Search for new genomic changes associated with high risk of cancer

Cezary Cybulski1, Wojciech Kluźniak1, Tomasz Huzarski1, Dominika Wokołorczyk1, Bogna Rusak1, Klaudia Stempa1, Aniruddh Kashyap1, Anna Jakubowska1, Marek Szwiec2, Tadeusz Dębniak1, Jacek Gronwald1, Steven A Narod3, Mohammad R Akbari3, Jan Lubiński1, the Polish Hereditary Breast Cancer Consortium

International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland

Genetic homogeneous population of Poland

Founder mutations associated with breast cancer

- BRCA1 3 alleles 0.5% freq.
- CHEK2 3 alleles 1% freq.
- NBS1 1 allele 0.6% freq.
- PALB2 2 alleles 0.2% freq

Togther 7 alleles 2% freq.

about 0.5 mln carriers

Gorski et al, AJHG 2000
Cybulski et al, JCO 2011

PALB2 mutations in Poland

	Total (n)	*PALB2* mutation-positive (n)	Prevalence (%)	Odds ratio (95% CI)	p value
Patients with unselcted breast cancer					
Any *PALB2* mutation	12 529	116	0·93%	4·39 (2·3–8·4)	<0·0001
509_510delGA	12 529	76	0·61%	4·09 (1·9–8·9)	<0·0001
172_175delTTGT	12 529	40	0·32%	5·02 (1·6–16·2)	0·0016

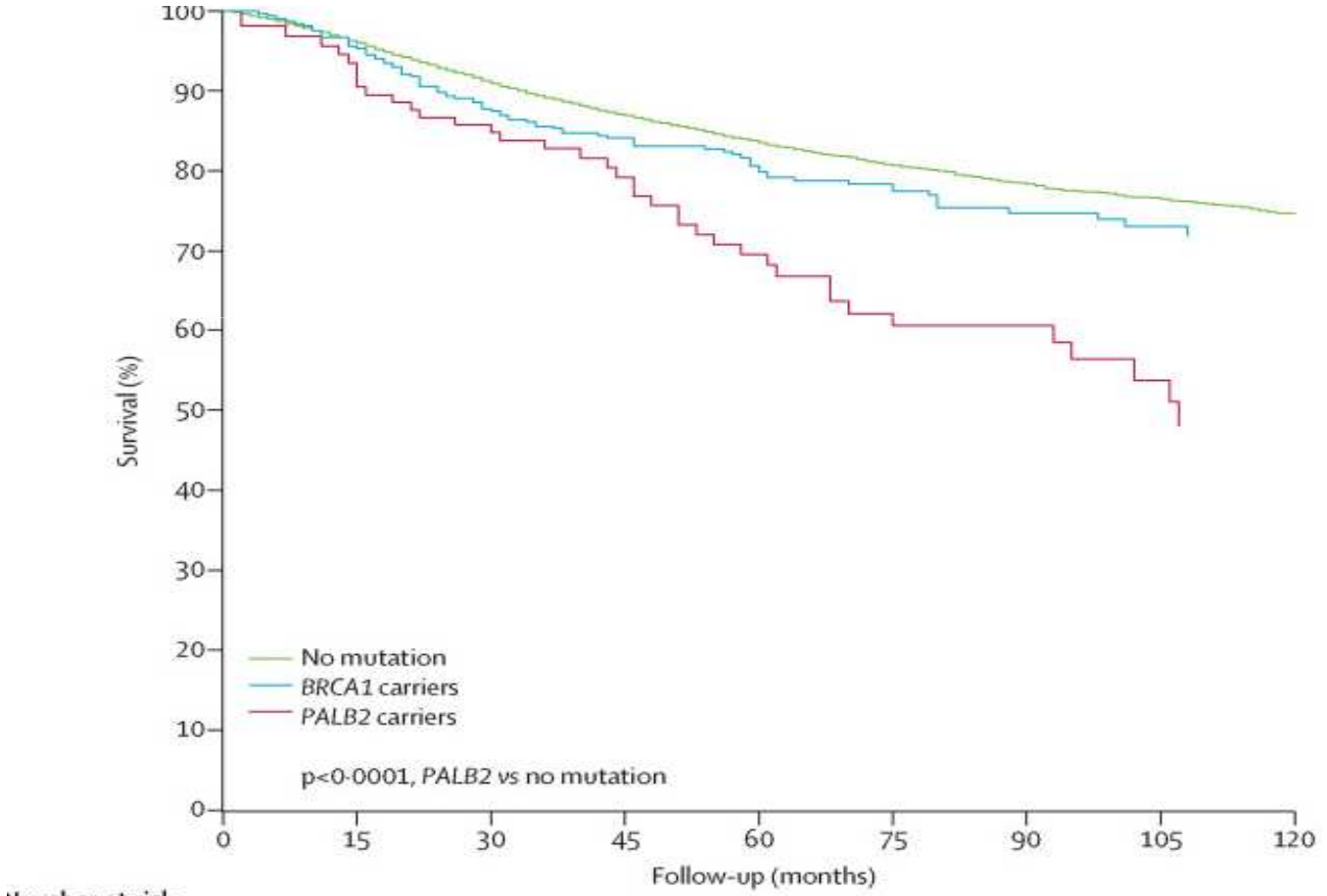
- 13 087 BC cases and 5488 controls from East Anglia, UK

Truncating variants in *PALB2*

OR=4.7, 95% CI 2.27 to 9.68

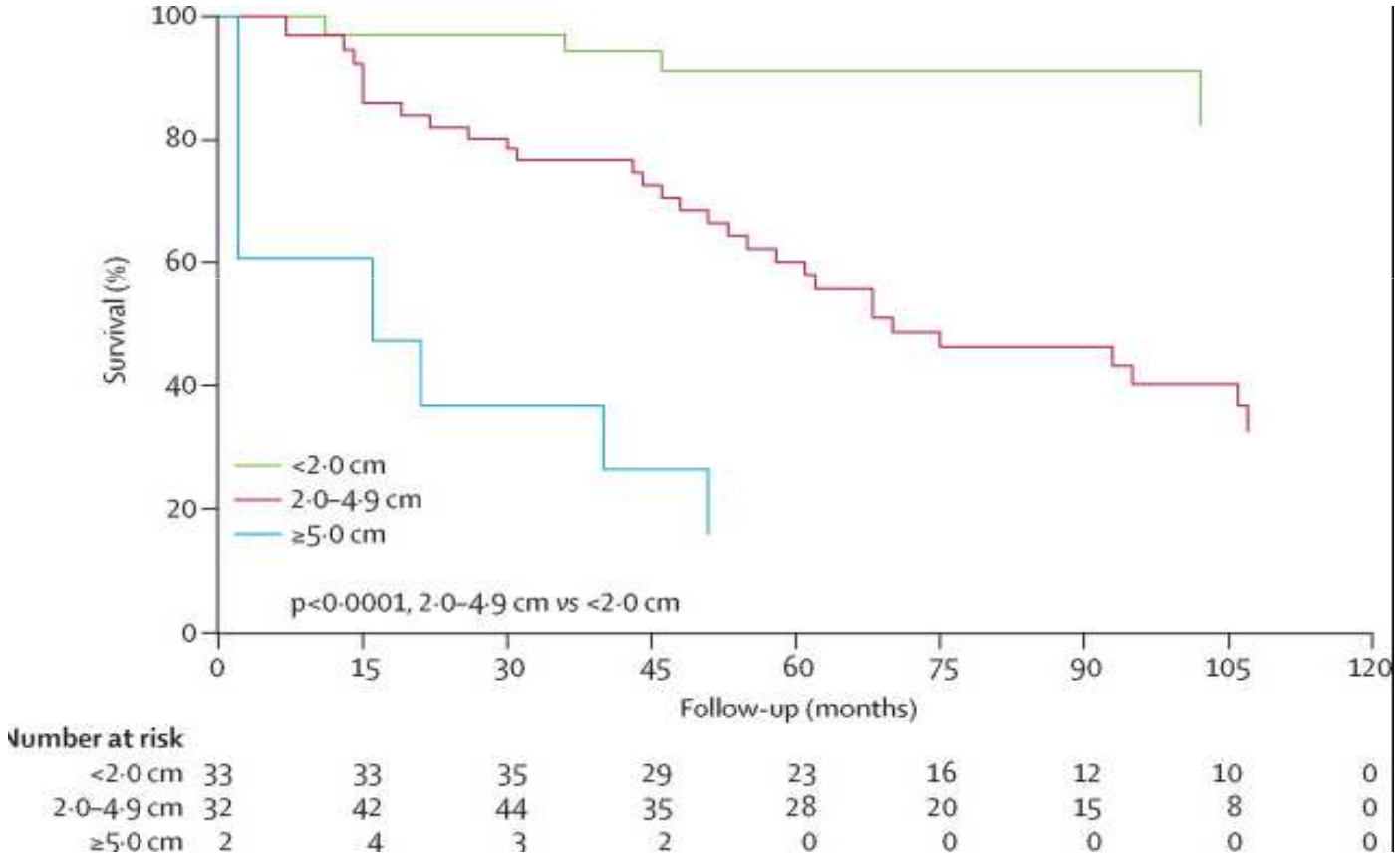
Decker B, J Med Genet. 2017

10-year survival after breast cancer in patients who carry a PALB2 mutation (n = 116), BRCA1 mutation (n = 435) and non-carriers (n = 11978)



Number at risk									
No mutation	4648	9881	9481	7117	5900	4250	2960	2087	1309
BRCA1 carriers	281	361	332	259	227	162	114	65	0
PALB2 carriers	51	92	87	67	53	38	28	16	0

10-year survival after diagnosis of breast cancer in patients with a *PALB2* mutation, by tumour size



PALB2 and breast cancer risk

10% baseline risk of BC

OR = 4.5; p<0,0001

45% lifetime risk

OR = 8.5; p<0,0001

85% familal cases of breast cancer

Exome sequencing – 2013r.

- 144 women with breast cancer from Polish HBC familes

  negative for fouder mutations of BRCA1, CHEK2, NBS1

New gene - RECQL

I Discovery phase

WES

144 Polish HBC cases

51 FC HBC cases

Mutation (DNA)*	Protein	Frequency	Frequency in NHLBI exome database‡
c.1219C>T	**p.Arg407***	**1/144**	**0/4300**
c.1513G>T	**p.Glu505***	**1/144**	**0/4300**
c.132_135delGAAA	p.Lys45fs	1/51	0/4300
c.426delT	p.Ser142fs	1/51	0/4300
c.1138A>T	p.Lys380*	1/51	2/4300
TOTAL		5/195 (2.6%)	2/4300 (0.05%)

RECQL

Validation phase 1

Sanger sequencing of RECQL

- 475 Polish BC families

- 475 FC BC families

Mutation (DNA)*	Protein	Freq.	Freq. in NHLBI exome data‡
c.634C>T	p.Arg215*	2/475 FC families	1/4300
c.1667_1667+3delAGTA	**p.K555delinsMYKLIHYSFR**	**2/475 Polish families**	**0/4300**

RECQL

Validation phase 2 ~ 26 000 subjects

of the 2 founder mutations

In Polish population:

c.1667_1667+3delAGTA

32/13611 unselected cases *vs* 2/4702 controls

OR = 5.5; p = 0.005

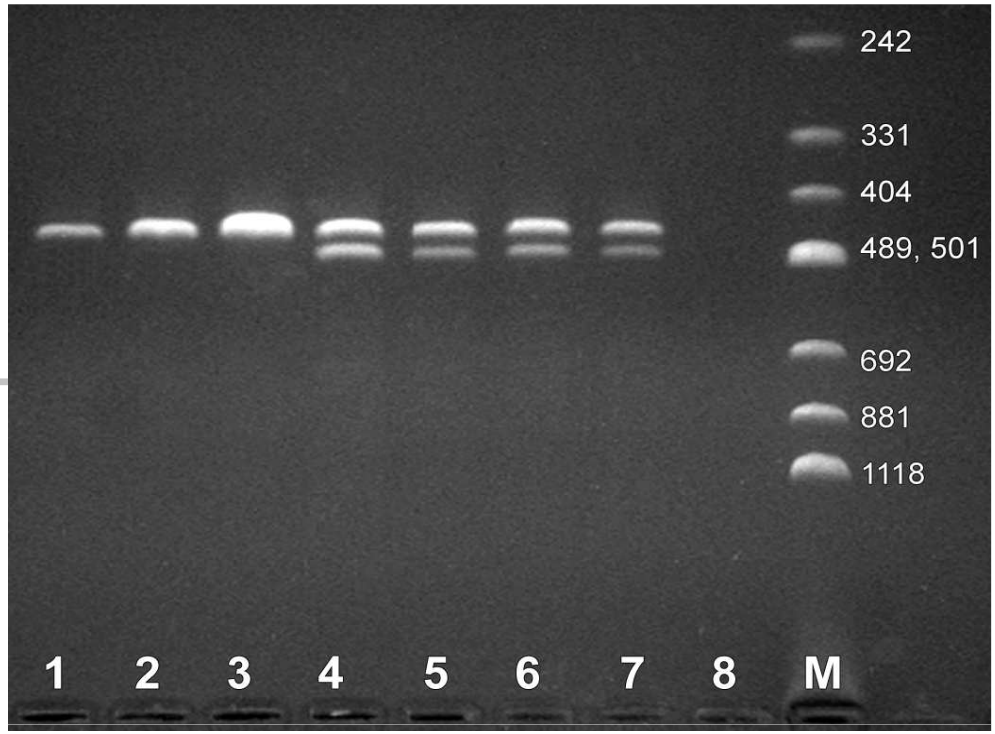
In FC population:

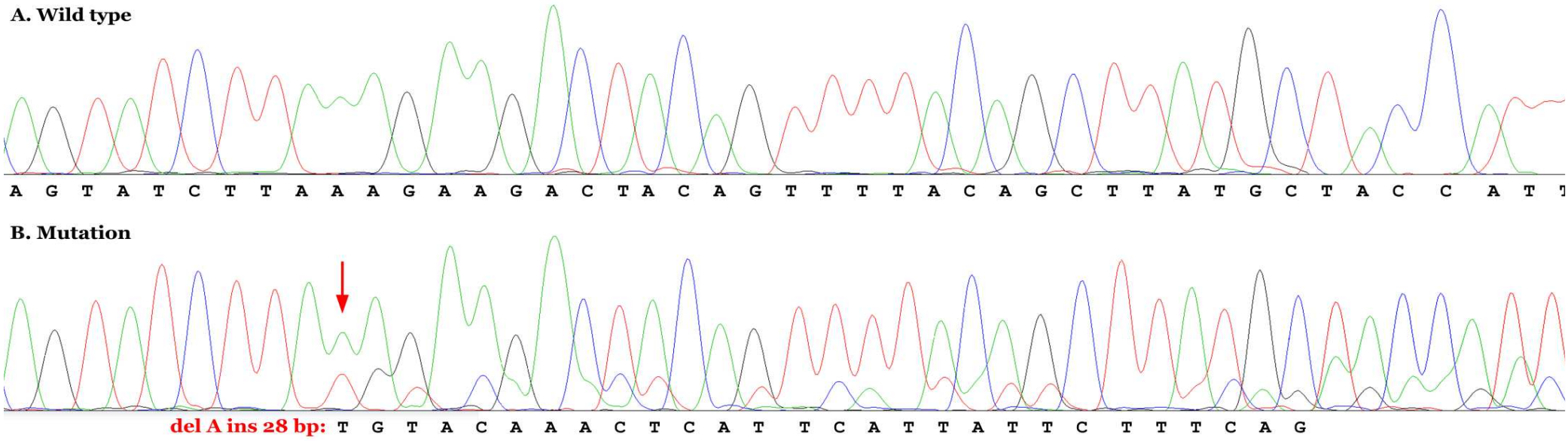
c.634C>T

7/1013 higher risk cases *vs* 1/7000 controls

OR = 16; p = 0.00004

Analysis of c.1667_1667+3delAGTA on RNA level





nature genetics

Home | Current issue | Comment | Research | Archive ▾ | Authors & referees ▾ | About the journal ▾

NATURE GENETICS | LETTER

Germline *RECQL* mutations are associated with breast cancer susceptibility

Cezary Cybulski, Jian Carrot-Zhang, Wojciech Kluźniak, Barbara Rivera, Aniruddh Kashyap, Dominika Wokołorczyk, Sylvie Giroux, Javad Nadaf, Nancy Hamel, Shiyu Zhang, Tomasz Huzarski, Jacek Gronwald, Tomasz Byrski, Marek Szwiec, Anna Jakubowska, Helena Rudnicka, Marcin Lener, Bartłomiej Masojć, Patrica N Tonin, Francois Rousseau, Bohdan Górski, Tadeusz Dębniak, Jacek Majewski, Jan Lubiński, William D Foulkes, Steven A Narod & Mohammad R Akbari

Affiliations | **Contributions** | **Corresponding author**

Nature Genetics (2015) | doi:10.1038/ng.3284

Received 21 November 2014 | Accepted 30 March 2015 | Published online 27 April 2015

PLoS Genet. 2015 May 6;11(5):e1005228. doi: 10.1371/journal.pgen.1005228. eCollection 2015.

Mutations in RECQL Gene Are Associated with Predisposition to Breast Cancer.

Sun J[1], Wang Y[1], Xia Y[2], Xu Y[1], Ouyang T[1], Li J[1], Wang T[1], Fan Z[1], Fan T[1], Lin B[1], Lou H[2], Xie Y[1].

Abstract

The genetic cause for approximately 80% of familial breast cancer patients is unknown. Here, by sequencing the entire exomes of nine early-onset familial breast cancer patients without BRCA1/2 mutations (diagnosed with breast cancer at or before the age of 35) we found that two index cases carried a potentially deleterious mutation in the RECQL gene (RecQ helicase-like; chr12p12). Recent studies suggested that RECQL is involved in DNA double-strand break repair and it plays an important role in the maintenance of genomic stability. Therefore, we further screened the RECQL gene in an additional 439 unrelated familial breast cancer patients. In total, we found three nonsense mutations leading to a truncated protein of RECQL (p.L128X, p.W172X, and p.Q266X), one mutation affecting mRNA splicing (c.395-2A>G), and five missense mutations disrupting the helicase activity of RECQL (p.A195S, p.R215Q, p.R455C, p.M458K, and p.T562I), as evaluated through an in vitro helicase assay. Taken together, 9 out of 448 BRCA-negative familial breast cancer patients carried a pathogenic mutation of the RECQL gene compared with one of the 1,588 controls (P = 9.14×10-6). Our findings suggest that RECQL is a potential breast cancer susceptibility gene and that mutations in this gene contribute to familial breast cancer development.

RECQL

Association :

Poland: 30 / 13,136 cases vs 2 / 4,702 controls (OR = 5.4; p = 0.008).

FC : 7/1,013 patients 1/7,136 newborns (OR = 49.3; p < 10-5).

China

- Sun et al. 5/448 patients vs compared 1/ 1,588 controls (OR = 31.9; p < 10-5).
- Sun, et al. 30/8,085 patients vs 1/ 1,588 controls (OR = 5.8)

Finland:

- Tervasmaki et al. (p.I156M) 6/ 1,946 breast cancer patients 0/1,539 controls

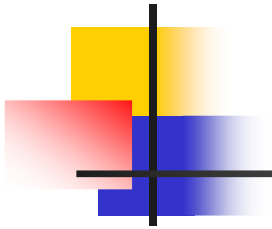
RECQL

No association:

- Bogdanova et al. (Belarusian and German) Polish *RECQL* mutation 9 of 2,596 cases (0.35%) vs 6 of 2,132 (0.28%) controls

- Li et al. (2018) RECQL mutation in 12 of 4,412 Australian patients (0.27%) and 25 of 4,576 controls (0.54%).

  They found the most common mutation possibly benign nonsense mutation (p.Ser620*) near the coding terminus, which accounted for the majority of RECQL mutations in both cases (50%) and in controls (64%).



- data on *RECQL* illustrate the difficulty of establishing the contribution of very rare variants to breast cancer susceptibility

New Breast cancer study 2017

- **~ 4000 unrelated Polish women with breast cancer** from families familial breast cancer negative for **BRCA1 C61G, 5382insC and 4153delA**

HBC families negative for BRCA1 C61G, 5382insC and 4153delA

- **715 HBC „strong" families were genotyped**

BRCA1 (3 mutations),

BRCA2 (5 alleles),

CHEK2 (3 mutations),

PALB2 (2 mutations)

NBS1 (1 mutations)

RECQL (1 mutation)

HBC families negative for C61G, 5382insC and 4153delA

- **98 of 715 (13.7%) women tested positive**
- 617 women tested negative for founder mutations – we did exome sequencing of these

Spectrum of mutations in breast cancer associated genes in 715 Polish HBC families (negative for 3 common founder

mutations of BRCA1 - C61G, 5382insC and 4153delA)

715 HBC families negative for BRCA1 C61G, 5382insC and 4153delA

Recurrent mutations:

- **3 BRCA1** 3819del5, 185delAG and 5370C>T - **3.4%**

- **5 BRCA2** mutations 886delGT, 4075delGT, 5467insT, 6174delT, 8138del5 – **1%**

<u>Founder BRCA1/2 mutations 4.4%</u>

HBC families negative for C61G, 5382insC and 4153delA

- Mutations detected by NGS

BRCA1 (28 mutations) – **6.8%**
BRCA2 (29 mutations) – **7.1%**

Other BRCA1/2 mutations - 14%

CHEK2

- 37 carriers (5 mutations) – **5.2%**
- 35 carries (3 founder mutations) – **4.8%**

3 CHEK2 mutations - 35/37 (95%)

PALB2

- 22 carriers (6 mutations) – **3.3%**
- 18 carriers (2 founder mutations) – **2.5%**

2 PLAB2 mutations - 18/22 (80%)

NBS1

- **1 mutation -** 1% (7 carriers)

RECQL

- **7 carriers** (4 mutations) – **1%**

Other genes

- **ATM** (4 mutations) – 1%
- **PTEN** (1 mutation) - 0.2%
- **RAD50** (1 mutation) - 0.2%
- **TP53** (1 mutation) - 0.2%

Conclusions

- **The most important genes associated with breast cancer susceptibility in Poland inlcude:**

  BRCA1, BRCA2, CHEK2, PALB2

Conclusions

- **Polish families with HBC should be first tested for a panel of at least 6 founder BRCA1/2 mutations**

- **Mutation negative HBC cases should be selected for NGS of BRCA1/2**

Conclusions

- **5% of HBC families carry a truncating mutation of CHEK2**
- **The sensivity of CHEK2 testing based on detecting 3 Polish founder mutation is about 95%**
- **In Poland CHEK2 mutation sceening should based on testing for 3 founder alleles**

Conclusions

- **3.3% of HBC families carry a truncating mutation of PALB2**
- **The sensivity of PALB2 testing based on detecting 2 Polish founder mutation is about 80%**
- **In Poland PALB2 mutation sceening should started from testing for 2 founder alleles**

- Still about a half of HBC families have no mutation detected in any of known susceptibility genes

- we need more studies


PORADNIE GENETYCZNE
POMORSKA AKADEMIA MEDYCZNA
BIBLIOTEKA GŁÓWNA
FILIA NR 2
Zachodniopomorskie
Centrum Zaawansowanych Technologii
KONSORCJUM