NON-BRCA HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES

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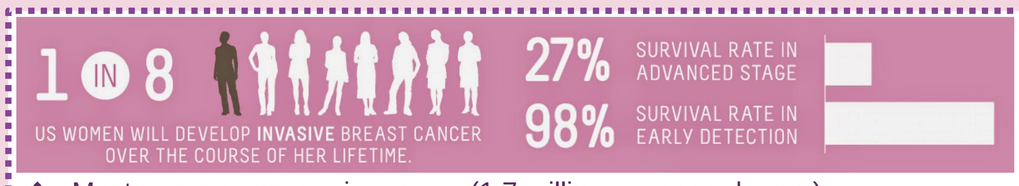
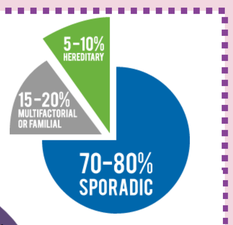
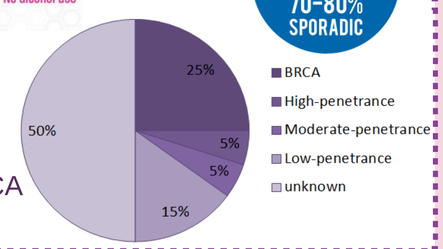
INTRODUCTION





- Most common cancer in women (1,7 million cases each year)
- Risk factors: genes, advanced age, smoke, alcohol, hormones, diet…
- Hereditary breast cancer? Multiple family cases, young ages (<40), bilateral, male BC
- BRCA are the most common BC predisposition genes (1:400-1:800 carrier)
- 5% caused by **HIGH PENETRANCE GENES** with AD inherited pattern and less known than BRCA
- Risk families diagnosis and adequate cancer surveillance can reduce mortality



OBJECTIVES

The aim of this review is search important high-penetrant genes that predispose to BC and are less-known than BRCA in order to do BC prevention and early diagnosis in high risk families

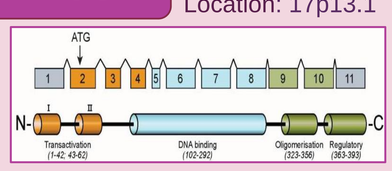
METODOLOGY

I have done a review of actual journal articles published in PubMed. I also have consulted several web pages like OMIM, GeneReviews, Genetic Home Reference, GeneCards, UniProt,…and I have read Genetic Counseling books

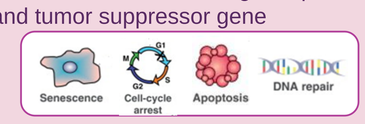
LI-FRAUMENI SYNDROME

TP53

Location: 17p13.1



FUNCTION: DNA damage response and tumor suppressor gene



MUTATIONS:
- 95% missense mutations exons 4-9 (early onset and high risk)
- 1% large rearrangements

FREQUENCY: 1:5,000-1:20,000
De novo: 7%-20%

CANCER RISK
50% by age 30 and 90% by age 50
45% of patients have >1 type of cancer
Life time risk:
- Female: 100% (median age at onset 29)
- Male: 73% (median age at onset 40)

Cause 0,1% of all BC

CLINICAL DIAGNOSIS
- Early onset and multiple tumors in a patient
- Multiple affected family members
- 1 or >1 family member with a sarcoma, BC, brain c, or adrenocortical c.

TESTING CRITERIA: Chompret criteria

MALIGNANCIES

*Median age at onset

Breast
♀ age 60: 90%
*20s-30s
Bilateral: 10-20 fold increased
♂ increased risk

Brain
14%
*0-10 or >20

Sarcoma
17,8% *0-10
Osteosarc
13,5% *11-20

Adrenocortical
6,5%
*0-10

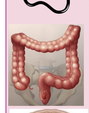
Leukemia, lymphoma, lung, colorectal, gastric, melanoma and ovarian

SURVEILLANCE

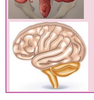
Clinical exam, MRI and echography: 20-25 years

Abdominal ultrasound and whole-body MRI (monitor sarcomas)

Physical examination and blood test

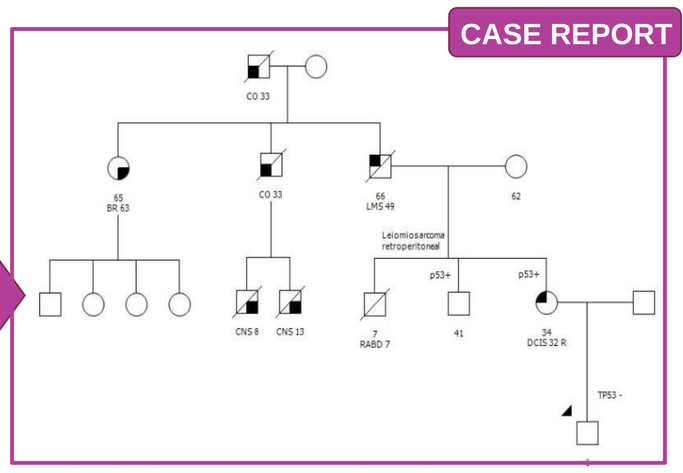


Colonoscopy: 25-30 y



Brain MRI

CASE REPORT

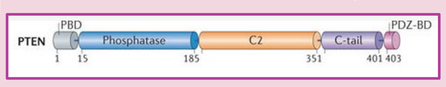


This family have Chompret criteria because the proband have BC <45 years and 1st degree of soft tissue sarcoma a part of pediatric brain tumors and all other cancers described

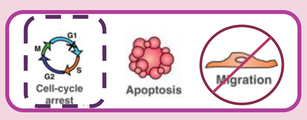
COWDEN SYNDROME

PTEN

Location: 10q23.3



FUNCTION: tumor suppressor gene with phosphatase activity



MUTATIONS:
- 80% in the codificant region
- 10% promoter mutations (associated with BC)
- 40% in phosphate core motif
- 76%: truncated, lack or dysfunctional protein

FREQUENCY: 1:200,000

CANCER RISK
Life time risk of 85% by age 70
- Female: 87% by age 60
- Male: 56% by age 60

BC typically ductal adenocarcinoma surrounded by hyalinised collagen
67-75% benign breast disease
Cause 0.02% of all BC

CLINICAL DIAGNOSIS
- 99% present skin manifestations at age 30 (hamartomatous lesions, trichilemmomas, acral keratosis and papillomatous papules)
- Other: gastrointestinal hamartomas, macrocephalia, developmental delay, autism, pigmented macules on the penis

MALIGNANCIES

*Median age at onset

Breast
♀50%-85%
50% at age 50
*36-46
♂increased risk

Thyroid
10%-35%
*10-15 or 36-46
usually follicular, rarely papillary, but never medullary
75% benign thyroid pathology

Endometrium
28%
*36-46

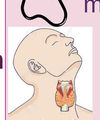
Other: Colon (9%), kidney (34%) and melanoma (6%).
35% of patients have digestive benign polyps

SURVEILLANCE

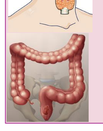
Clinical exam, MRI, Mammogram: 25-30 y

Blind endometrial biopsy and echography: 30-35 y

Physical exam: skin, mucous membranes: 18 y

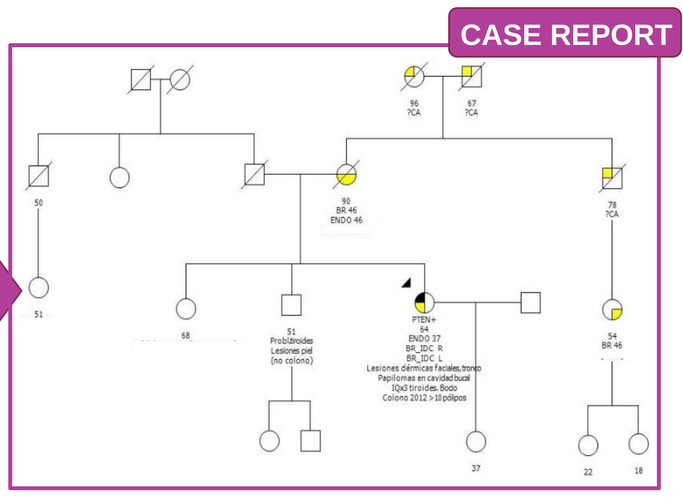


Thyroid clinical exam and ultrasound: 18 y



Endoscopy and colonoscopy: 30-35 y

CASE REPORT

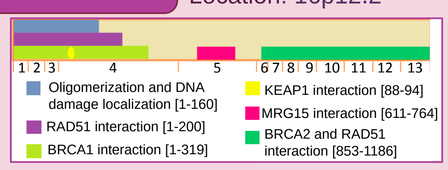


This family met two major criteria (breast and endometrial cancer)

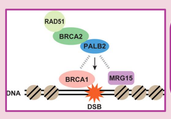
PALB2 HEREDITARY BREAST CANCER

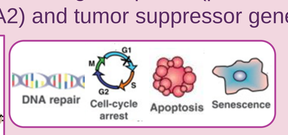
PALB2

Location: 16p12.2



FUNCTION: DNA damage response (partner /localizer of BRCA2) and tumor suppressor gene





MUTATIONS:
- 10 known mutations associated with BC
- In carriers, BRCA protein levels are reduced
- Biallelic mutations cause Fanconi anemia

FREQUENCY: 1:1,000

CANCER RISK
- Truncating mutations are more associated with BC
- 30% are triple-negative
- Different risk depending of the family history
- Cause 2.4% of all BC (0.4-3.9%) and 3-4% of all families with pancreatic cancer.

CLINICAL DIAGNOSIS:
Several individuals with BC and pancreatic cancer

TESTING CRITERIA:
- 3 or >3 family members with BC
- Test is done when a mutation in BRCA is not found

MALIGNANCIES

*Median age at onset

Breast
♀35%-47,5%
♂8,3 fold increased risk

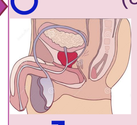
Pancreas
10-32 fold increased risk

Other: Ovary 2,3 fold increase risk
Increased risk of lung and prostate

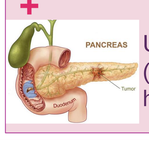
SURVEILLANCE

Clinical exam, MRI, mammogram, echography: 25-30 y

Transvaginal ultrasound and serum [CA-125] : 35 y (ovarian surveillance)

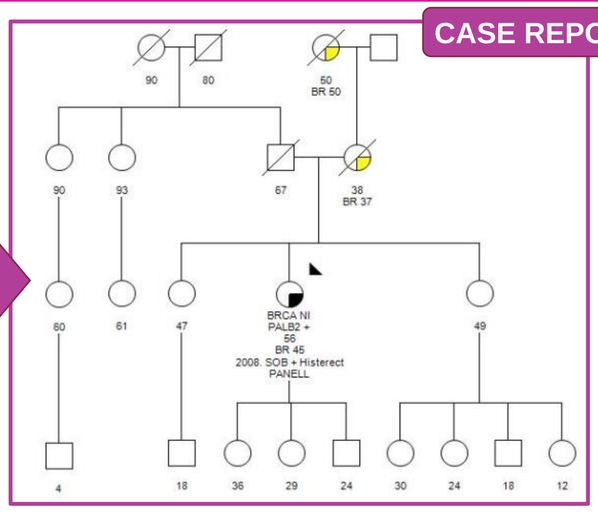


Digital rectal examination: 40 y (prostate surveillance)



Ultrasound and MRI (if pancreatic family history is positive)

CASE REPORT



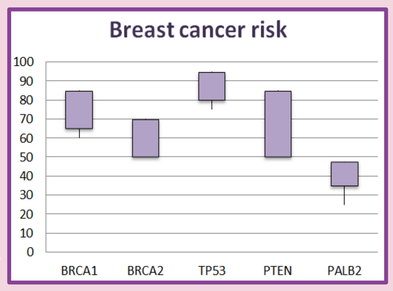
Testing criteria: three BC cases, one in each generation

BENEFITS

- **Specific surveillance** for carriers: early tumor detection
- **Preventive surgery**: reduce risk
- **Prenatal/preimplantational** diagnosis
- Non carriers have general population risk even if the family history is positive so they **avoid unnecessary screening**

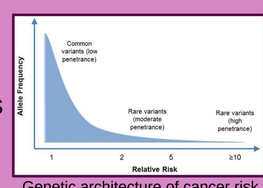
RISKS

- **Psychological effects** (feeling anxious, depressed…)
- **Variants of uncertain significance** can lead a difficult genetic counseling
- **Violation of confidentiality** can affect employment, health insurances…



CONCLUSIONS

- BRCA only cause 25-30% of hereditary BC, there are other important predisposition genes
- High-penetrance genes are important to be diagnosed to follow adequate surveillance (early detection), optional prophylactic surgeries, targeted therapies…
- Is important to inform oncology professionals to identify at-risk families
- Gene panels to study several genes at the same time
- Future studies: BC caused for an accumulation of frequent low-penetrance mutations



Genetic architecture of cancer risk
Extracted from Genereviews

REFERENCES Genereviews; National Cancer institude; Economopoulou P., "Beyond BRCA: New Hereditary Breast Cancer Susceptibility Genes" Cancer treat rev 1. 1-8 (2015); Antoniou AC, "Breast-Cancer Risk in Families with Mutations in PALB2." NEJM 6. 497–506 (2014)