

**3ο Συνέδριο της Ελληνικής Εταιρείας Φαρμακευτικής Ιατρικής  
Βιοϊατρική Έρευνα: Στοχεύοντας στην Καινοτομία**

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**Διευθυντής Ερευνών  
Εργαστήριο Μοριακής Διαγνωστικής  
ΙΠΡΕΤΕΑ  
Εθνικό Κέντρο Έρευνας Φυσικών Επιστημών Δημόκριτος**

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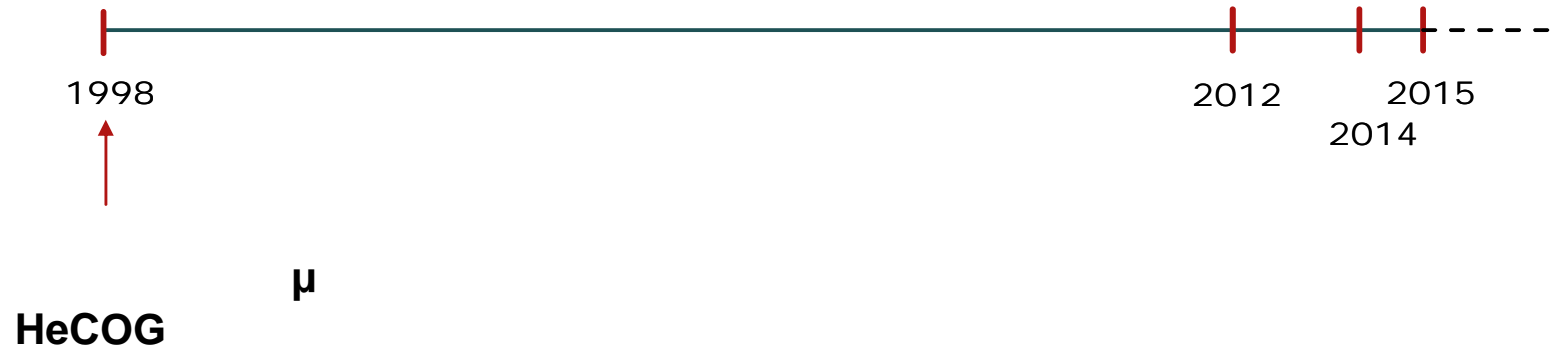


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*BRCA1, BRCA2*, other genes after genetic counseling (*TP53, STK11, MLH1, MSH2* etc) – Sanger seq

BROCA panel  
Mayo Clinic  
in-house panel – NGS

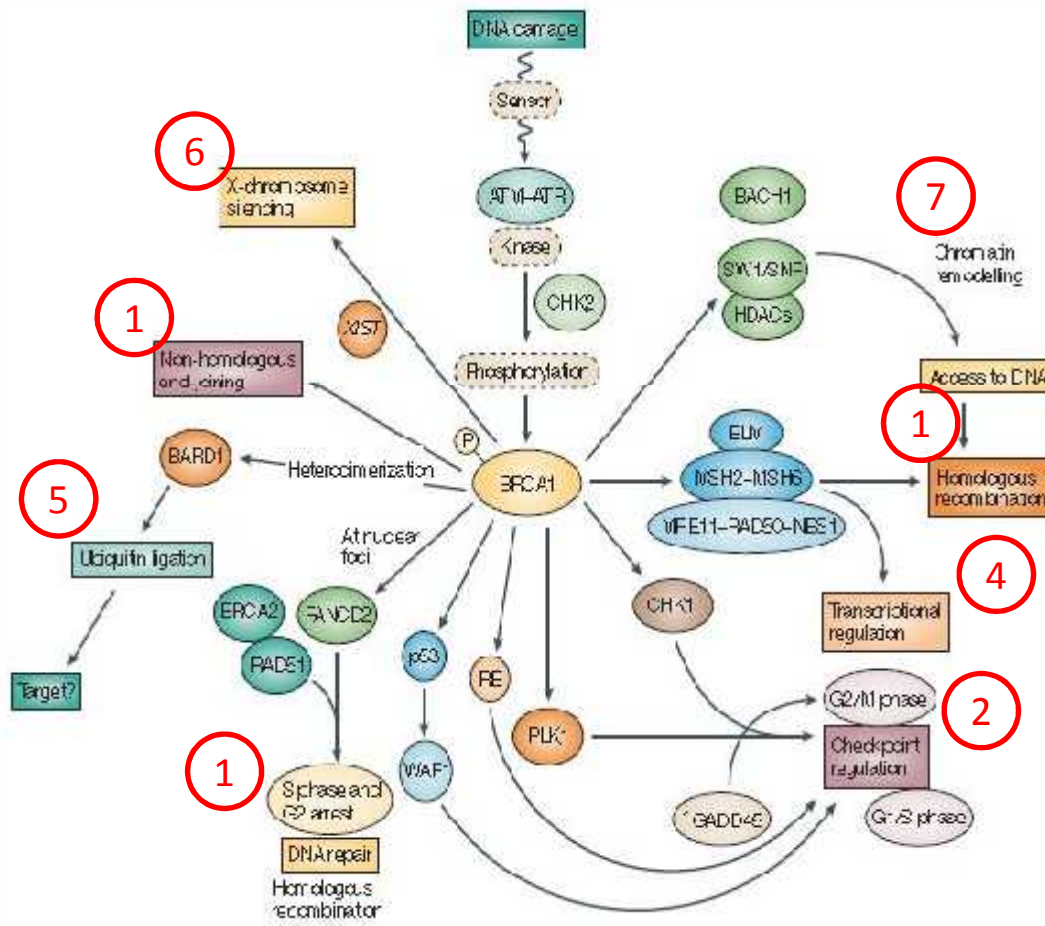




# Hereditary Cancer Predisposition Syndromes

<u>Syndrome</u>	<u>Gene</u>	<u>Organs affected</u>
breast/ ovarian	BRCA1	breast, ovaries
HBOC	BRCA2	breast, ovaries, prostate, pancreas
CHEK2	CHEK2	breast, thyroid, colon, kidney, osteo-, chondro-sarcomas ??
FAP	APC	colon, polyps
HNPCC	MLH1 , MSH2 PMS2, MSH6	colon, endometrium, ovaries, brain, urinary tract, biliary, other types of cancer
Peutz Jeghers	STK11/LKB1	Melanin pigmentation lips, hamartomatous intestinal polyps small bowel, colon, pancreatic, breast
Multiple Endocrine Neoplasia	1 RET	parathyroid, pituitary gland, pancreas, many others adrenals, thyroid, parathyroid
•Li-Fraumeni	p53,	breast, sarcomas, leukemia, brain
•Von-Hippel-Lindau	VHL	retina, kidney, cerebellum, spinal cord, adrenals
•Cowden	PTEN	breast, thyroid, ovaries, skin
•HDGC	CDH1	lobular breast ca, diffuse gastric ca

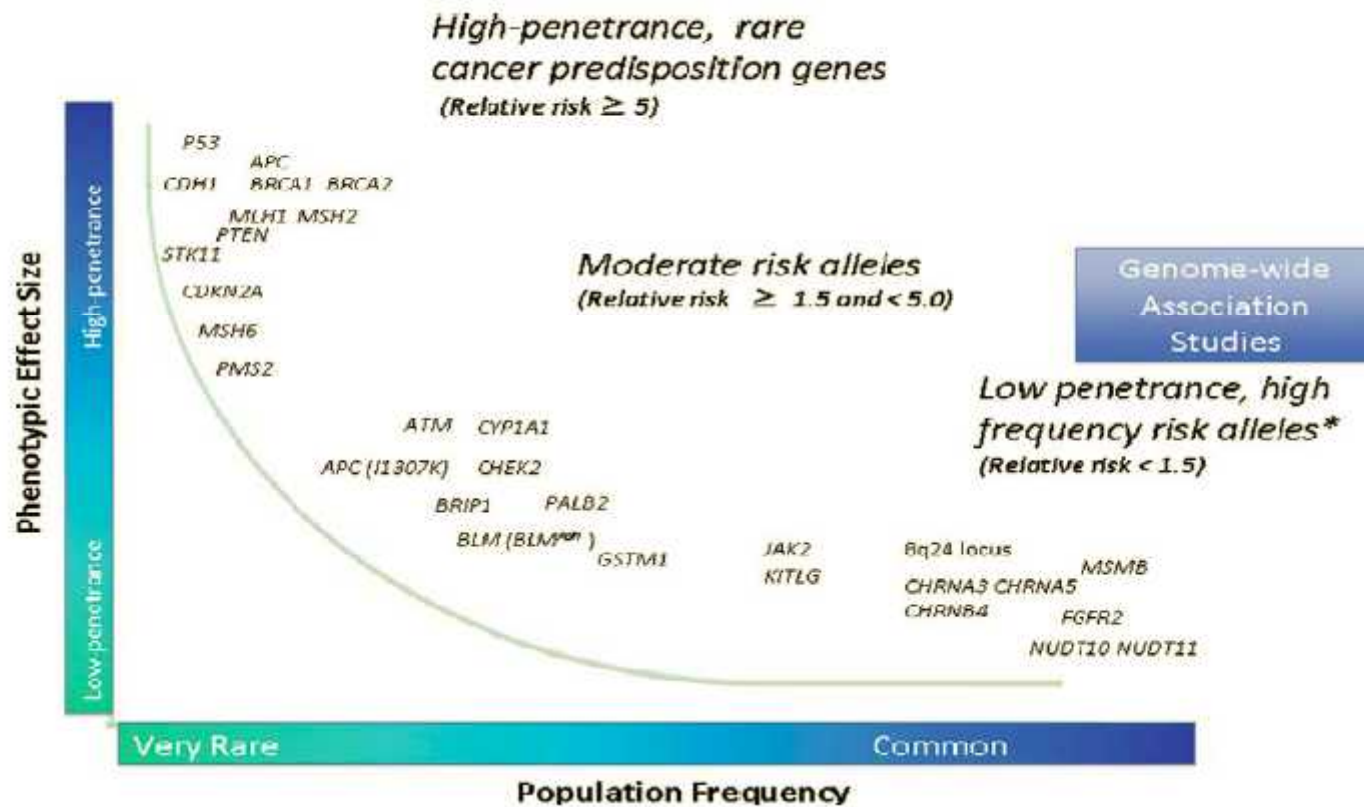
# Δίκτυο αλληλεπιδράσεων πρωτεϊνών που εμπλέκονται στον κληρονομικό καρκίνο



1. επιδιόρθωση DNA
2. έλεγχος κυτταρικού κύκλου
3. διατήρηση σταθερότητας γονιδιώματος
4. ρύθμιση μεταγραφής
1. ουβικιτινίωση πρωτεϊνών
2. αποσιώπηση X-χρωμοσώματος
3. αναδιαμόρφωση χρωματίνης



## Cancer Susceptibility Loci and Genes



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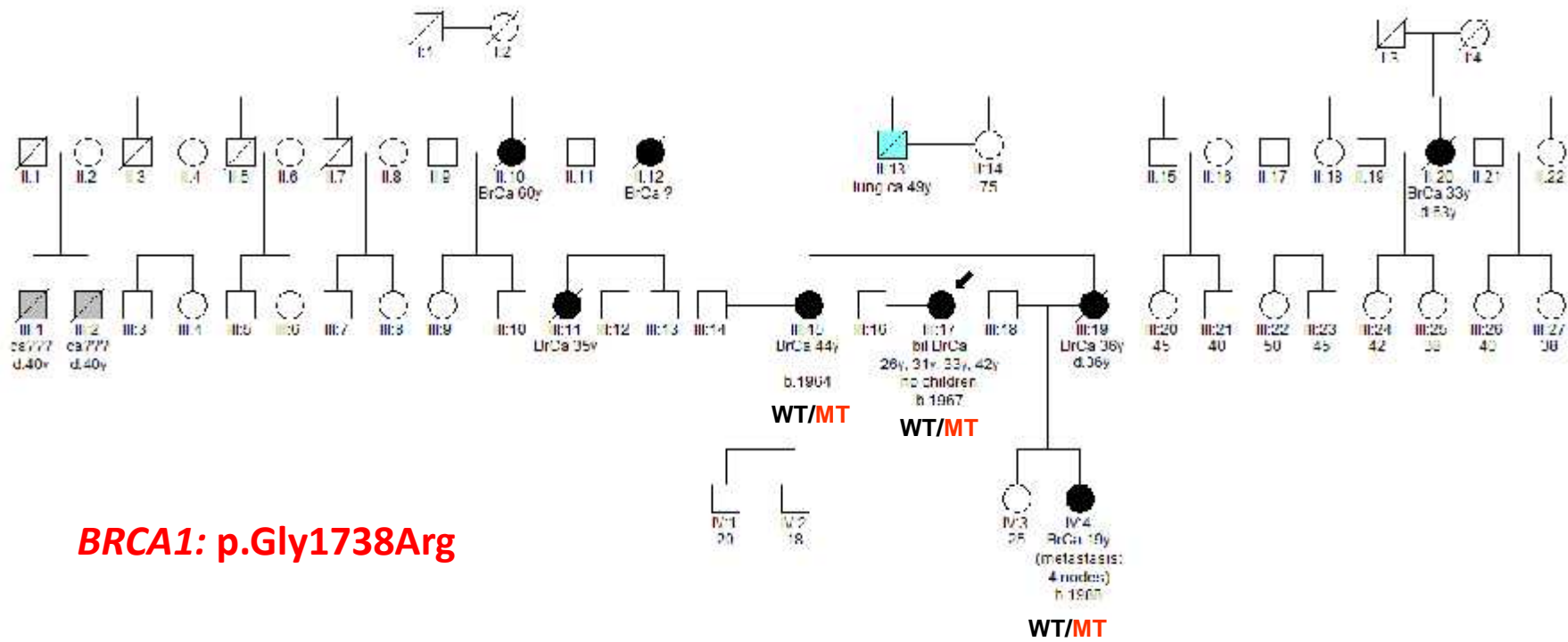
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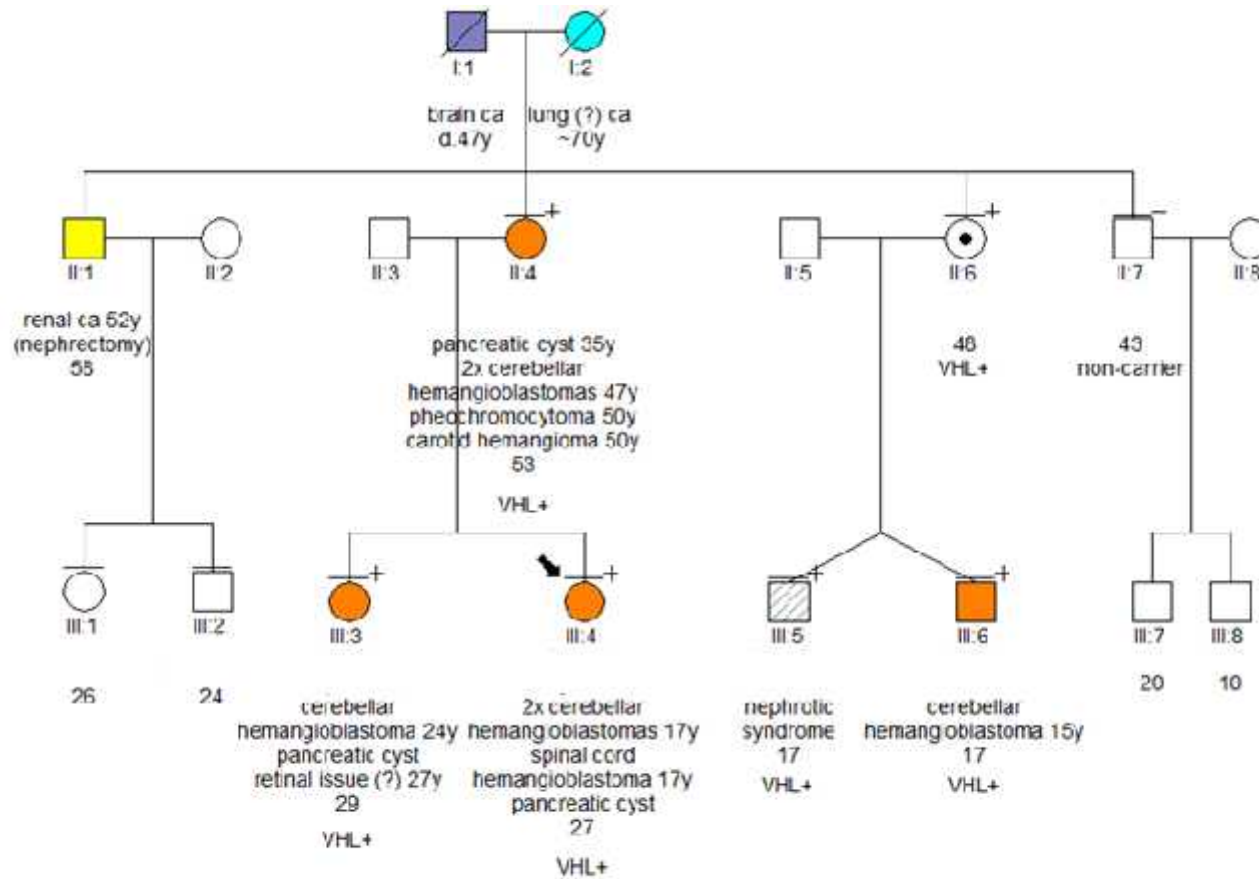
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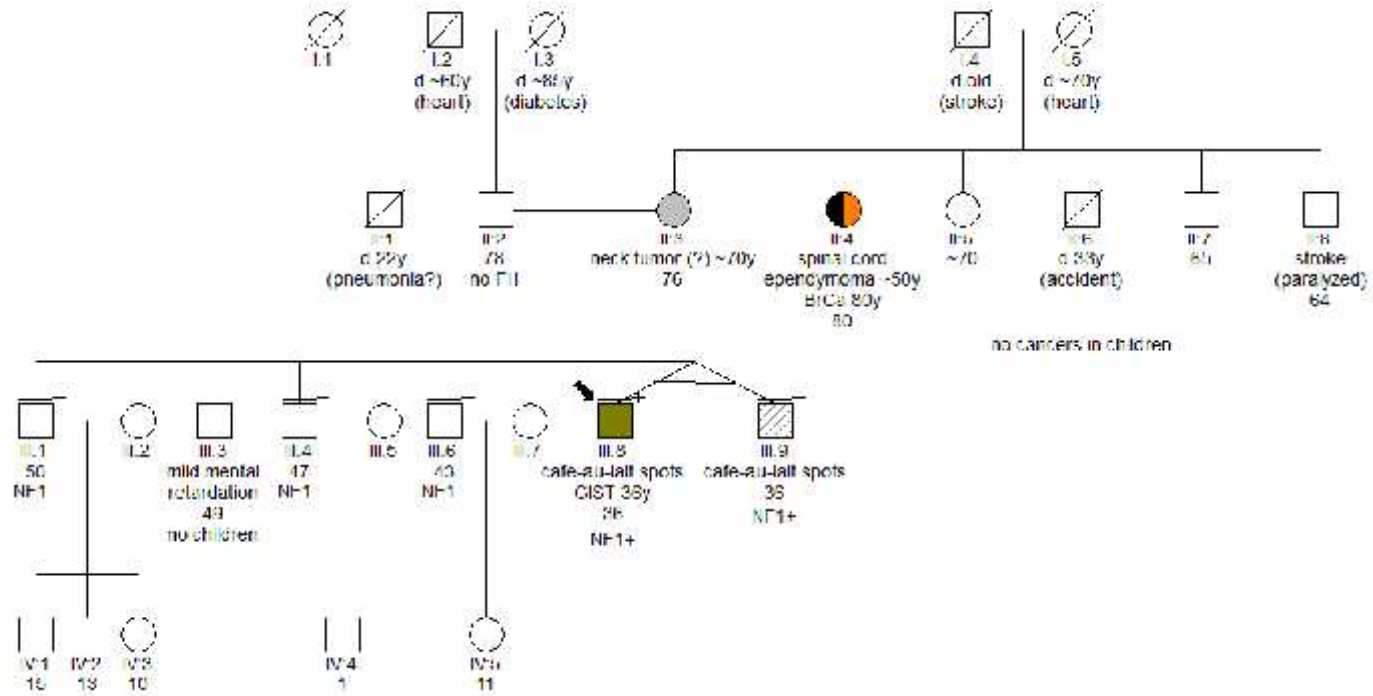


**BRCA1: p.Gly1738Arg**

# VHL

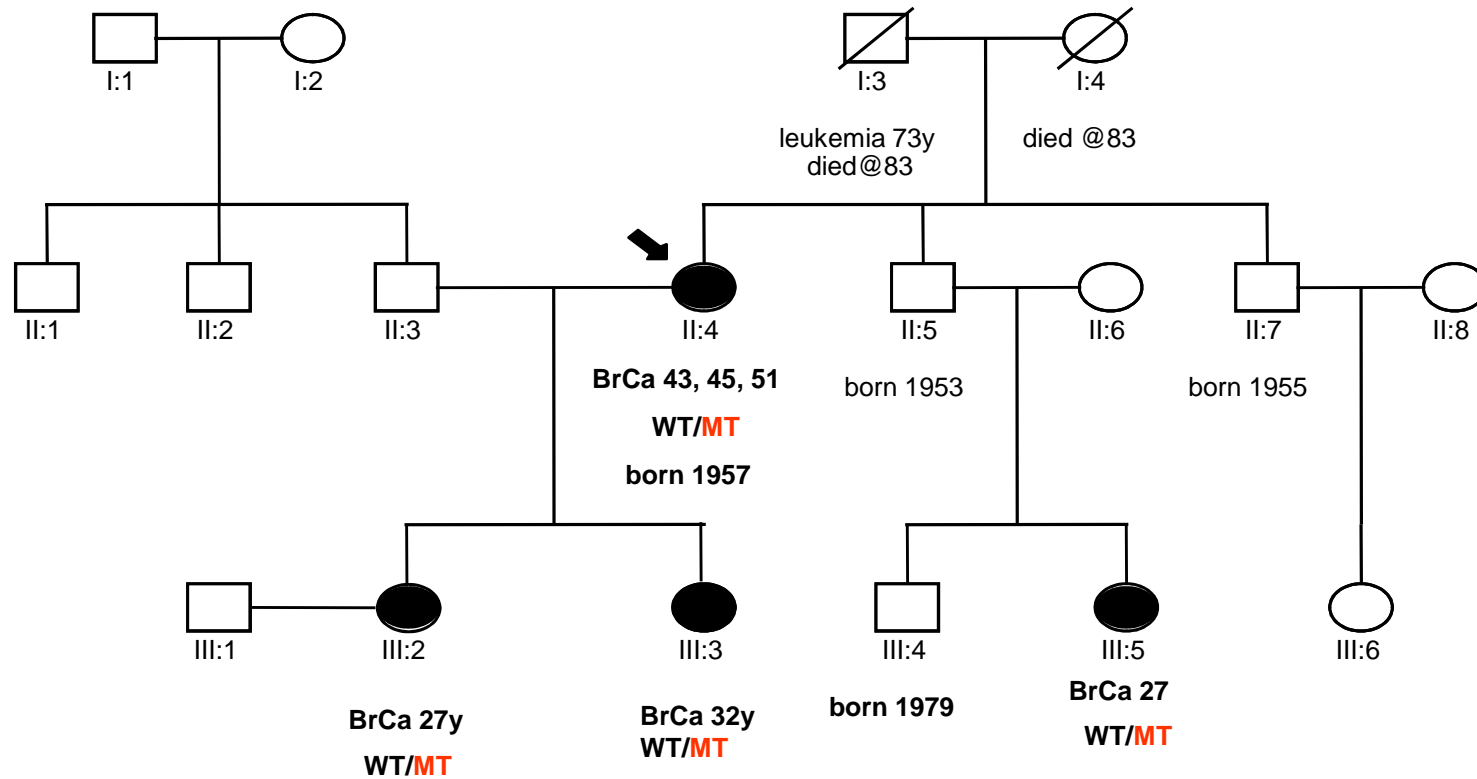


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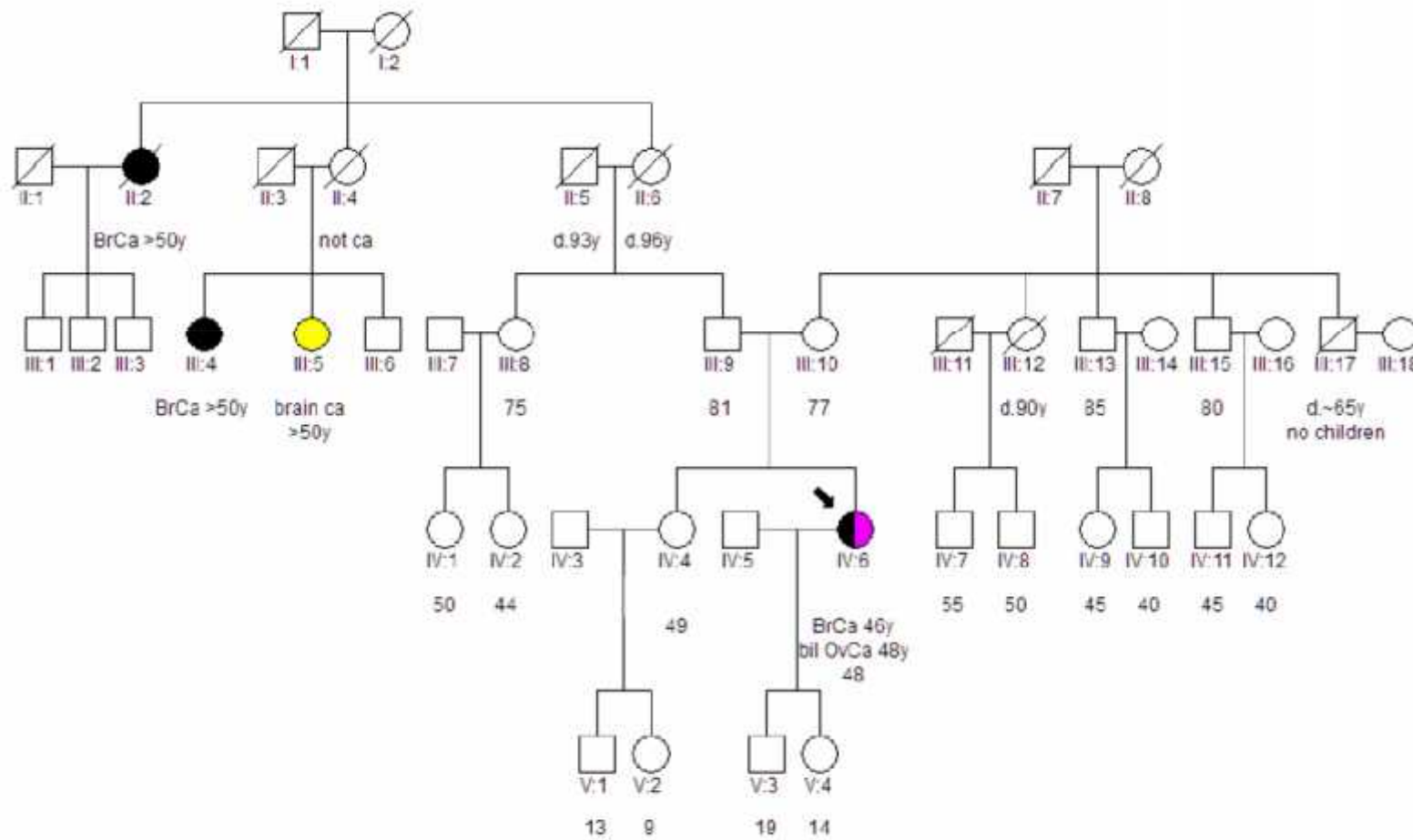


## BRCA1 5586G>A exon 23 skipping





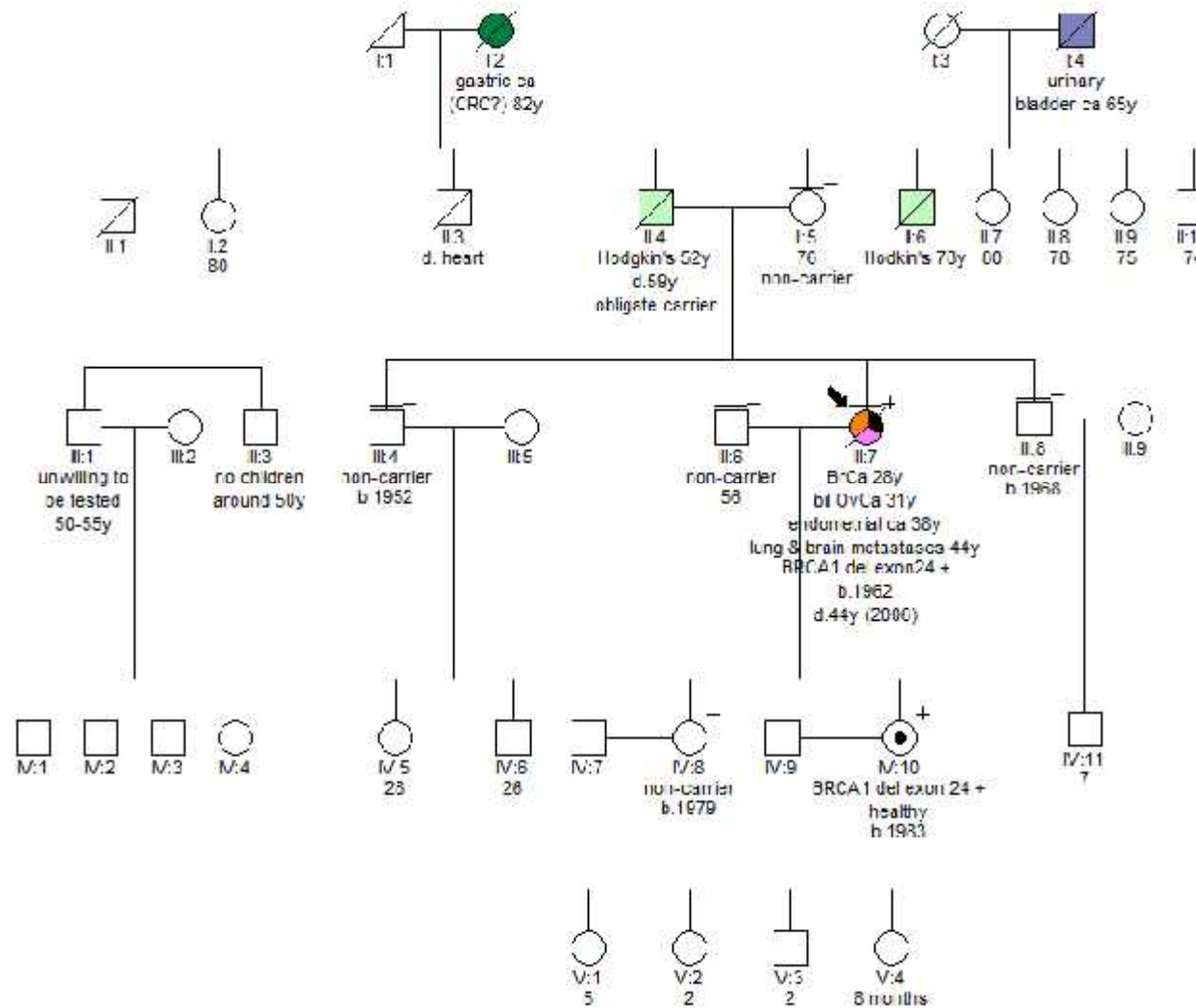
## BRCA1 exon 20 deletion





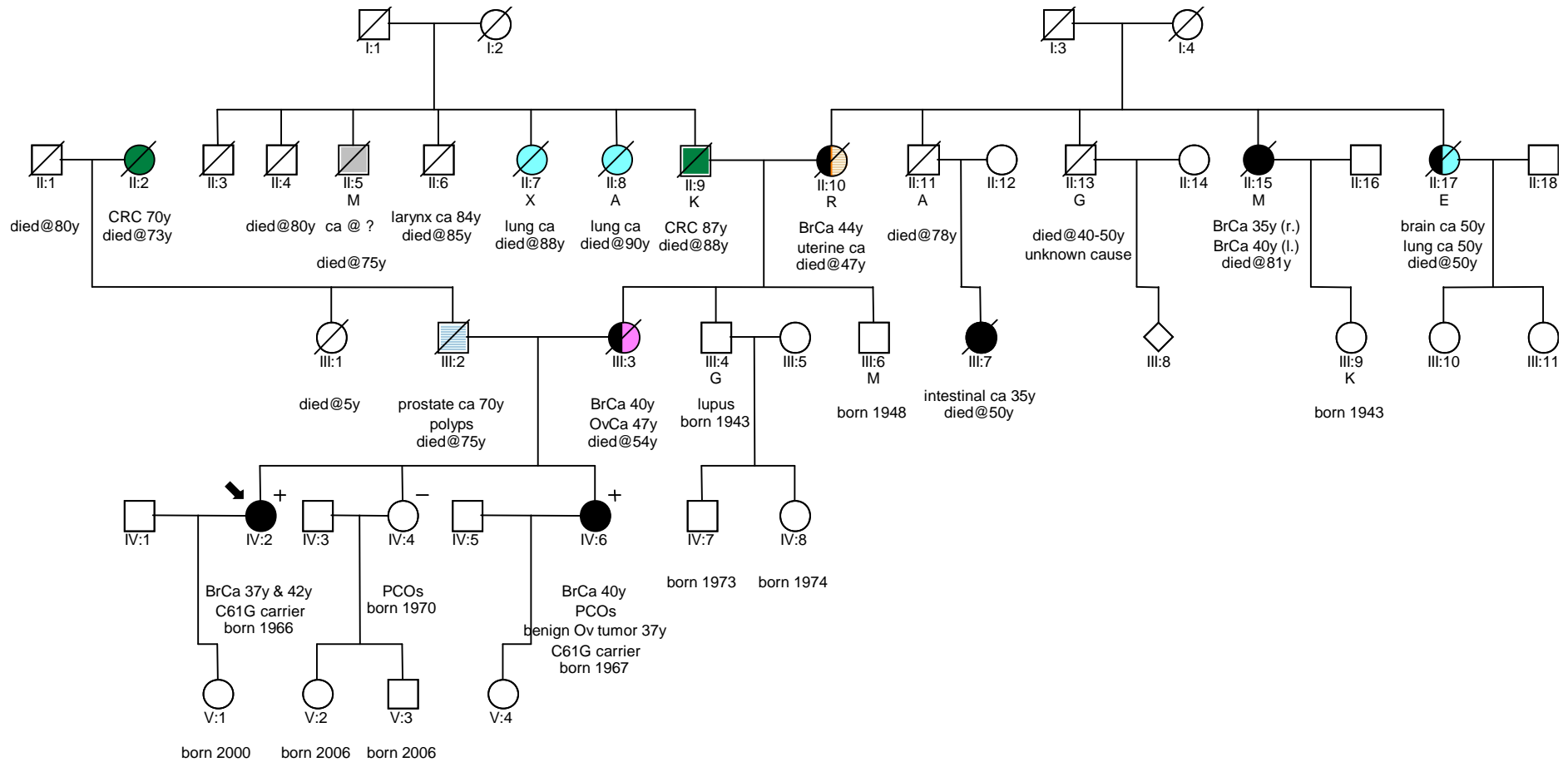


# BRCA1 exon 24 deletion



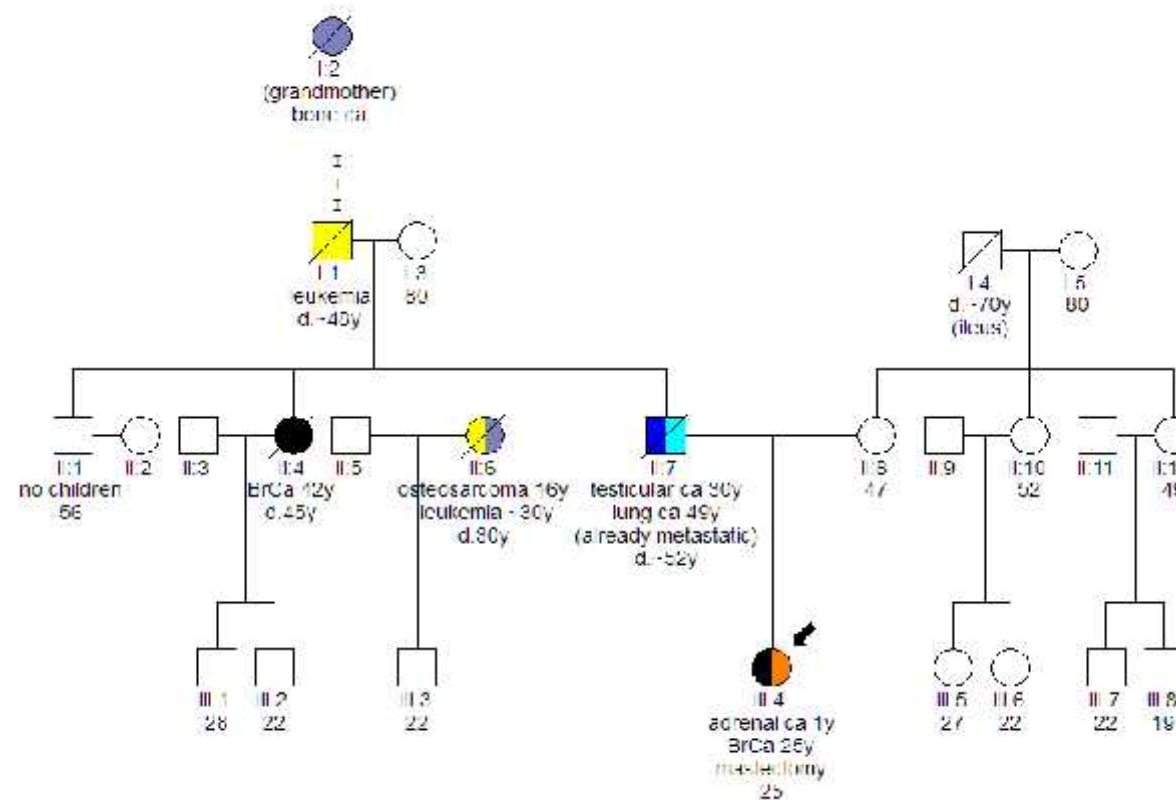


# BRCA1 C61G





# P53, p.C275X, Li-Fraumeni



grade II, 0/7 nodes+

**ER: + (20%)**

**PR: ++ (60%)**

**HER2: 3+**



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2010-2017

Επικοινωνήσαν  
περισσότερες από 600  
γυναίκες

183 μ μ

Αξιολογήθηκαν  
περισσότερες από 400  
γυναίκες





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2010-2017

μ 77

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✓ 64

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μ

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✓ 11 μ

✓ 2 μ

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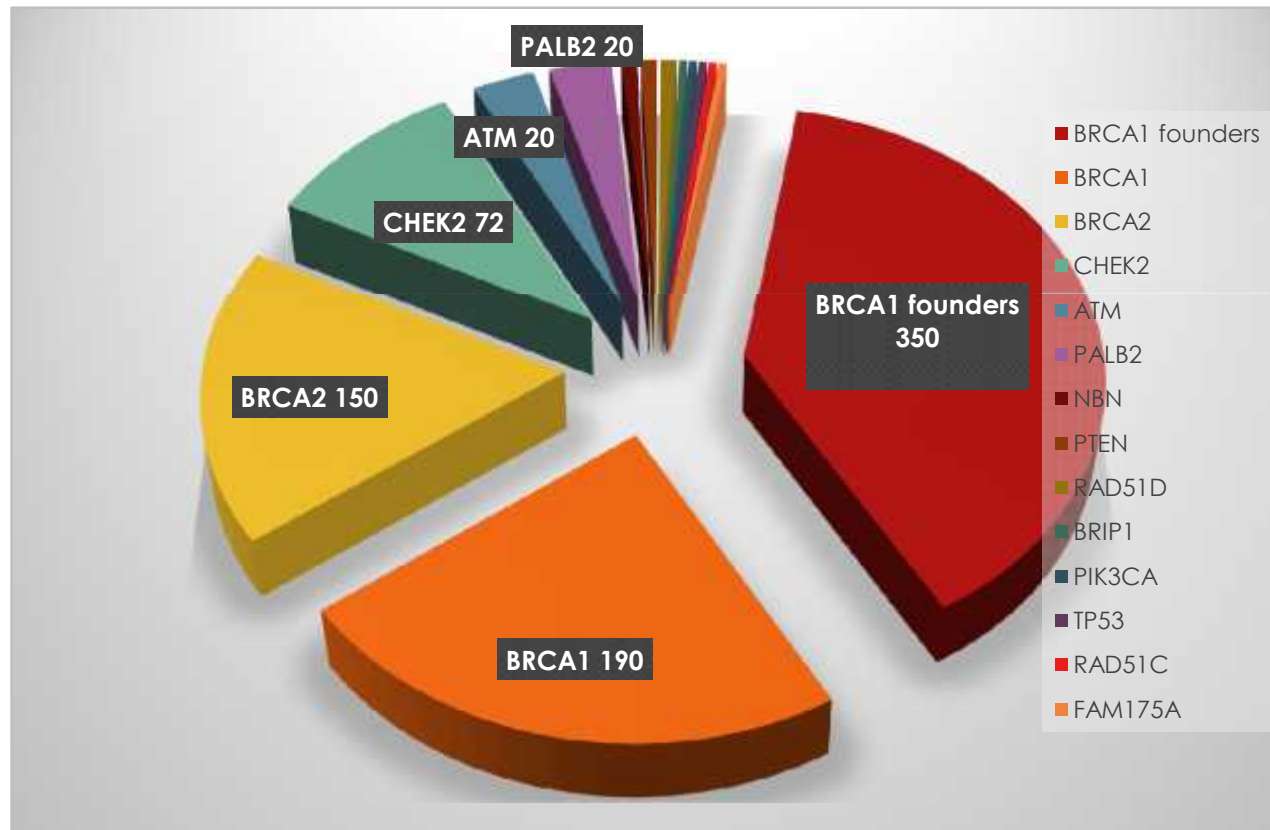




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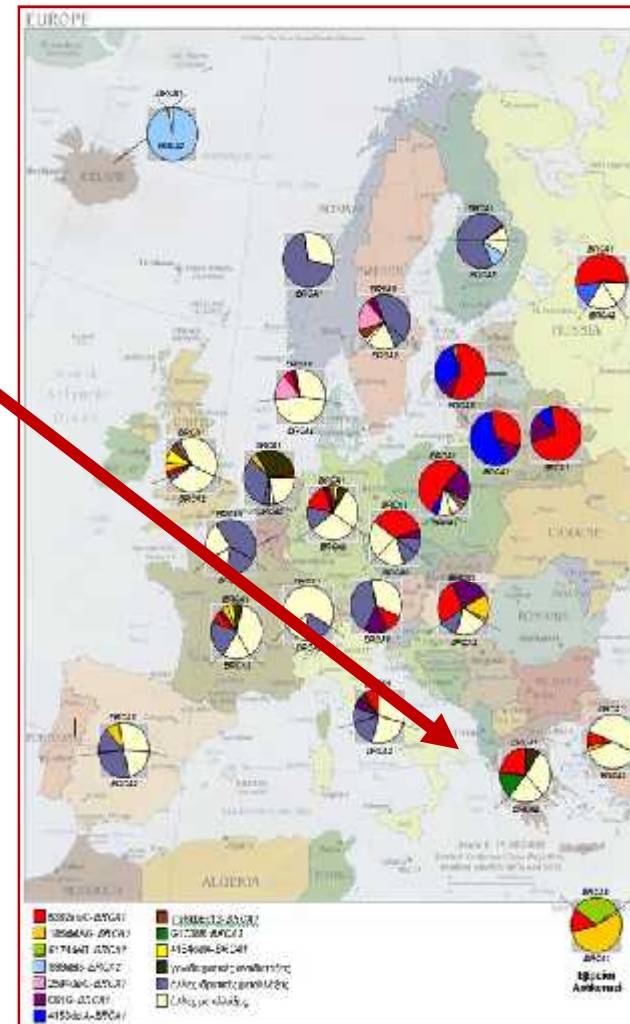
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## Number of families per founder mutation

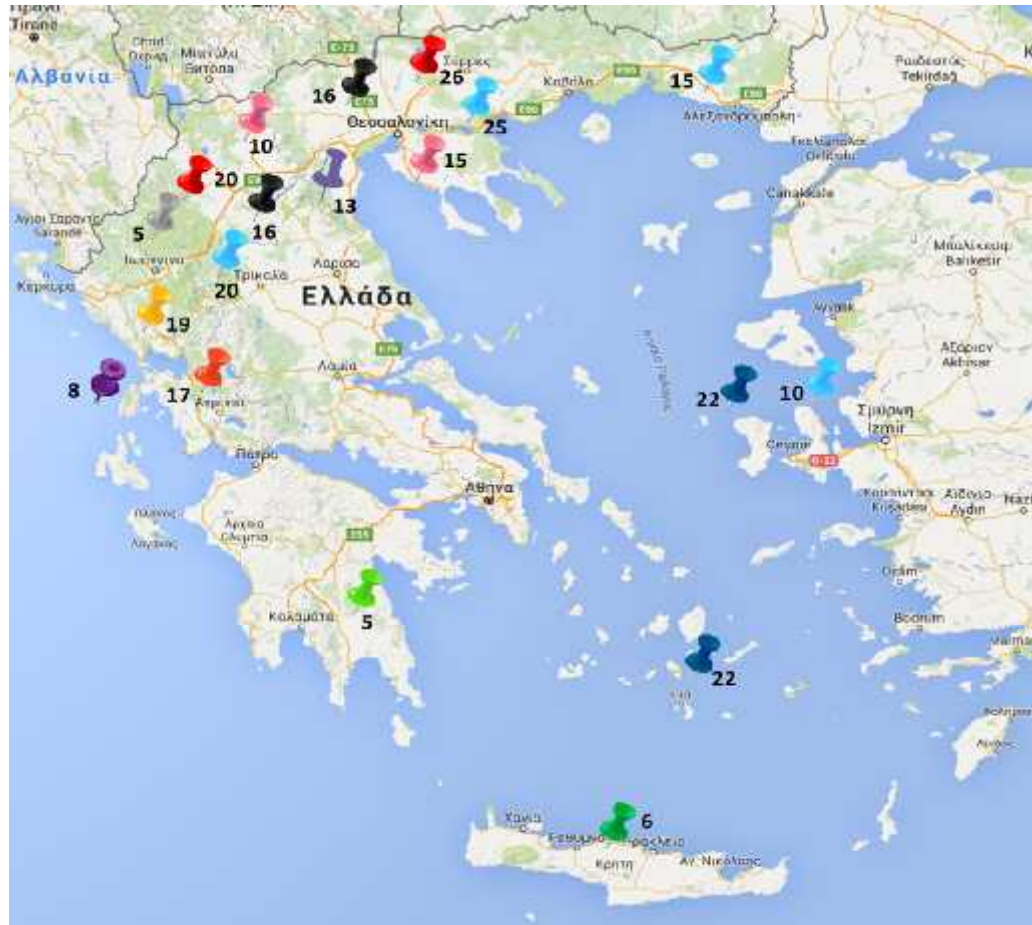
	Founder Mutation	# Families
1		
2	<b>BRCA1</b>	
3	exon 5 300T>G-Cys61Gly (C61G)	17
4	exon11 3725C>T Arg1203ter (R1203X)	12
5	exon11 3819del5-ter1241	13
6	exon20 5331G>A-Gly1738Arg (G1738R)	45
7	exon20 5370C>T-Arg1751ter (R1751X)	19
8	exon20 5263_5264insC (c.5265dupC)	70
9	exon23 5585G>A (skipping_ex23)	8
10	exon24 5615G>A-Val1833Met (V1833M)	20
11	del exon20 (del3.2KbEx20) (g.71660_74860del3200)	25
12	del exons 23 & 24 (g.80280_91331del11052 / L78833)	44
13	del exon24 (del4429ins5Ex24) (g.82651_87079del4429_Ins5)	32
14		
15	<b>BRCA2</b>	
16	del exons12-13	5
17		
18	<b>CHEK2</b>	
19	Δ exon 5 (g.30219_37793del7555)	5
20		
21		
22	<b>PALB2</b>	
23	p.A1g759X	5
24		
25	<b>RAD51C</b>	
26	c.706-2A>G	17



BLUE: haplotype analysis performed







c.5266dupC likely entered the AJ gene pool in Poland approximately 400-500 years ago










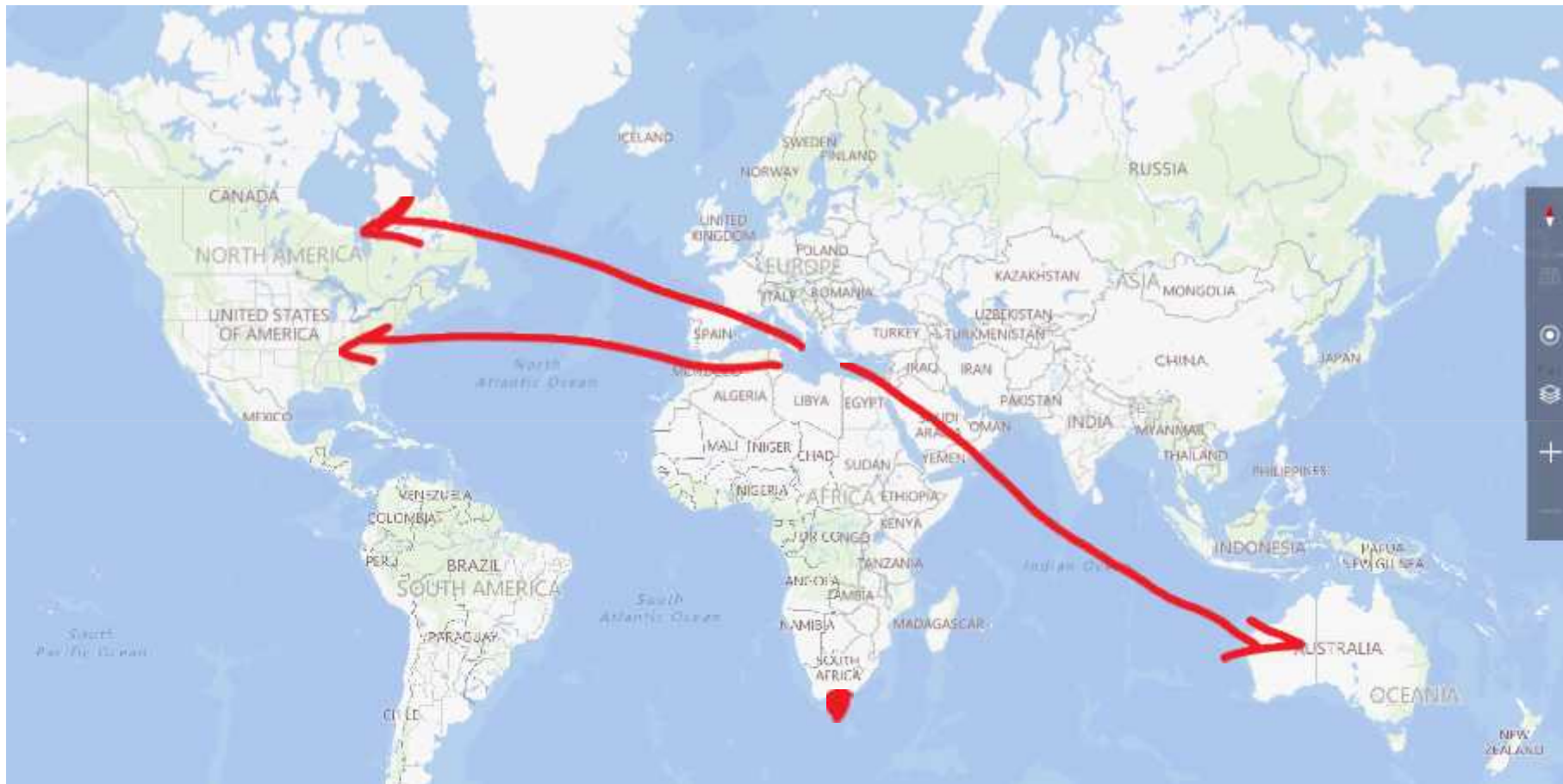
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-  **BRCA1, p.C61G**
-  **BRCA1, p.P1125fsX6**
-  **BRCA1, p.G1738R**
-  **BRCA1, 5382insC**
-  **BRCA1, del exon20**
-  **BRCA1, p.1803\_1822del20**

-  **BRCA1, del exon23-24**
-  **BRCA1, del exon24**
-  **BRCA2, del exon12-13**
-  **CHEK2, del exon6**
-  **RAD51C, c.706-2 A>G**

Greek founder mutations are found in places where Greeks have migrated the last two centuries



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## Funding

**ARISTEIA:** "Extreme Phenotypes in Breast-Ovarian Cancer: Whole exome analysis in very early onset (17-35yrs) cases". Duration 2012-2015.

**THALIS:** "Molecular Typing of Triple Negative Breast Cancer". Duration 2012-2015.

**SYNERGASIA:** "Detection of new breast cancer predisposing alleles through whole genome sequencing". Duration 2012-2015.

Hellenic Cooperative Oncology Group

Panhellenic Association of Women with Breast Cancer "Alma Zois"

### Provision of Services

#### Participation in international consortia

**Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA).** Coordinated by Dr Georgia Chenevix-Trench, Queensland Institute of Medical Research, Brisbane, Australia.

**Breast Cancer Association Consortium.** Coordinated by Prof. Doug Easton, Cambridge University, UK.

**Evidence-based Network for the Interpretation of Germline Mutant Alleles – ENIGMA.** Coordinated by Prof. A. Monteiro, Univ. S. Florida, Tampa, USA. <http://enigmaconsortium.org/>

**Ovarian Cancer Association Consortium – OCAC.** Coordinated by Prof. Paul Pharoah, Cambridge University

**Collaborative Oncological Gene-environment Study – COGS.** Coordinated by Prof. Per Hall, Karolinska Institute, Sweden <http://cogseu.org>

**Collaborative genomics for human health and cooperation in the Mediterranean region.** Coordinated by Prof. Mary-Claire King, University of Washington, Seattle.





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**Mary-Claire King, University of Washington School of Medicine Seattle**

**F. Couch, Mayo Clinic**

**W. Foulkes, Department of Human Genetics, McGill University, Canada**

**D. Goldgar, Department of Medical Informatics, University of Utah, Salt Lake City**

**J. Benitez, CNIO, Madrid**

**D. Easton, Cambridge University**

**D. Stoppa-Lyonnet, Chef du Service de Genetique Oncologique de l' institut Curie, Paris**

**J Lubinski, Pomeranian Academy of Medicine, Szczecin, Poland**

**P. Devilee, Univ. of Leiden NL, Breast Cancer Linkage Consortium**

**A. Monteiro, Rockefeller University, New York**