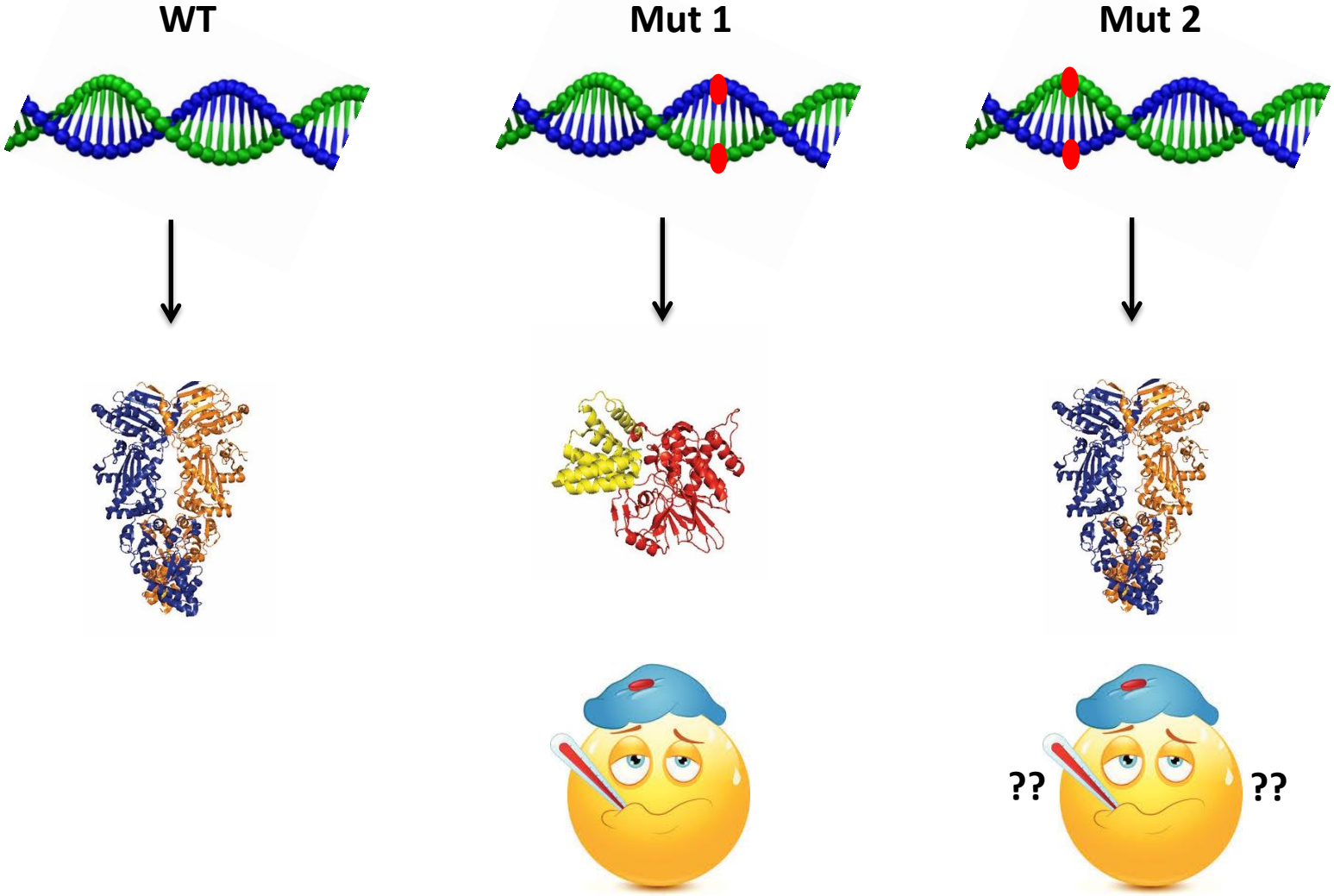
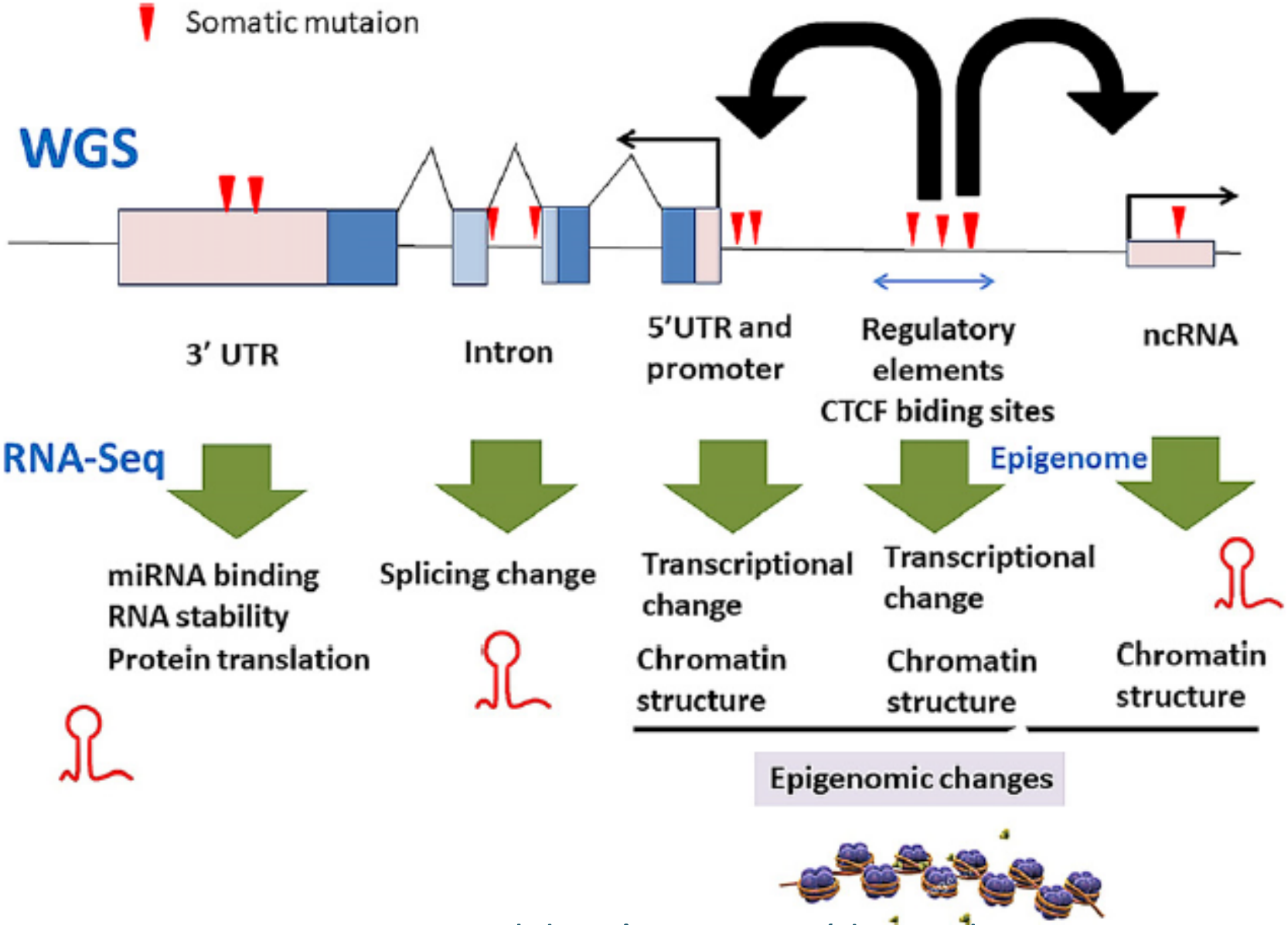
26 outubro 2019

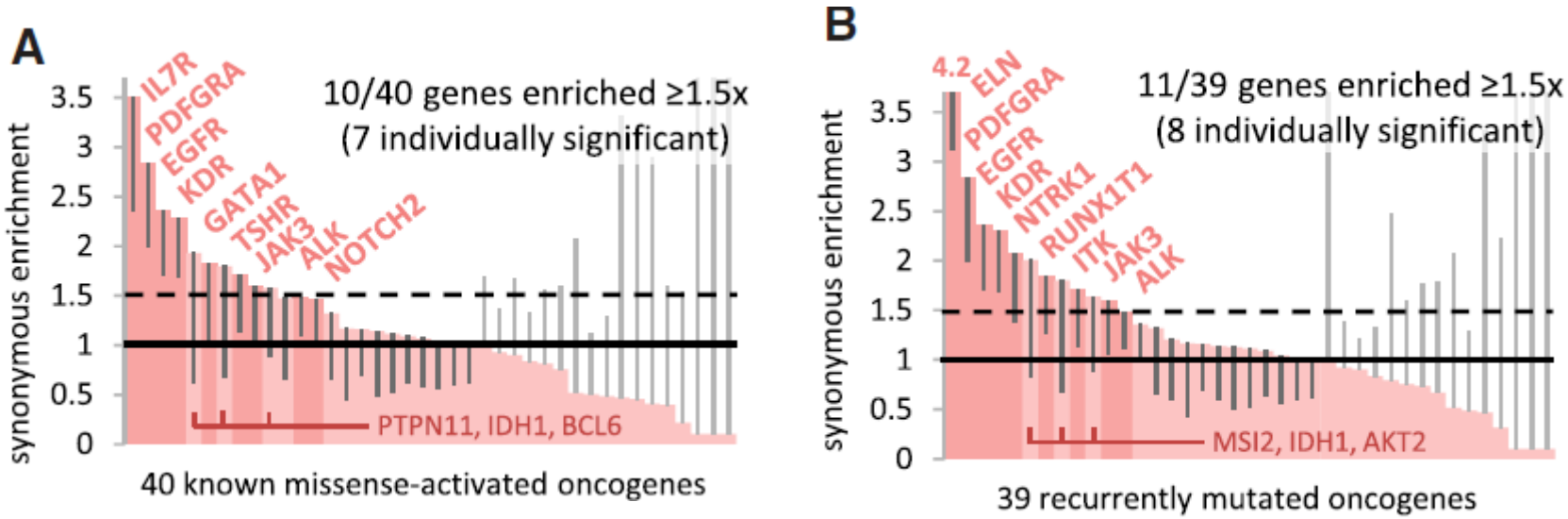
Ciências Biomédicas Laboratoriais


WT
Mut 1
Mut 2
??
??

Mutação sinónima vs silenciosa



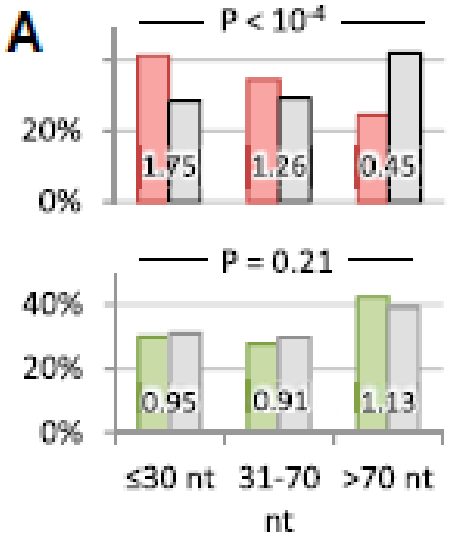
Contribuição mutações sinónimas cancro



Supek, F., et. al Cell (2014)

Contribuição mutações sinónimas cancro

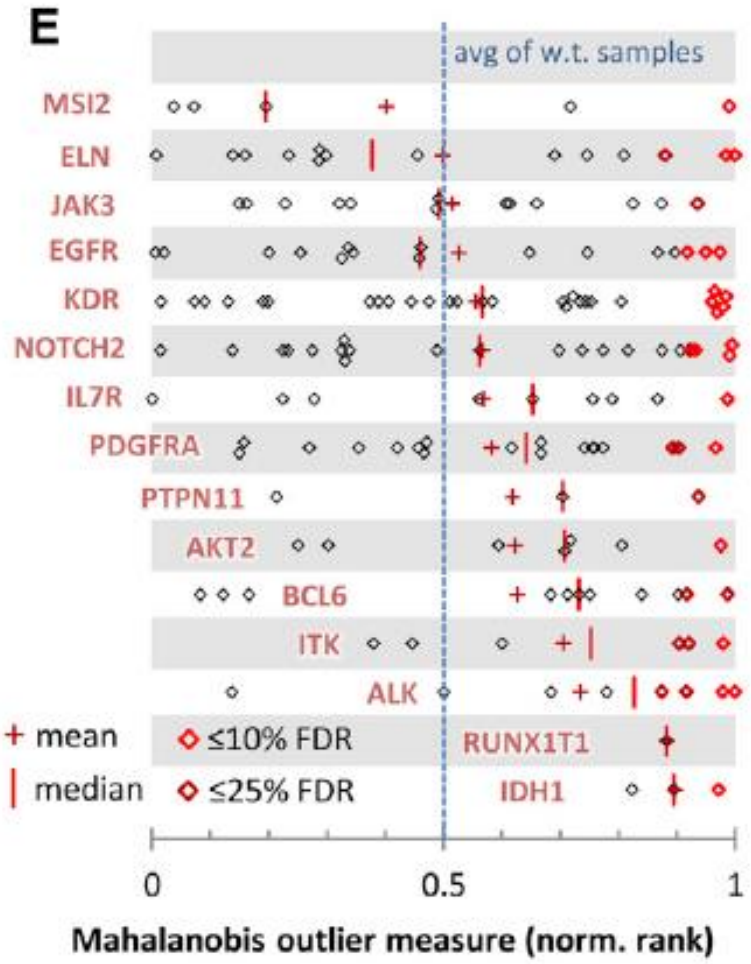
- Mutações sinónimas constituem 6-8% das mutações driver



- Ganho de *exonic splicing enhancer* (ESE)
- Perda de *exonic splicing silencer* (ESS)

Supek, F., et. al Cell (2014)

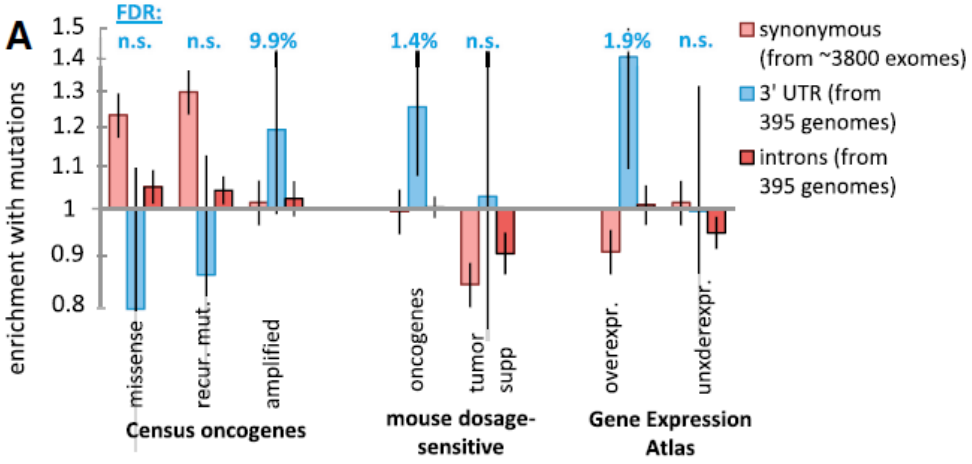
Alterações splicing

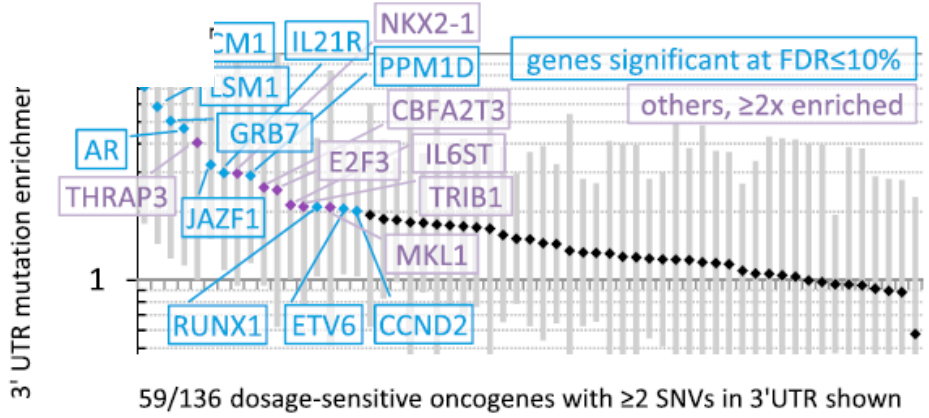


Cerca de metade mutações sinónimas driver alteram o *splicing*

Supek, F., et. al Cell (2014)

Alterações expressão

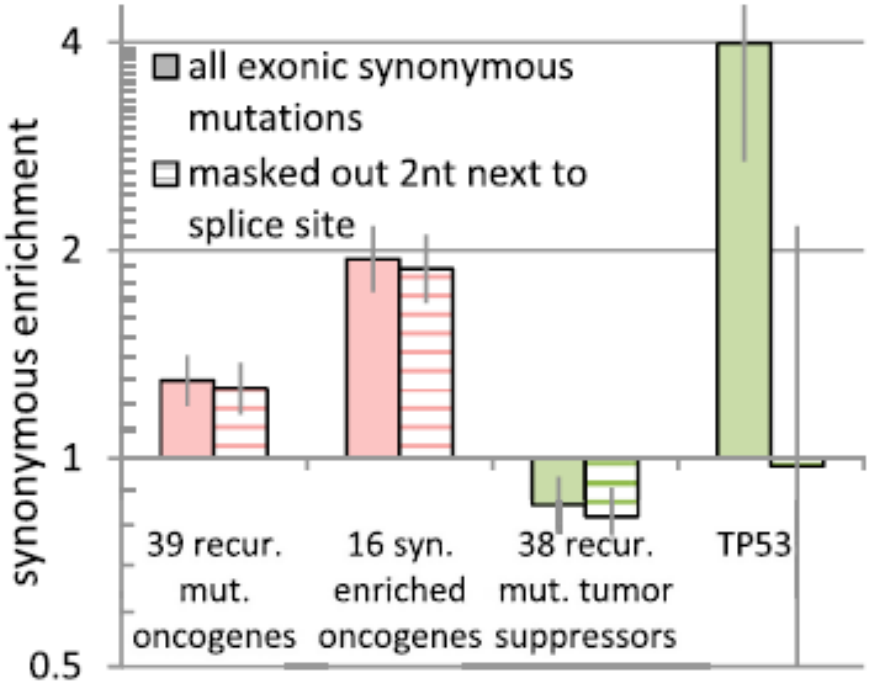




- Elevada frequência de mutações 3'UTR presentes em oncogenes sensíveis à dose (sobre-expressão)

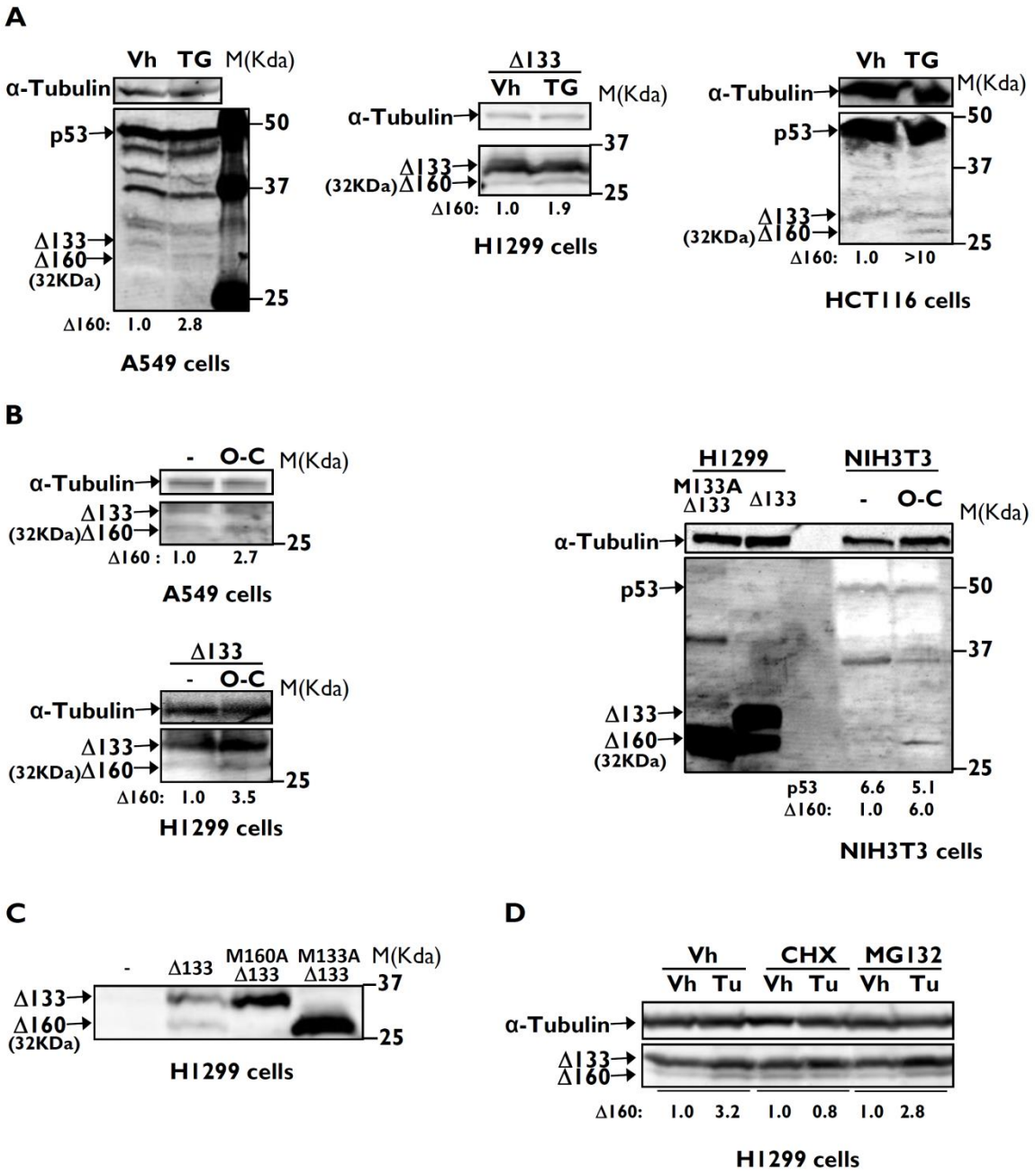
Supek, F., et. al Cell (2014)

TP53

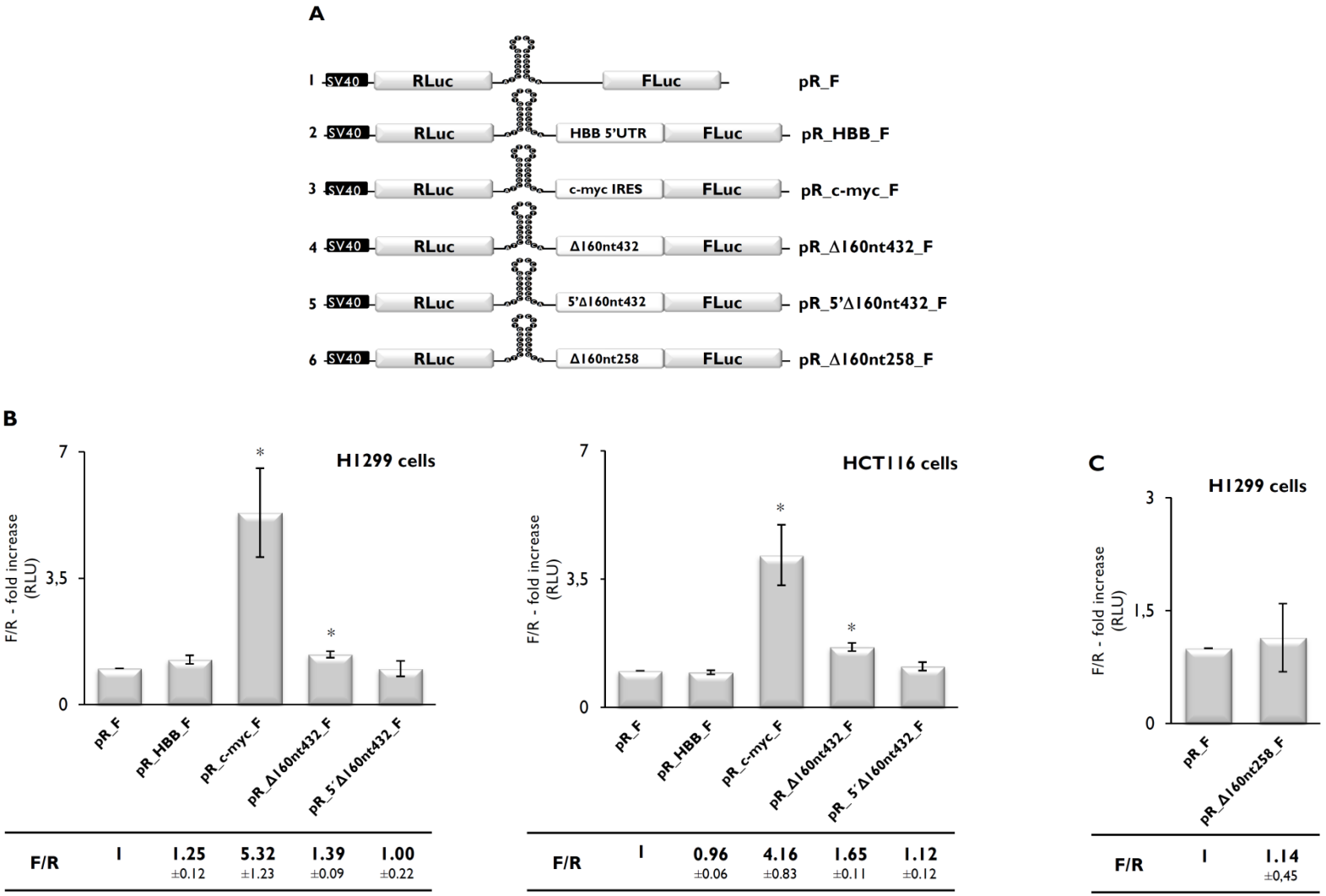


Mutações sinónimas resultam em inactivação de locais de *splicing*

Supek, F., et. al Cell (2014)



Candeias MM and Marques-Ramos A (unpublished data)



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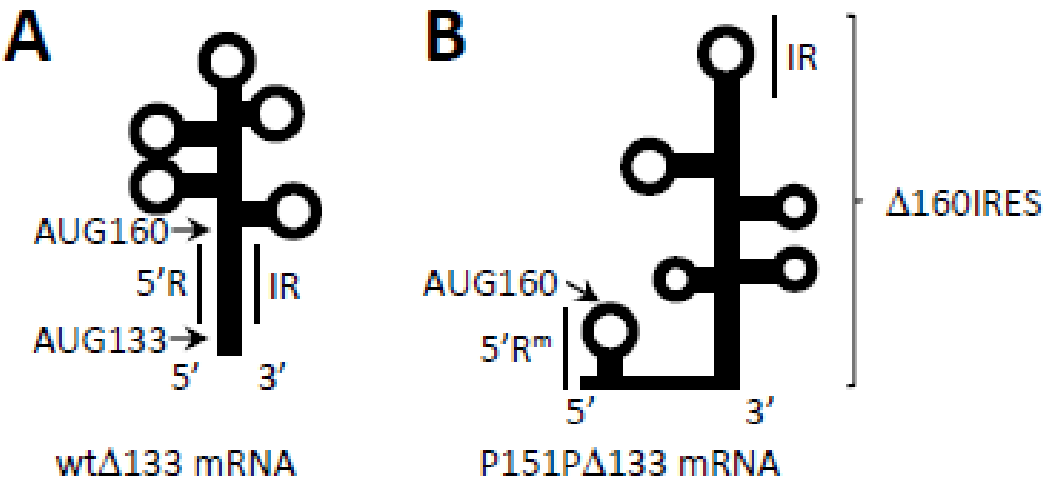

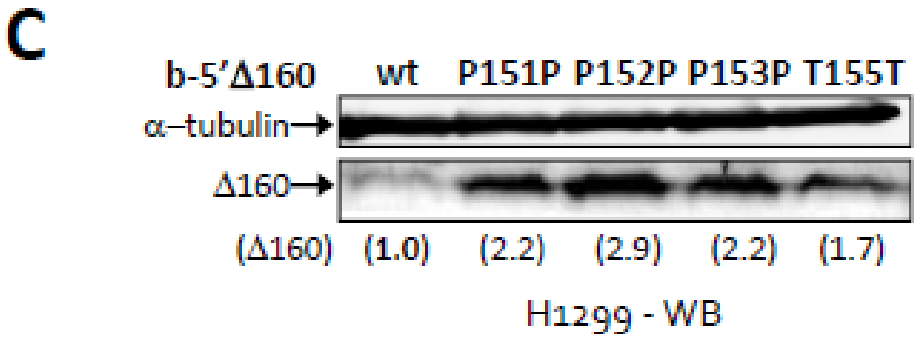

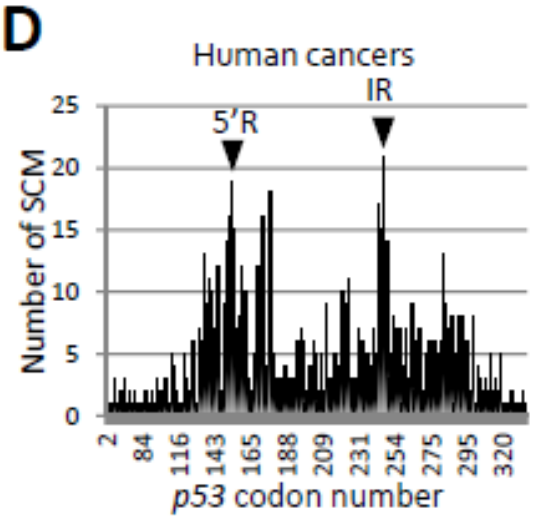

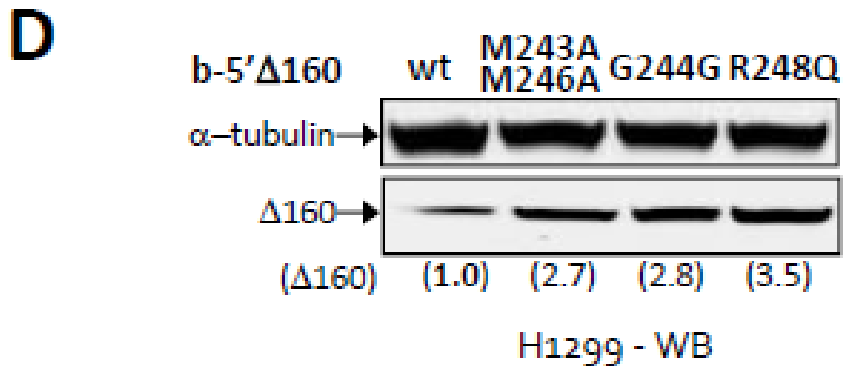

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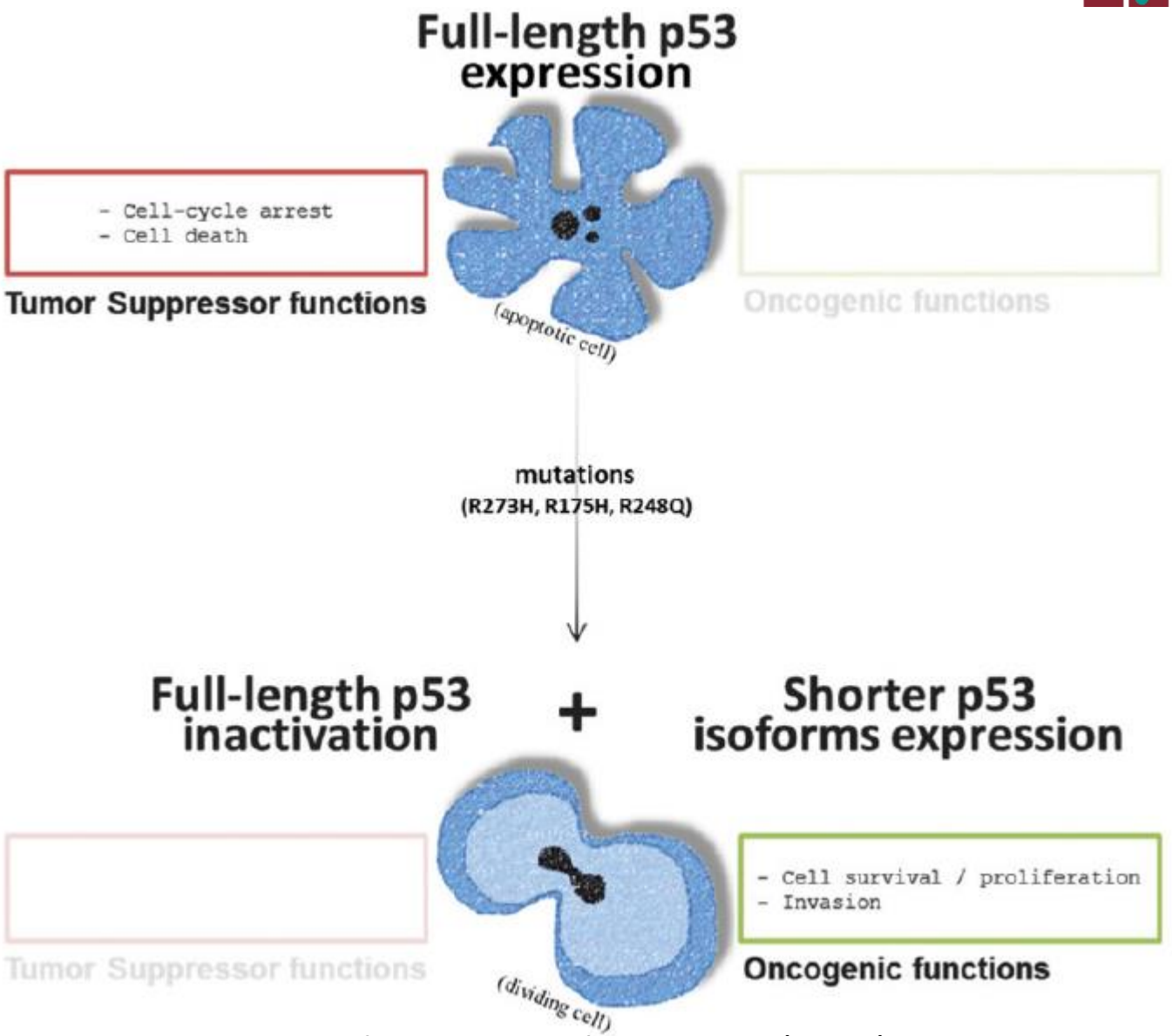
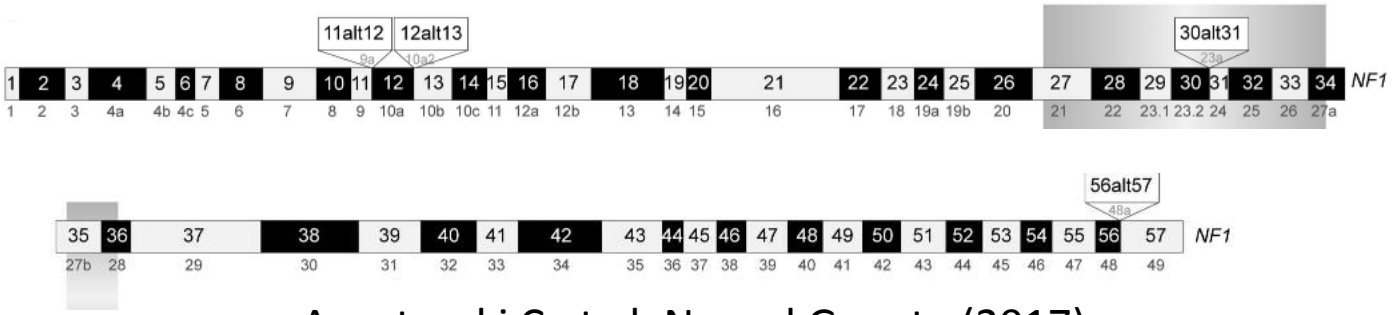
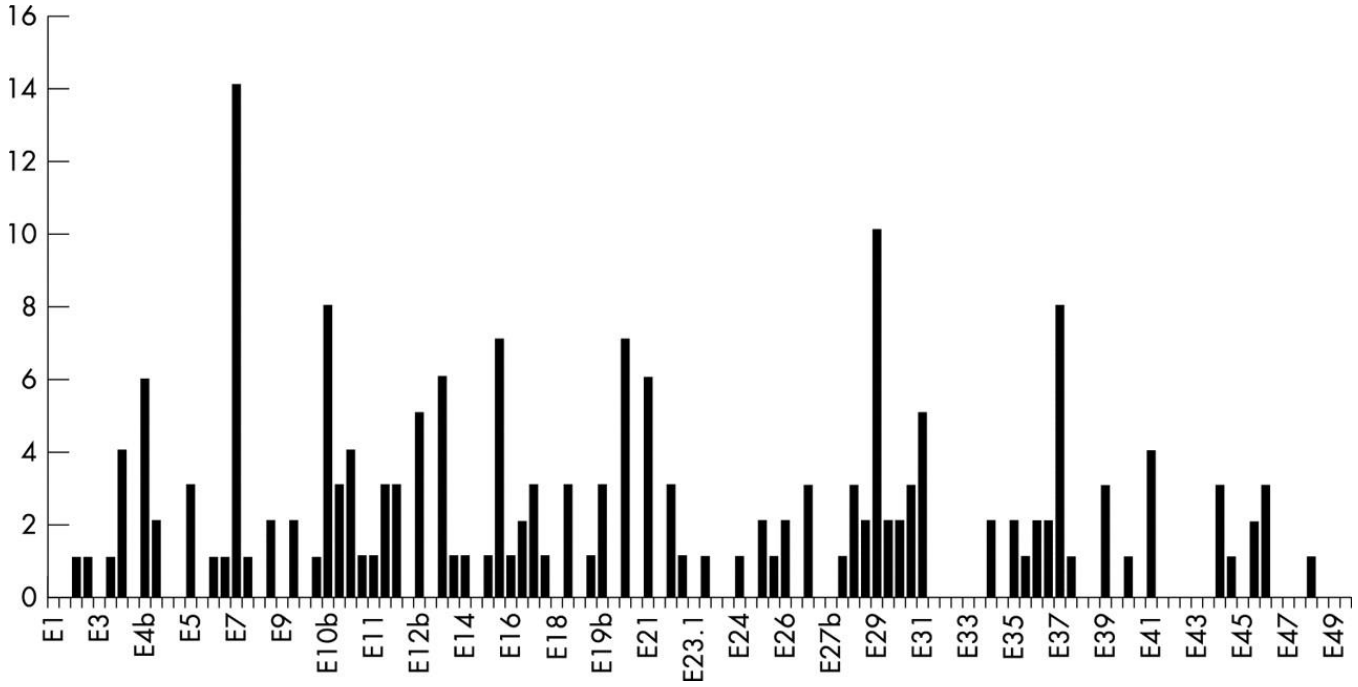


Candeias MM Embo Reports (2016)

NF1

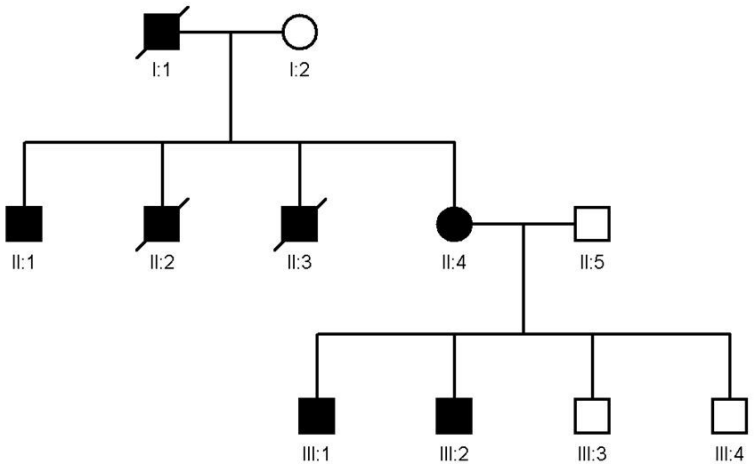


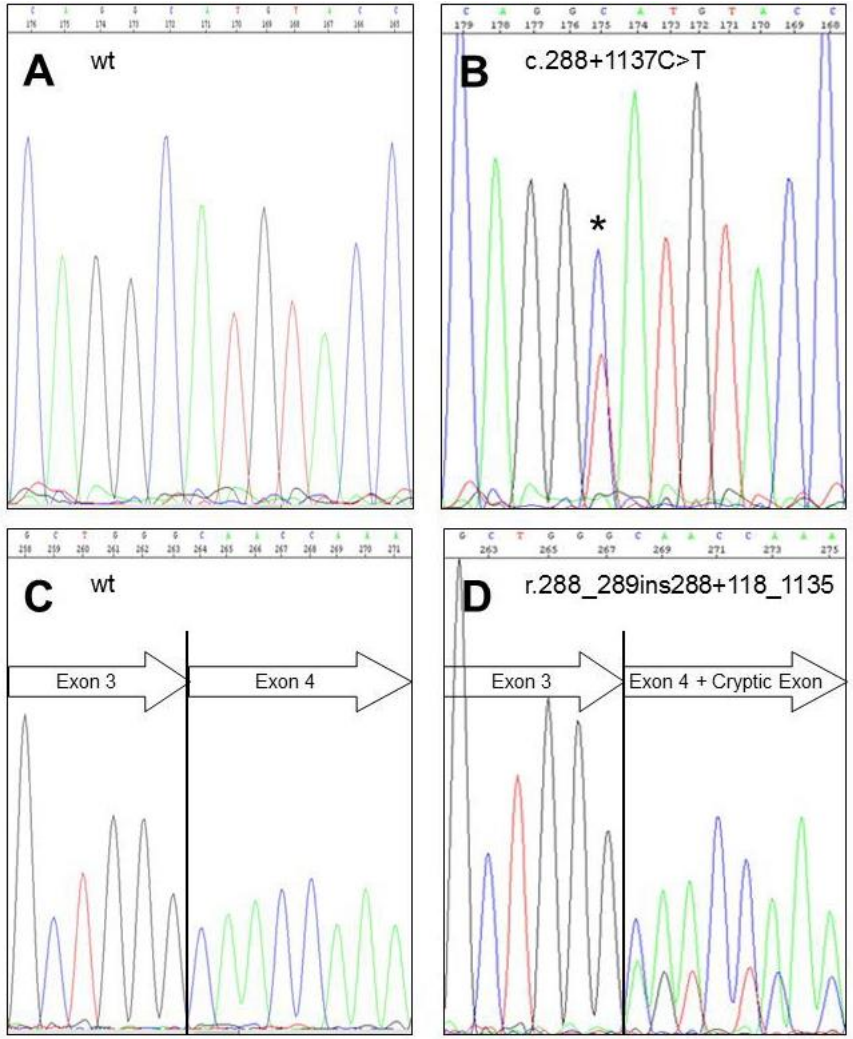
Anastasaki C et al. Neurol Genet. (2017)



E Ars et al. J Med Genet (2003)

NF1





c.288+1137C>T

Svaasand et al. Hereditary Genet (2015)

Deep-intronic mutations

Mutation	mRNA effect	Protein	LOVD NF1 ID	Ref
c.60+9032_60+9036del5	r.60_61ins60+8962_60+9030	p.Gln20_Leu21ins23	_01129	[22]
c.61-7486G>T	r.60-61ins61-7565_61-7492	p.Gln20_Leu21insThr*	_01132	[22]
c.288+2025T>G	r.288_289ins288+1917_288+2024	p.Gln97*	ND	[23]
c.288+1137C>T	r.288_289ins288+1018_288+1135	p. Gln97Serfs*49	ND	This study
c.888+651T>A §	r. 888_889ins888+653_888+784ins	p.Lys297_Val2818delinsGluLysTyrSer*	ND	[20]
c.888+789A>G	r.888_889ins888+710_888+784	p.Lys297fs	_01154	[22]
c.888+10312A>G	r.888_889ins888+10233_888+10311	p.Lys297fs	_01155	[22]
c.889-942G>T	r.888_889ins889-931_889-873	p.Lys297Valfs*11	ND	[23]
c.1062+113A>G	r.1062_1063ins113	p.Asn355fs	_01620	Italy: Milano
c.1260+1604A>G	r.1260_1261ins1260+1605_1260+1646	p.Asn420_Ser421insLeuThrThr*	_00035	[22,24]
c.1393-592A>G	r.1392_1393ins1393-671_1393-596	p.Ser465Alafs*9	_01179	[22,23]
c.1527+1159C>T	r.1527_1528ins1527+1103_1527+1157	p.Asn510Aspfs*8	ND	[16,23,27]
c.1642-449A>G	Not described	Not described	ND	[28]
c.1721+542A>G	r.1721_1722ins1721+362_1721+537	p.Ser574_Ser575insPhePhe GluLeu*	_01186	[22]
c.3198-314G>A	r.3197-3198ins3198-214-3198-312, sr.3197-3198ins3198-245-3198-312 #	p.Asp1067TrpfsX7	ND	[29]
c.4110+945A>G	r.4110_4111ins105	p.Gln1370_Val1371ins35*27	ND	[25]
c. 4173+278A>G ¤	r.4173_4174ins4173+279_4173+358	p.Val1392Ilefs*9	ND	[26]
c.5749+332A>G	r.5749_5750ins5749+155_5749+331	p.Ser1917Argfs*12	_01315	[16,22,30,33,this study]
c.5750-279A>G	r.5749_5750ins5750_278_5750-108	p.Ser1917delins58	ND	[31,32]
c.7908-321C>G	r.7907_7908ins7908-322_7908-391	p.His2637SerfsX2	ND	[4,23]

Svaasand et al. Hereditary Genet (2015)

Deep-intronic mutations

Disease (OMIM)	Gene	Deep intronic variant
Monogenic diseases		
β-Thalassemia7 (6713985)	*HBB*	IVS2+705T>G
Gyrate atrophy of choroid and retina with or without ornithinemia (258870)	*OAT*	IVS3+303C>G
Cystic Fibrosis (2197700)	*CFTR*	3849+10KbC>T
Mucopolysaccharidosis II (309900)	*IDS*	1131-133A>G
Hyperphenylalaninemia, BH4-deficient, C (261630)	*QDPR*	IVS3+2552A>G
Maple syrup urine disease, type II (248600)	*DBT*	IVS8-550A>G
Mucopolysaccharidosis type VII (253220)	*GUSB*	IVS8+0.6kbdelTC
Tuberous sclerosis (613254)	*TSC2*	IVS8+281C>T
Congenital cataracts facial dysmorphism neuropathy syndrome (604168)	*CTDP1*	IVS6+389C>T
Central core disease (117000)	*RYR1*	IVS100+2990A>G
Hyper IgM Syndrome, type 1 (308230)	*CD40L*	IVS3-915A>T
Chronic granulomatous disease (306400)	*CYBB*	IVS6-1157A>G
Leber congenital amaurosis 10 (611755)	*CEP290*	c.2991+1655A>G
Schwartz-Jampel Syndrome (255800)	*HSPG2*	c.574+481C>T
Congenital disorder of glycosylation, type Ia (212065)	*PMM2*	c.639-15479C>T
Afibrinogenemia (202400)	*FGG*	IVS6-320A>T
Methylmalonic aciduria, mut(0) type (251000)	*MUT*	IVS11+3691C>A
Propionicacidemia (606054)	*PCCB*	IVS6+462A>G
Leigh syndrome (256000)	*NDUFS7*	c.17-1167C>G
Mitochondrial trifunctional protein deficiency (609105)	*HADHB*	IVS7+614A>G
Deafness, autosomal dominant 22 (606346)	*MYO6*	IVS23+2321T>G
Polycystic kidney and hepatic disease (263200)	*PKHD1*	IVS46+1653A>G
Amyotrophic lateral sclerosis 1 (105400)	*SOD1*	c.358–304C>G
Niemann-Pick disease, type C1 (250227)	*NPC1*	c.1554-1009G>A
Retinitis pigmentosa 11 (600138)	*PRPF31*	c.1374+654C>G
Duchenne muscular dystrophy (310200)	*DMD*	c.3787-843C>A c.9807+2714C>T
Becker muscular dystrophy (30376)	*DMD*	c.9225-285A>G
5-fluorouracil toxicity (274270)	*DPYD*	c.1129–5923C>G

Disease (OMIM)	Gene	Deep intronic variant
Gitelman's Syndrome (263800)	*SLC12A3*	c.1670-191C>T c.2548+253C>T
Megalencephalic leukoencephalopathy with subcortical cysts (604004)	*MLC1*	c.895-226T>G
Retinitis pigmentosa (300424)	*OFD1*	IVS9+706A>G
Coffin–Lowry syndrome (303600)	*RPS6KA3*	c.1228-279T>G
Hyperinsulinemic hypoglycemia, familial, 1 (256450)	*ABCC8*	c.1333-1013A>G
Inherited growth-hormone insensitivity (604271)	*GHR*	c.618+792A>G
Hemophilia A (306700)	*F8*	c.5998+530C>T
Stargardt disease 1 (248200)	*ABCA4*	c.5196+1056A>G
Marfan syndrome (154700)	*FBN1*	c.6872-961A>G
Gorlin syndrome (109400)	*PTCH1*	c.2561-2057A>G
Menkes disease (309400)	*ATP7A*	c.2406+1117A>G
Miyoshi muscular dystrophy 1(254130)	*DYSF*	c.4886+1249G>T
Hyperinsulinemic hypoglycemia, familial, 4 (609975)	*HADH*	c.636+471G>T
Ocular albinism (300500)	*GPR143*	c.659-131T>G
Ushar syndrome type II (276901)	*USH2A*	c.9959-4159A>G c.5573-834A>G c.8845+628C>T
Complete androgen insensitivity syndrome (300068)	*AR*	c.2450-118A>G
Duchenne muscular dystrophy (310200)	*DMD*	deletion 18 bp[a]
Hereditary tumor syndromes		
Retinoblastoma (180200)	*RB1*	IVS23-1398A>G
Lynch syndrome (120435)	*MSH2*	c.212-478T>G
Breast cancer (114480)	*BRCA2*	c.6937+594T>G
Familial Adenomatous Polyposis (175100)	*APC*	c.532-941G>A c.1408+731C>T c.1408+735A>T
Neurofibromatosis type 2 (101000)	*NF2*	c.1447-240T>A
Neurofibromatosis type 1 (162200)	*NF1*	c.288+1137C>T
Ataxia-telangiectasia (208900)	*ATM*	IVS28-159A>G[a]

Vaz-Drago et al. Human Genet (2017)

Deep-intronic mutations

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Disease (OMIM)	Gene	Deep intronic variant
Monogenic diseases		
Alport Syndrome (301050)	*COL4A3*	
	COL4A5	IVS29+2733A>G
Choroideremia (303100)	*CHM*	314+10127T>A
Ornithine transcarbamylase deficiency (311250)	*OTC*	c.540+265G>A
Myopathy with lactic acidosis, hereditary (255125)	*ISCU*	IVS5+382G>C
Duchenne muscular dystrophy (310200)	*DMD*	c.5326-215T>G
Becker muscular dystrophy (30376)	*DMD*	c.93+5590T>A
Werner syndrome (277700)	*WRN*	c.3234-160A>G
Lesch–Nyhan syndrome (300322)	*HPRT*	g.36221T>A c.5998+941G>A
Limb-girdle muscular dystrophy type 2A (253600)	*CAPN3*	c.1782+1072G>C
Optic atrophy plus syndrome (125250)	*OPA1*	c.610+360G>A c.610+364G>A
Kindler syndrome (173650)	*FERMT1*	c.1139+740G>A
Pompe disease (232300)	*GAA*	c.2190-345A>G

Disease (OMIM)	Gene	Deep intronic variant
ESE creation		
Monogenic diseases		
Alport Syndrome (301050)	*COL4A5*	IVS6+1873G>A
Propionicacidemia (606054)	*PCCA*	IVS14-1416A>G
Afibrinogenemia (202400)	*FGB*	c.115-600A>G
Homocystinuria, type cbIE (236270)	*MTRR*	c.903+469T>C
Becker muscular dystrophy (300376)	*DMD*	c.3603+2053G>C
Complete androgen insensitivity syndrome (300068)	*AR*	c.2450-118A>G
ESS disruption		
Monogenic diseases		
Cystic Fibrosis (219700)	*CFTR*	c.1002–1110_1113delT
Fabry disease (301500)	*GLA*	c.639+919G>A
Hereditary tumor syndrome		
Ataxia-telangiectasia (208900)	*ATM*	IVS20-579_IVS20-576

Vaz-Drago et al. Human Genet (2017)

Detecção de mutações

	DNA chip	Target-Seq	Exome	RNA-Seq	WGS
Coding SNV		△	○	△	○
Coding indels		△	○	△	○
Splicing alteration			△	○	○
Promoter mutation					○
Regulatory regions					○
Copy-number alteration	○		△		○
Structural variant				△ (fusion)	○
Pathogen				○	○
Mitochondria			△	△	○
Mutational signature			△		○
Neo-antigen/ HLA			○	○	○
Sequence (Gb)	—	0.5-1	10	5-10	90-150
Assay cost ($)	100	200-500	500	500	1000

SNV, single nucleotide variants; WGS, whole genome sequencing.

Nakagawa H. and Fujita M., Cancer Science (2018)

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MUTAÇÕES SINÓNIMAS NA PATOGÉNESE

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26 outubro 2019

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