NON-BRCA HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES

Andrea Otero González, Genetics degree
Universitat Autònoma de Barcelona (Spain)

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

LI-FRAUMENI SYNDROME

TP53

Location: 17p11.2

FUNCTION: DNA damage response and tumor suppressor gene

MUTATIONS:
- 85% missense mutations exons 4-11 (early onset and high risk)
- 17% large rearrangements

CANCER RISK
- Life time risk of 85% by age 70
  - Female: 87% by age 60
  - Male: 56% by age 50
- BC typically ductal adenocarcinoma surrounded by hyalinated collagen
- 67-75% benign breast disease
- Cause 0.02% of all BC

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

TESTING CRITERIA: Chompret criteria

MALIGNANCIES

- Median age at onset

SURVEILLANCE

Brain
- Clinical exam, MRI and echography: 20-25 y
- Abdominal ultrasound and whole body MRI (monitor sarcomas)
- Physical examination and blood test
- Colonoscopy: 25-30 y
- Brain MRI

COWDEN SYNDROME

PTEN

Location: 10q23.3

FUNCTION: tumor suppressor gene with phosphatase activity

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

CANCER RISK
- Life time risk of 85% by age 70
  - Female: 90% by age 60
  - Male: 56% by age 50
- BC typically ductal adenocarcinoma surrounded by hyalinated collagen
- 67-75% benign breast disease
- Cause 0.02% of all BC

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PAL2 HEREDITARY BREAST CANCER

PALB2

Location: 16p12.2

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

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

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

SURVEILLANCE

Pancreas
- Clinical exam, MRI, mamrogram, echography: 25-30 y
- Transaxial ultrasound and serum (CA125): 35 y (ovarian surveillance)
- Digital rectal examination: 40 y (prostate surveillance)

CASE REPORT

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

REFERENCES

- Non-BRCA Calcium Sensitivity and DNA Damage Resistance
- BRCA1 and BRCA2: Hereditary Breast Cancer at Social Genetics
- Breast cancer Malignancies and BRCA
- Cancer risk and BRCA1/2: Carriers in Spain

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

BENEFITS

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