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Gene Section
Mini Review

BRAF (v-raf murine sarcoma viral oncogene homolog B1)

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Identity

Other names: v-raf murine sarcoma viral oncogene homolog B1; BRAF1; RAFB1

HGNC (Hugo): BRAF

Location: 7q34

Local order: Between the NDUFB2 and MRPS33 genes.

Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description

The BRAF gene is composed of 18 exons spanning in a region of 190284 bp.

Transcription

The transcribed mRNA has 2478 bp.

Pseudogene

BRAF2 in Xq13.3.

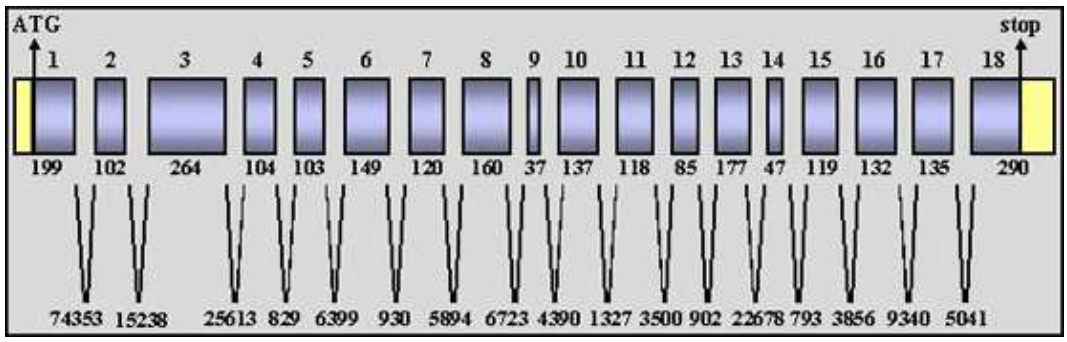

Diagram of the BRAF gene. Exons are represented by boxes (in scale) transcribed and untranscribed sequences in blue and yellow, with exon numbers on top and number of base pairs at the bottom. Introns are represented by black bars (not in scale) and the number of base pairs indicated. The arrows show the ATG and the stop codons respectively.

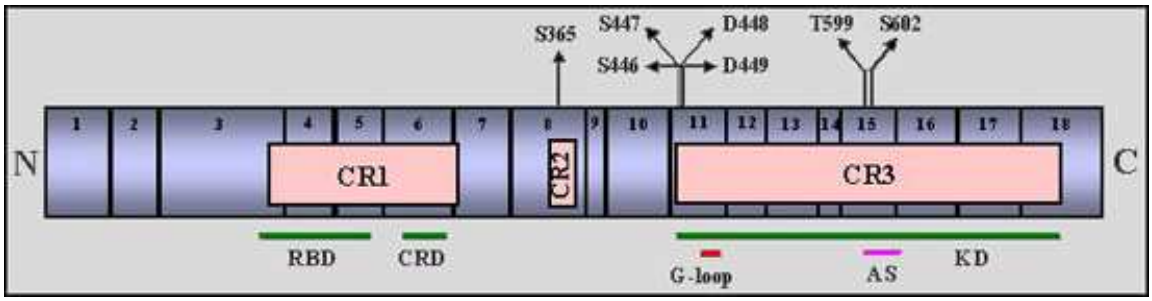

Diagram of the BRAF protein in scale. Numbers inside the blue boxes indicate the exon from which is translated each part of the protein. The three boxes inside represent the conserved regions of the protein with the ARAF and RAF-1 genes (CR1, CR2 and CR3). With green bars are represented three different domains: RBD (Ras binding domain), CRD (Cysteine-rich domain) and KD (Kinase domain). A conserved glycine motif (G-loop) in exon 11 is indicated with a red bar and the activation segment (AS) in exon 15 with a pink bar. The black arrows indicate the major phosphorylation sites of the protein. C: Carboxyl-terminal; N: Amino-terminal.

Protein

Note

The real sequence A31 G32 A33 was erroneously considered R31 P32. As the A33 was missing in previous sequences, some articles have erroneously assigned wrong numbers to coding mutations and amino acids (i.e. V599E mutation instead of V600E).

Description

Amino acids: 766. Molecular Weight: 84436 Daltons. The BRAF gene is a proto-oncogene that belongs to the serine/threonine kinase family. It is also a member of the RAF Subfamily together with the ARAF and RAF1 genes.

Expression

BRAF is expressed in most tissues with high expression in neuronal tissue.

Localisation

Cytoplasmic.

Function

BRAF is a serine/threonine kinase that belongs to the RAS/RAF/MEK/ERK/MAPK pathway, which is involved in the transduction of mitogenic signals from the cell membrane to the nucleus. RAS is inactive when binded to GDP, but when it binds to GTP becomes active and promotes phosphorylation and activation of BRAF and the activation of the pathway signal. Several genes have been found to be activated by this pathway, among them, cyclin D1, cyclin D2 and cyclin D3 (self-sufficiency in growth), VEGF (angiogenesis), c-myc (insensitivity to antigrowth signals), b3-integrin (tissue invasion and metastasis) and mdm2 (apoptosis evasion, limitless replicative potential and angiogenesis).

Homology

BRAF shares three conserved regions (CR1, CR2 and CR3) with the other two RAF genes: ARAF and RAF1. CR1, which has 131 aa, contains the cysteine-rich domain (CRD) and most of the Ras binding domain (RBD). These two domains bind to RAS-GTP. CR2, which has 16 aa, is rich in serine and threonine residues, including S365 as an inhibitory phosphorylation site. Finally CR3, which has 293 aa and has the kinase domain, contains also the G-loop GXGXXG motif (highly conserved in most of the human kinases), the activation segment and the regulatory phosphorylation sites S446, S447, D448, D449, T599 and S602.

Mutations

Note

Single nucleotide polymorphism (SNP) found in BRAF: A1023G (P341P); A1227G (S409S); A1383G (Q461Q); A1797C (T599T); A1929G (G643G); G2272A (G758R).

Germinal

No germinal mutations described.

Somatic

BRAF presents somatic mutations in different sort of tumors, predominantly in malignant melanoma, sporadic colorectal tumors showing mismatch repair defects in microsatellites (MSI), low-grade ovarian serous carcinoma and thyroid papillary cancer. 80% of these mutations correspond to the hotspot transversion mutation T1799A that causes the amino acidic substitution V600E. The other 20% accounts for a wide variable range of missense mutations and all of them reside in the glycines of the G-loop in the exon 11 or in the activation segment in exon 15 near the V600. The mutation V600E confers transformant activity to the cells because it mimics the phosphorylation of T599 and/or S602 in the activation segment and so BRAF rests constitutively active in a RAS independent manner. Mutations in or NRAS are not concomitant with the BRAF mutation V600E. This mutation has not been found in other tumors like gastric cancer, endometrial cancer, uveal melanoma, biliary tract cancer or hepatocellular carcinoma.

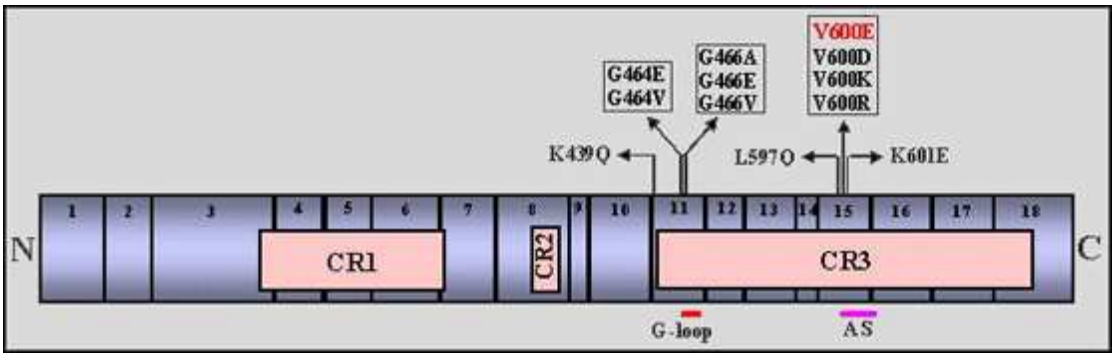

Diagram with BRAF mutations found in melanoma. The black arrows indicate the mutations. The mutations inside a box are in the same amino acid. The hotspot mutation V600E is in red. Numbers inside the blue boxes indicate the exon from which is translated each part of the protein. The three boxes inside represent the conserved regions of the protein with the ARAF and RAF-1 genes (CR1, CR2 and CR3). A conserved glycine motif (G-loop) in exon 11 is indicated with a red bar and the activation segment (AS) in exon 15 with a pink bar. C: Carboxyl-terminal; N: Amino-terminal.

Implicated in

Melanoma

Note

BRAF is mutated in 70% of malignant melanomas. The mutation V600E is an early event and alone is insufficient for the development of melanoma as it is present in 80% of primary melanomas and 80% of nevi, which are the first lesions associated with this tumor. No BRAF mutations are associated with uveal melanoma.

Colorectal cancer

Note

BRAF mutation V600E is associated with mismatch repair deficiency (MSI) and found in 40% of the cases while in mismatch repair proficient tumors (MSS) the frequency is around 5%. Gastric and endometrial MSI and MSS tumors do not have BRAF mutations. In sporadic MSI colon cases this mutation is found in proximal colon tumors with MLH1 methylation (80% of cases), while in tumors from the hereditary nonpolyposis colorectal cancer (HNPCC), either with MLH1, MSH2 or MSH6 germline mutations or none, no BRAF mutations are detected. Because of this it has been proposed the use of the BRAF V600E mutation for HNPCC diagnostic as a exclusion criteria for germline mutation in mismatch repair genes.

Prognosis

Even though its association with sporadic MSI suggest BRAF as a good prognosis factor, it has been also associated to metastatic colorectal MSS cancers. In this cases, BRAF associates with poor prognosis.

Ovarian cancer

Note

The only BRAF mutation is V600E which is found in 30% of low-grade serous carcinoma and borderline tumors. The mutation seems to occur very early in the development. High-grade tumors do not show BRAF mutations.

Thyroid cancer

Note

In thyroid papillary cancer the only BRAF mutation present is V600E with a frequency around 50%. The K601E mutation has also been found in some cases of the follicular variant of thyroid cancer.

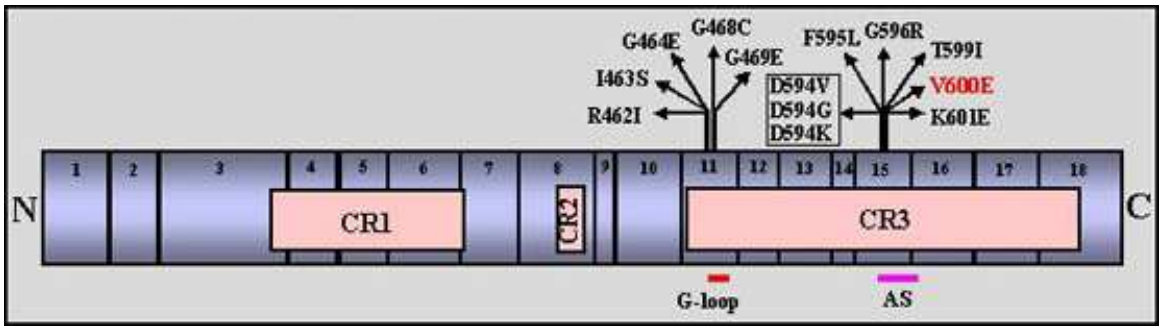

Diagram with BRAF mutations found in colorectal cancer. The black arrows indicate the mutations. The mutations inside a box are in the same amino acid. The hotspot mutation V600E is in red. Numbers inside the blue boxes indicate the exon from which is translated each part of the protein. The three boxes inside represent the conserved regions of the protein with the ARAF and RAF-1 genes (CR1, CR2 and CR3). A conserved glycine motif (G-loop) in exon 11 is indicated with a red bar and the activation segment (AS) in exon 15 with a pink bar. C: Carboxyl-terminal; N: Amino-terminal.

Cell lines

Tissue type	Cell Line	MSI status	BRAF	KRAS	Tissue type	Cell Line	BRAF	NRAS
Colorectal	ALA	MSS	-	G12D	Melanoma	1205Lu	V600E	-
Colorectal	CACO2	MSS	-	-	Melanoma	451Lu	V600E	-
Colorectal	CBS	MSS	-	G13D	Melanoma	A101D	V600E	-
Colorectal	Colo205	MSS	V600E	-	Melanoma	A2058	V600E	-
Colorectal	Colo320	MSS	-	G12D	Melanoma	A375	V600E	-
Colorectal	EB	MSS	-	G12D	Melanoma	C32	V600E	-
Colorectal	FET	MSS	-	G12D	Melanoma	CHL	-	-
Colorectal	FRI	MSS	-	G12D	Melanoma	Colo679	V600E	-
Colorectal	HT29	MSS	V600E	-	Melanoma	Colo800	V600E	-
Colorectal	IS1	MSS	-	G12D	Melanoma	Colo829	V600E	-
Colorectal	IS2	MSS	-	G12D	Melanoma	FOM74	-	-
Colorectal	IS3	MSS	-	G12D	Melanoma	G-361	V600E	-
Colorectal	LS1034	MSS	-	-	Melanoma	HMCB	-	Q61K
Colorectal	LS123	MSS	-	-	Melanoma	HMVII	-	Q61K
Colorectal	LS513	MSS	-	G12D	Melanoma	HT-144	V600E	-
Colorectal	NCI-H508	MSS	G595R	-	Melanoma	Hx117	-	-
Colorectal	NCI-H747	MSS	-	G13D	Melanoma	Hx118	-	-
Colorectal	SK-CO1	MSS	-	G12V	Melanoma	Hx126	-	-
Colorectal	SW1116	MSS	-	G12D	Melanoma	Hx129	-	Q61R
Colorectal	SW1417	MSS	V600E	-	Melanoma	Hx34	-	-
Colorectal	SW1463	MSS	-	G12C	Melanoma	HxLe	-	-
Colorectal	SW403	MSS	-	G12V	Melanoma	HxLL	V600E	-
Colorectal	SW480	MSS	-	G12V	Melanoma	HxMm	-	-
Colorectal	SW620	MSS	-	G12V	Melanoma	LOXIN-IV	V600E	-
Colorectal	SW948	MSS	-	Q61L	Melanoma	M14	V600E	-
Colorectal	T84	MSS	-	G13D	Melanoma	Malme	V600E	-
Colorectal	V9P	MSS	-	-	Melanoma	RPMI-7951	V600E	-
Colorectal	WIDR	MSS	V600E	-	Melanoma	SBcl2	-	-
Colorectal	SW837	MSI-L	-	G12C	Melanoma	SH-4	V600E	-
Colorectal	Co115	MSI	V600E	-	Melanoma	SK-MEL-1	-	-
Colorectal	Colo741	MSI	V600E	-	Melanoma	SK-MEL-100	V600E	-
Colorectal	HCT116	MSI	-	G13D	Melanoma	SK-MEL-103	-	Q61R
Colorectal	HCT15 / DLD1	MSI	-	G13D	Melanoma	SK-MEL-147	-	Q61R
Colorectal	KM12	MSI	-	-	Melanoma	SK-MEL-173	-	-
Colorectal	LoVo	MSI	-	G13D	Melanoma	SK-MEL-187	-	-
Colorectal	LS174	MSI	-	G12D	Melanoma	SK-MEL-19	V600E	-
Colorectal	LS411	MSI	V600E	-	Melanoma	SK-MEL-192	V600E	-
Colorectal	RKO	MSI	V600E	-	Melanoma	SK-MEL-197	-	-
Colorectal	SNU-C2A	MSI	-	-	Melanoma	SK-MEL-2	-	Q61R
Colorectal	SW48	MSI	-	-	Melanoma	SK-MEL-24	V600E	-
Colorectal	TC71	MSI	-	G12D	Melanoma	SK-MEL-28	V600E	-
Gastric	AGS	MSS	-	G12D	Melanoma	SK-MEL-29	V600E	-
Gastric	GTL16	MSS	-	-	Melanoma	SK-MEL-3	V600E	-
Gastric	HGT1	MSS	-	-	Melanoma	SK-MEL-31	-	-
Gastric	KatoIII	MSS	-	-	Melanoma	SK-MEL-5	-	-
Gastric	MKN1	MSS	-	-	Melanoma	SK-MEL-85	G469S	-
Gastric	MKN28	MSS	-	-	Melanoma	SK-MEL-94	V600E	-
Gastric	MKN74	MSS	-	-	Melanoma	UACC-257	-	-
Gastric	N87	MSS	-	-	Melanoma	UACC-62	V600E	-
Gastric	SNU16	MSS	-	-	Melanoma	WM115	-	-
Gastric	SNU216	MSS	-	-	Melanoma	WM1158	V600E	-
Gastric	SNU484	MSS	-	-	Melanoma	WM1361A	-	-
Gastric	SNU5	MSS	-	-	Melanoma	WM1361B	V600E	-
Gastric	SNU601	MSS	-	G12D	Melanoma	WM1361C	V600E	-
Gastric	SNU620	MSS	-	-	Melanoma	WM1617	V600E	-
Gastric	SNU668	MSS	-	-	Melanoma	WM1789	K601E	-
Gastric	SNU719	MSS	-	-	Melanoma	WM-266-4	V600E	-
Gastric	TMK1	MSS	-	-	Melanoma	WM278	V600E	-
Gastric	SNU1	MSI	-	G12D	Melanoma	WM35	-	-
Gastric	SNU520	MSI	-	-	Melanoma	WM39	V600E	-
Gastric	SNU638	MSI	P453P	-	Melanoma	WM75	V600E	-
Endometrial	AN3-CA	MSI	-	-	Melanoma	WM793	V600E	-
Endometrial	HEC-1-A	MSI	-	G12D	Melanoma	WM9	V600E	-
Endometrial	HEC-1-B	MSI	-	-	Melanoma	WM902B	V600E	-
					Melanoma	WM983A	V600E	-
					Melanoma	WM983B	V600E	-
					Thyroid	ARO	V600E	-
					Thyroid	FRO	V600E	-
					Thyroid	KTC-1	V600E	-
					Thyroid	NPA	V600E	-
					Thyroid	TPC-1	-	-
					Thyroid	WRO	-	-

Mutations of BRAF in cell lines from colorectal cancer, gastric cancer, endometrial cancer, melanoma and thyroid cancer. It is indicated the MSI status and KRAS mutations in the colorectal, gastric and endometrial cell lines. NRAS mutations are indicated in melanoma and thyroid cell lines.

References

Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. Nature. 2002 Jun 27;417(6892):949-54

Yin Q, Jacobsen SB, Yamashita K, Blichert-Toft J, Télouk P, Albarède F. A short timescale for terrestrial planet formation from Hf-W chronometry of meteorites. Nature. 2002 Aug 29;418(6901):949-52

Cohen Y, Xing M, Mambo E, Guo Z, Wu G, Trink B, Beller U, Westra WH, Ladenson PW, Sidransky D. BRAF mutation in papillary thyroid carcinoma. J Natl Cancer Inst. 2003 Apr 16;95(8):625-7

Mercer KE, Pritchard CA. Raf proteins and cancer: B-Raf is identified as a mutational target. Biochim Biophys Acta. 2003 Jun 5;1653(1):25-40

Oliveira C, Pinto M, Duval A, Brennetot C, Domingo E, Espín E, Armengol M, Yamamoto H, Hamelin R, Seruca R, Schwartz S Jr. BRAF mutations characterize colon but not gastric cancer with mismatch repair deficiency. Oncogene. 2003 Dec 11;22(57):9192-6

Pollock PM, Harper UL, Hansen KS, Yudt LM, Stark M, Robbins CM, Moses TY, Hostetter G, Wagner U, Kakareka J, Salem G, Pohida T, Heenan P, Duray P, Kallioniemi O, Hayward NK, Trent JM, Meltzer PS. High frequency of BRAF mutations in nevi. Nat Genet. 2003 Jan;33(1):19-20

Tuveson DA, Weber BL, Herlyn M. BRAF as a potential therapeutic target in melanoma and other malignancies. Cancer Cell. 2003 Aug;4(2):95-8

Domingo E, Espín E, Armengol M, Oliveira C, Pinto M, Duval A, Brennetot C, Seruca R, Hamelin R, Yamamoto H, Schwartz S Jr. Activated BRAF targets proximal colon tumors with mismatch repair deficiency and MLH1 inactivation. Genes Chromosomes Cancer. 2004 Feb;39(2):138-42

Domingo E, Laiho P, Ollikainen M, Pinto M, Wang L, French AJ, Westra J, Frebourg T, Espín E, Armengol M, Hamelin R, Yamamoto H, Hofstra RM, Seruca R, Lindblom A, Peltomäki P, Thibodeau SN, Aaltonen LA, Schwartz S Jr. BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. J Med Genet. 2004 Sep;41(9):664-8

Shih IeM, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol. 2004 May;164(5):1511-8

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