



# P13.108.D: Low-level constitutional mosaicism in breast cancer patients

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## Background / Objectives

**Mosaicism** refers to the presence of two or more genetically distinct cell populations within an individual's body. In some cases, individuals may carry a **mosaic germline variant** in a breast cancer-associated gene, such as *BRCA1* or *BRCA2*.

**Mosaicism** is just one aspect that can contribute to the overall risk of developing **breast cancer**.

The development of **next-generation sequencing (NGS)** technologies has revealed a significant contribution of **mosaic variants** to cancer predisposition genes.

In **this study** we describe the occurrence of very low-level constitutional mosaicism in **breast cancer** predisposition genes.

## Methods

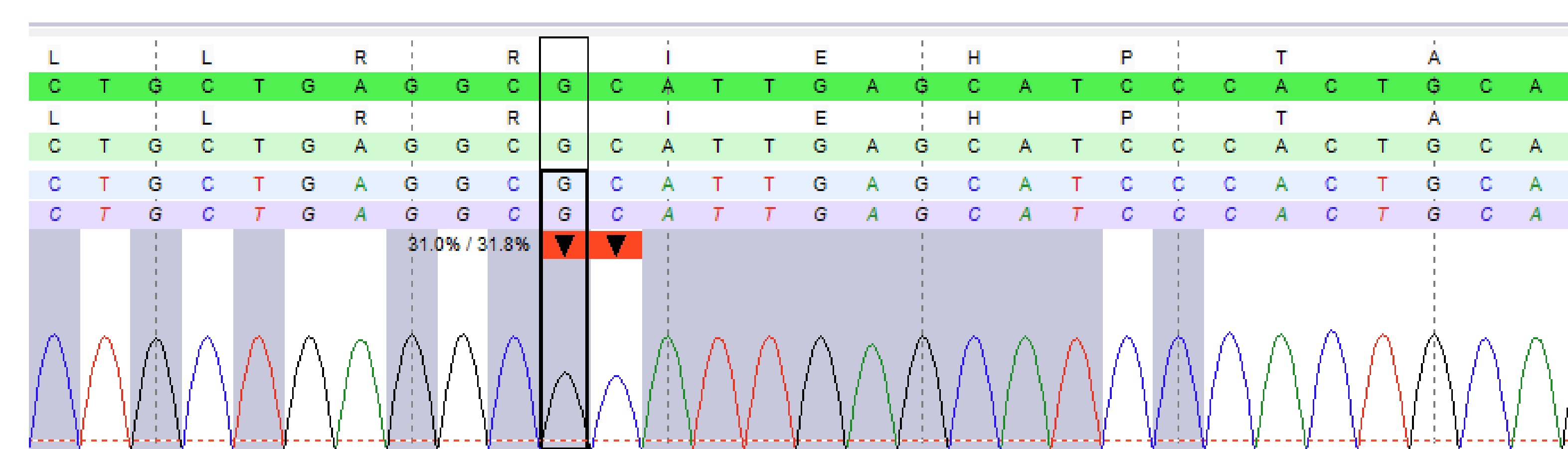
A cohort of **patients** diagnosed with **breast cancer** and referred to our laboratory for genetic testing using a **NGS panel of 52 genes** (*APC, ATM, ATR, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCA, FANCL, FANCM, GALNT12, GEN1, HOXB13, MEN1, MLH1, MRE11, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, PPP2R2A, PTEN, RAD50, RAD51B, RAD51C, RAD51D, RET, RNF43, RPS20, SMAD4, SMARCA4, STK11, TP53, VHL*) was evaluated for the occurrence of **very low-level constitutional mosaicism** in breast cancer predisposition genes.

In all cases suspected of mosaicism, DNA was isolated from the **buccal swab** to confirm the state of mosaicism.

## Results

NGS analysis of **7 patients** diagnosed with breast cancer in peripheral blood and buccal swab DNA revealed low-level constitutional mosaicism variants in **four genes**.

- In the ***NF1*** gene the following variants were detected c.2294\_2295del, p.(Arg765Hisfs\*2) (Figure 1) and c.3197+1G>A at 31% and 32%, respectively.
- A gross deletion of the genomic region the full coding sequence of the ***BRCA2*** gene (Figure 2).
- Also, the variant c.1117G>T, p.(Glu373\*) was identified in ***PTEN*** at 25%.
- Finally, in ***TP53*** mosaicism was identified in variants: c.814delinsCTT, p.(Val272Leufs\*74) (32%), c.916C>T, p.(Arg306\*) (32%) and c.722C>G, p.(Ser241Cys) (31%).



**Figure 1.** Example of a patient with a pathogenic variant in *NF1* gene in 31%. This is a deletion of two nucleotides from exon 19 of the *NF1* mRNA (c.2294\_2295del), causing a frameshift after codon 765. It creates a novel stop codon 2 amino acid residues later [p.(Arg765Hisfs\*2)] and is expected to result in a truncated, non-functional protein. The mutation database ClinVar contains an entry for this variant (Variation ID: 846756). For these reasons, this variant has been classified as pathogenic.

Probe target info	AllSamples			ReferenceSamples		
	BR2_NORM...	BR2_BLOOD	BR2_SALIVA	R1	R2	R3
FRSS (n=7)	100%	100%	100%	100%	100%	100%
CAS (n=5)	OK	OK	Warning	OK	OK	OK
BRCA2-Up	0.97	0.81	0.81	1	1	1
BRCA2-1	1	0.82	0.89	0.99	1.03	0.99
BRCA2-2	1.01	0.82	0.88	0.97	1.06	0.97
BRCA2-3	0.99	0.81	0.87	0.99	1.02	0.99
BRCA2-3 (WT)	0.98	0.79	0.83	0.99	1.01	0.99
BRCA2-4	0.93	0.79	0.83	1.01	0.98	1.01
BRCA2-5	1.01	0.77	0.81	1	1.01	1
BRCA2-6	0.97	0.76	0.76	0.99	1.03	0.99
BRCA2-7	0.98	0.79	0.82	1	1	1
BRCA2-8	1	0.76	0.75	0.99	1.01	0.99
BRCA2-9	0.96	0.76	0.76	1.01	0.99	1.01
BRCA2-10	0.99	0.78	0.88	0.99	1.02	0.99
BRCA2-11	1.01	0.74	0.78	0.99	1.01	0.99
BRCA2-12	1.01	0.77	0.76	1	1	1
BRCA2-13	0.99	0.74	0.82	1	1.01	1
BRCA2-14	0.97	0.77	0.81	1	1.01	1
BRCA2-15	0.98	0.77	0.79	0.99	1.03	0.99
BRCA2-16	0.95	0.79	0.79	0.99	1.01	0.99
BRCA2-17	0.96	0.77	0.77	1	1	1
BRCA2-18	0.94	0.74	0.74	1.01	0.98	1.01
BRCA2-19	0.95	0.7	0.79	0.99	1.01	0.99
BRCA2-20	0.94	0.78	0.92	1	0.99	1
BRCA2-21	1	0.7	0.83	1	1	1
BRCA2-22	0.95	0.78	0.78	0.99	1.02	0.99
BRCA2-23	0.99	0.75	0.77	1	1.01	1
BRCA2-24	1	0.74	0.77	1	0.99	1
BRCA2-25	0.95	0.77	0.79	1.01	0.99	1.01
BRCA2-26	1.02	0.77	0.78	1	0.99	1
BRCA2-27	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-28	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-29	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-30	0.96	0.78	0.78	1	0.99	1
BRCA2-31	0.95	0.79	0.8	1	0.99	1
BRCA2-32	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-33	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-34	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-35	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-36	1	0.77	0.78	1	1	1
BRCA2-37	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-38	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-39	1.01	0.75	0.88	0.99	1.01	0.99
BRCA2-40	0.95	0.78	0.78	1	0.99	1
BRCA2-41	0.95	0.79	0.8	1	0.99	1
BRCA2-42	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-43	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-44	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-45	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-46	1	0.77	0.78	1	1	1
BRCA2-47	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-48	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-49	1.01	0.75	0.88	0.99	1.01	0.99
BRCA2-50	0.95	0.78	0.78	1	0.99	1
BRCA2-51	0.95	0.79	0.8	1	0.99	1
BRCA2-52	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-53	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-54	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-55	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-56	1	0.77	0.78	1	1	1
BRCA2-57	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-58	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-59	1.01	0.75	0.88	0.99	1.01	0.99
BRCA2-60	0.95	0.78	0.78	1	0.99	1
BRCA2-61	0.95	0.79	0.8	1	0.99	1
BRCA2-62	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-63	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-64	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-65	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-66	1	0.77	0.78	1	1	1
BRCA2-67	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-68	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-69	1.01	0.75	0.88	0.99	1.01	0.99
BRCA2-70	0.95	0.78	0.78	1	0.99	1
BRCA2-71	0.95	0.79	0.8	1	0.99	1
BRCA2-72	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-73	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-74	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-75	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-76	1	0.77	0.78	1	1	1
BRCA2-77	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-78	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-79	1.01	0.75	0.88	0.99	1.01	0.99
BRCA2-80	0.95	0.78	0.78	1	0.99	1
BRCA2-81	0.95	0.79	0.8	1	0.99	1
BRCA2-82	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-83	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-84	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-85	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-86	1	0.77	0.78	1	1	1
BRCA2-87	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-88	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-89	1.01	0.75	0.88	0.99	1.01	0.99
BRCA2-90	0.95	0.78	0.78	1	0.99	1
BRCA2-91	0.95	0.79	0.8	1	0.99	1
BRCA2-92	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-93	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-94	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-95	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-96	1	0.77	0.78	1	1	1
BRCA2-97	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-98	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-99	1.01	0.75	0.88	0.99	1.01	0.99
BRCA2-100	0.95	0.78	0.78	1	0.99	1
BRCA2-101	0.95	0.79	0.8	1	0.99	1
BRCA2-102	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-103	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-104	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-105	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-106	1	0.77	0.78	1	1	1
BRCA2-107	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-108	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-109	1.01	0.75	0.88	0.99	1.01	0.99
BRCA2-110	0.95	0.78	0.78	1	0.99	1
BRCA2-111	0.95	0.79	0.8	1	0.99	1
BRCA2-112	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-113	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-114	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-115	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-116	1	0.77	0.78	1	1	1
BRCA2-117	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-118	0.96	0.78	0.79	1.01	0.97	1.01
BRCA2-119	1.01	0.75	0.88	0.99	1.01	0.99
BRCA2-120	0.95	0.78	0.78	1	0.99	1
BRCA2-121	0.95	0.79	0.8	1	0.99	1
BRCA2-122	0.95	0.75	0.72	1.01	0.98	1.01
BRCA2-123	0.98	0.78	0.81	1.01	0.98	1.01
BRCA2-124	0.95	0.75	0.77	1.02	0.97	1.02
BRCA2-125	0.96	0.75	0.8	1.01	0.98	1.01
BRCA2-126	1	0.77	0.78	1	1	1
BRCA2-127	0.99	0.77	0.78	0.99	1.02	0.99
BRCA2-128	0.96	0.78	0.79	1.01		