Supplementary Materials

Families with BAP1-Tumor Predisposition Syndrome in the Netherlands: Path to Identification and a Proposal for Genetic Screening Guidelines

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Table S1. Malignancies found in proband, tested non-proband carriers and untested members from families with germline variants in *BAP1.*

Family Identifier	Tumor Proband (Age)	Number of Nonproband Variant Carriers	Tumor in Nonproband Variant Carriers (Age)	Number of Untested Relatives	Tumor in Untested Relatives
NL-1	UM (67)	9	- UM (65), GI cancer (?) - UM (61), NMSC (59) - NMSC (65), Breast cancer (55), Endometrial cancer (66) - GI cancer (?)	12	UM, Breast cancer
NL-2	BIN x2 (39, 39) NMSC (39)	7	- CM (41) - MMe pl (72), GI cancer (55), Breast cancer (59) - MMe pl (63) - MMe pl (64), fibrosarcoma (64) - NMSC (49), Warthin tumor (?) - NMSC (48) - Breast cancer x2 (52, 55)	61	UM, CM x3, MMe pl x3, MMe pt x2, NMSC x3, Skin cancer x10, GI cancer, Breast cancer, Multiple myeloma
NL-3	BIN x5 (29, 29, 29, 29, 29)	0	-	11	CM, NMSC x4, Ewing sarcoma, Hodgkin lymphoma
NL-4	MMe pt (39)	1	Lung cancer	18	CM, MMe pl, MMe pt, NMSC x2, Ocular tumor, Breast cancer, Unknown tumor
NL-5	UM (66) NMSC (66) Meningioma (44) Vestibular schwannoma (51)	0	-	36	UM, CM, RCC, Meningioma, Skin tumor, Lung cancer x4, GI cancer, Mouth cancer
NL-6	UM (30)	8	- CM (29) - MMe pt (?) - NMSC x9 (56, 60, 62, 62, 63, 63, 64, 65, 66), Prostate cancer (65), Urothelial cell cancer (66)	19	CM, RCC, Ocular tumor, Skin tumors, Breast cancer, Leukemia

NL-7	BIN x2 (22, 22)	0	-	N/A [a]	N/A
NL-8	CM (49) Conjunctival melanoma (44) Lung cancer (54)	0	-	39	CM, RCC, NMSC, Lung cancer x2
NL-9	UM (57) - iris MMe pl (61) RCC (61) NMSC (57) B-cell lymfoma (58)	0	-	20	RCC, Prostate cancer, Pancreatic cancer, Unknown malignancy
NL-10	BIN x2 (20, 26) NMSC (27)	1	- NMSC x3 (57, 59)	19	Urothelial cell cancer, Tongue cancer, Unknown metastatic cancer in liver
NL-11	BIN (55) Breast cancer (48)	4	- NMSC x5 (48, ?) - CM (51), NMSC x8 (45, 47, 54, 54, 57, 57, 57)	30	UM, Skin cancer, Bone cancer, Unknown malignancy x5
NL-12	UM (53) CM (56) NMSC (38, 52)	3	- MMe pl (54), RCC (58)	20	CM, Lung cancer x2, GI cancer, Breast cancer
NL-13	BIN x4 (15, 15, 18, 18)	0	-	N/A[a]	N/A
NL-14	CM x2 (23, 27) NMSC x2 (50, 53)	5	- CM (49), NMSC x36 (?), Schwannoma (52) - CM x2 (70, 83), NMSC x6 (50, 75, 76, 79, 79, 80) - NMSC (50) - NMSC (40)	26	CM x3, Metastatic (liver) melanoma of unknown origin, NMSC x3, Lung cancer, Non-hodgkin lymphoma
NL-15	BIN x2 (21, 25)	4	-	12	UM, Unknown malignancy x2
NL-16	CM (65)	0	-	25	CM x3, RCC, Lung cancer x2, Breast cancer, Liver cancer, Brain tumor, Abdominal malignancy
NL-17	BIN x2 (14, 14)	1	- CM (44)	2	RCC, Meningioma, Prostate cancer
NL-18	UM (72) Hepatocellular carcinoma (68)	5	- MMe pl (61), NMSC x3 (67, 67, 67), Hepatocellular carcinoma (53) - Hepatocellular carcinoma (51) - Breast cancer (51) - NMSC x2 (58)	31	MMe pl, MMe pt, Ocular tumor x2, GI tumor, Liver tumor, Brain tumor, Thyroid tumor
NL-19	CM (44)	1	-	29	UM, NMSC, Lung cancer, Prostate cancer x2
NL-20	CM (45)	0	-	24	CM x3, Lung cancer x2, GI cancer, Liver cancer, Pleuritis carcinomatosa -primairy likely lung or thyroid
NL-21	UM (44) CM (55)	2	-	89	CM, RCC, Lung cancer x4, Breast cancer, Bone cancer x2, Throat cancer, Abdominal tumor x2, Unknown malignancy
NL-22	CM (47) NMSC x7 (54, ?) Prostate cancer (55)	1	- CM (23)	10	CM, NMSC >2, Lung cancer

UM: uveal melanoma, CM: cutaneous melanoma, MMe: malignant mesothelioma, pl: pleural, pt: peritoneal, RCC: renal cell cancer, BIN: *BAP1*-inactive nevus, NMSC: non-melanoma skin cancer (mostly basal cell carcinomas), GI: gastro-intestinal.

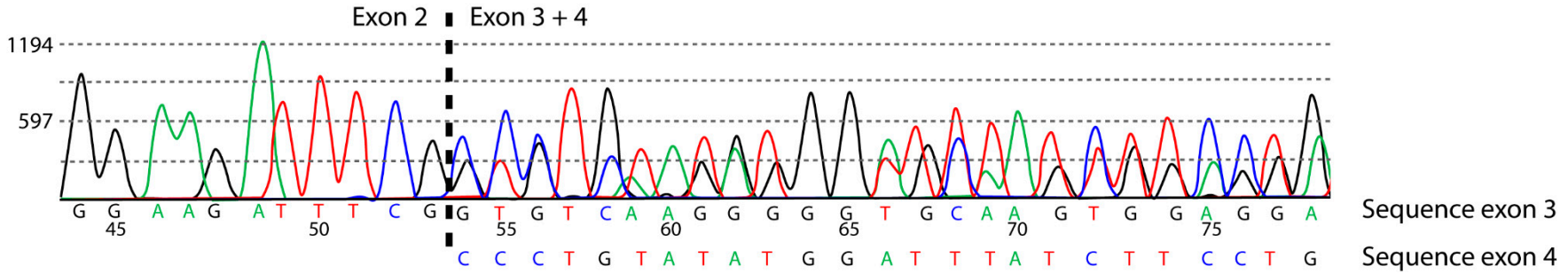
Supplementary Data 1.

RNA Analysis of *BAP1* Variant c.122+5G>C (NL-17)

Method

RNA was isolated from cultured lymphocytes in the presence of nonsense mediated decay-inhibitor cycloheximide essentially as described by Vreeswijk et al. [35]. Complementary DNA (cDNA) was sequenced by PCR using a forward primer in exon 1 (GAATAAGGGCTGGCTGGAG) and a reverse primer in exon 4 (GGACGTATCATCCACCAAGG) followed by Sanger sequencing.

Sequencing chromatogram (forward strand) of the cDNA shows the transition of exon 2 to exon 3 and to exon 4 of the mutated allele, which demonstrates skipping of exon 3 at the mutated allele.



The variant leads to a skip of exon 3 from the transcript. The nomenclature of the found change in the RNA is r.68_122del (p.(Gly23fs)). Although the data is suggestive for a complete deletion, it cannot be excluded that some full-length transcript is still transcribed from the mutant allele; the variant is therefore classified as likely pathogenic.