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Polymorphisms in estrogenic metabolic pathway genes: clinical significance and lifetime outcome.

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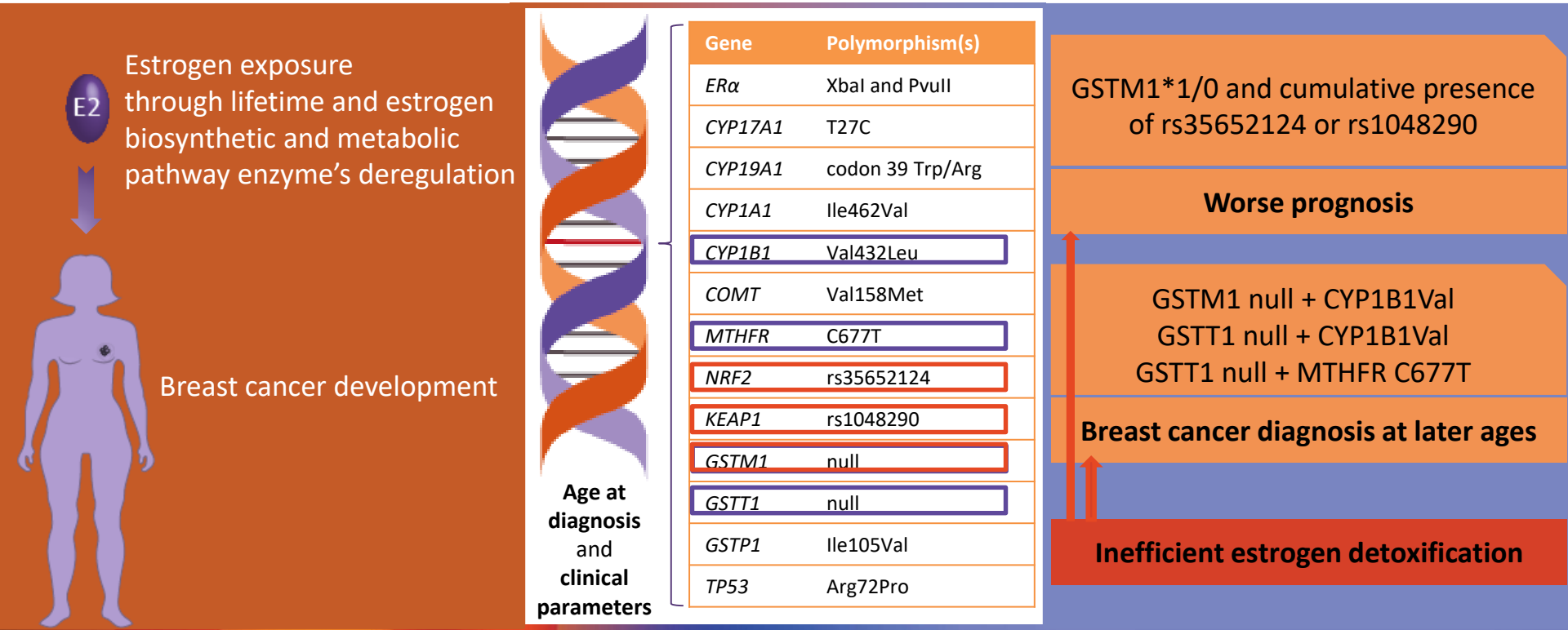
Polymorphisms in estrogenic metabolic pathway genes: clinical significance and lifetime outcome.

Graphical Abstract



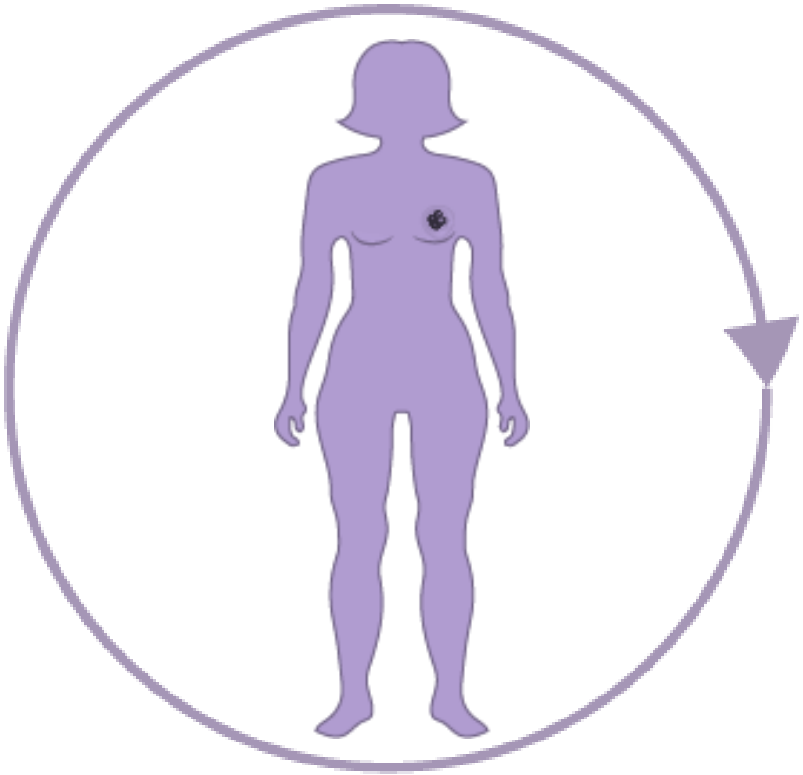
Abstract: Polymorphisms in estrogenic metabolic pathway genes: clinical significance and lifetime outcome.

Lifetime exposure to high estrogens levels and deregulation of enzymes of estrogen biosynthetic and metabolic pathway are considered breast cancer risk factors. Our research team has previously evaluated, in women with hormone-dependent breast cancer, *NRF2* and *KEAP1* polymorphisms (alone or in association), with breast cancer prognosis, in cases with *GSTM1*-present genotype. We identified that *GSTM1**1/0 genotype and cumulative presence of at least one allele mutated in *KEAP1* and/or *NRF2* polymorphisms might be associated with worse prognosis. Moreover, older women were carriers of both *GSTM1* null and *CYP1B1*Val genotypes, similar results were found for the cumulative presence of *GSTT1* null and *CYP1B1*Val genotypes and for *MTHFR* C677T and *GSTT1* null polymorphism. These results lead us to genotype other enzymes involved in estrogen biosynthetic/metabolic pathways, namely: *CYP17A1* T27C, *CYP19A1* codon 39 Trp/Arg, *COMT* Val158Met, *CYP1A1* Ile462Val, *GSTP1* Ile105Val, *ERα* PvuII and XbaI polymorphisms and TP53 Arg72Pro (DNA damage signalling and repair pathway) polymorphism. The genotyping analysis was evaluated, alone or in association, with breast cancer prognosis and with age at breast cancer diagnosis, we found no association (*p-value*>0.05). These results emphasize that polymorphisms in NRF2/KEAP1 complex and the null polymorphisms of *GSTM1*/*GSTT1* should be further investigated as targets for breast cancer therapy. In addition, polymorphisms related to inefficient estrogen detoxification might be a trigger to hormone-dependent breast cancer development at later ages, and should be considered in breast cancer risk assessment models.

Keywords: Breast Cancer, estrogens, polymorphisms, risk model, targeted therapy

Introduction

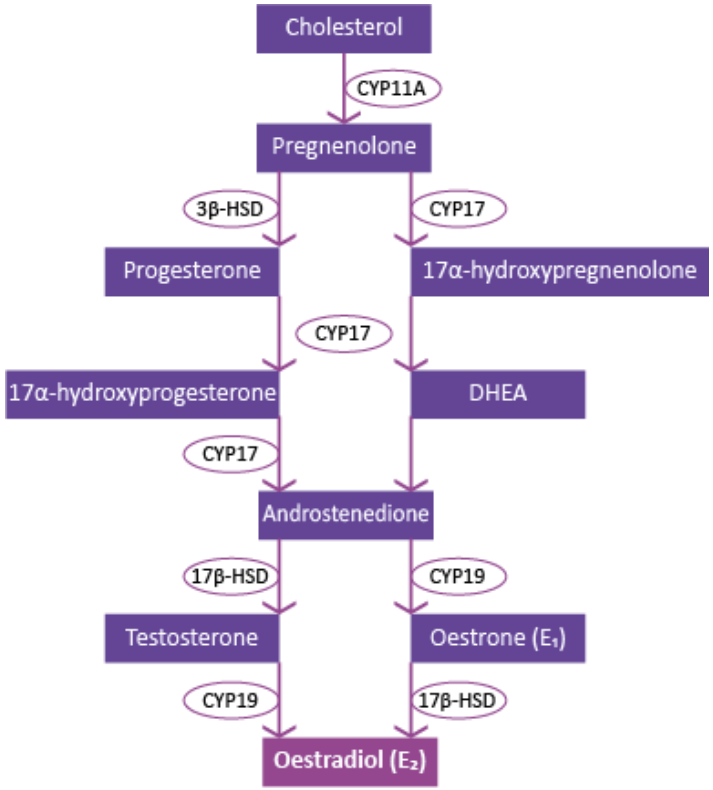
Estrogens have been identified has carcinogens, and most of the risk factors for breast cancer are related to an increased or prolonged exposure to estrogens.

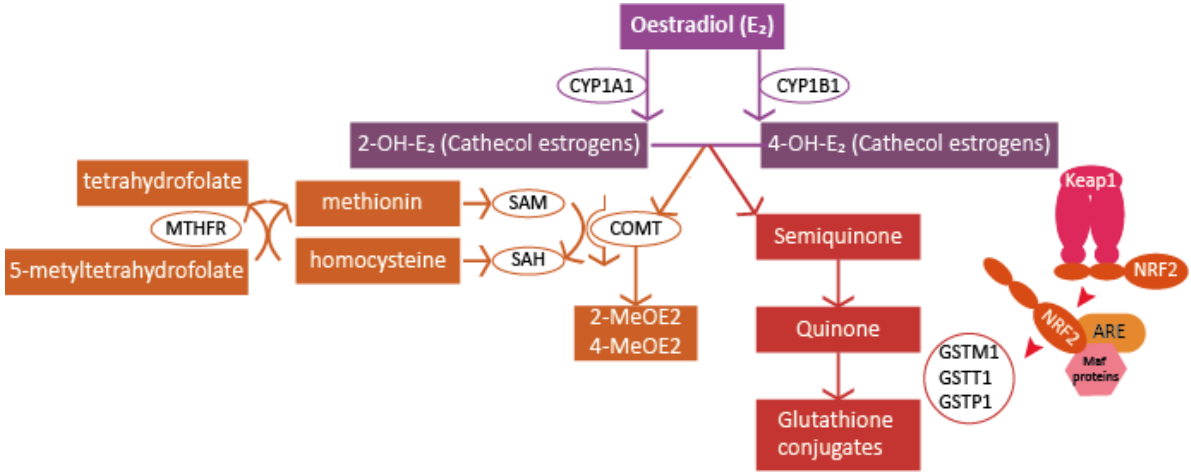


- Biosynthetic pathway
- Metabolic pathway
- Estrogen signalling
  Estrogen Receptor (ER)
- Apoptosis inhibition

Introduction

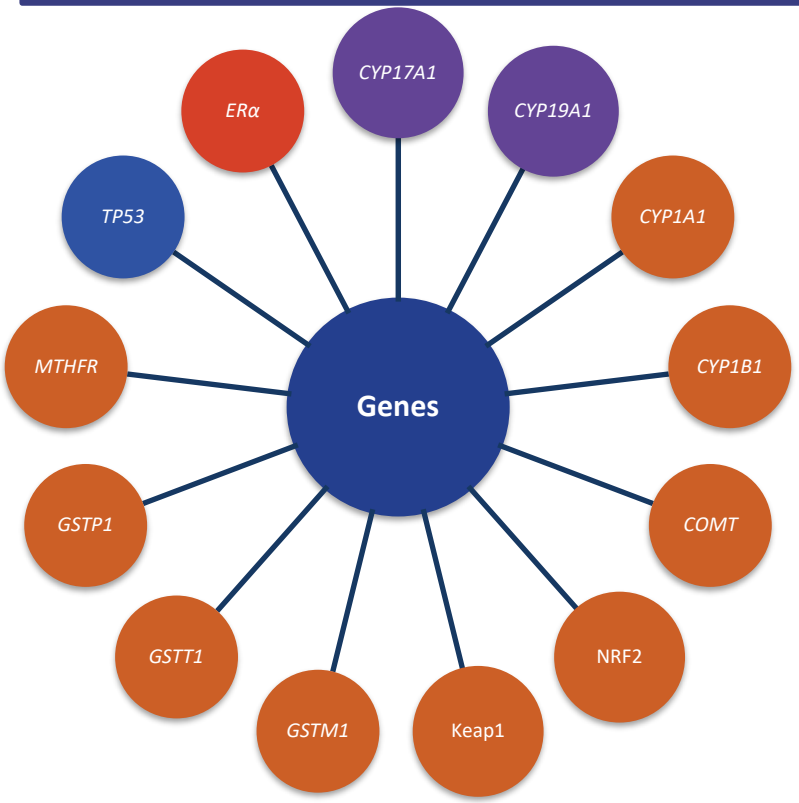
Biosynthetic and metabolic pathways





Introduction

Genes



- Biosynthetic pathway
- Metabolic pathway
- Estrogen signalling
  Estrogen Receptor (ER)
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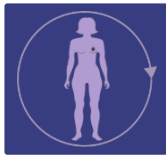
Free-radical-mediated DNA damage, single-strand breaks, estrogen–DNA adducts formation, protein oxidation and lipid peroxidation, what triggers genetic instability and cellular damage.

Introduction



Framework

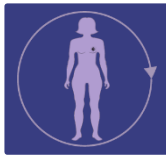
Our research team correlated:

- GSTM1 and GSTT1 null
- CYP19A1 arginine (C) allele
- TP53 proline allele

→ Increased risk of breast cancer development.

Carriers of xx genotype of Erα XbaI → Reduced risk of breast cancer development.

Introduction



Framework

GSTM1 null polymorphism taking into concern the three genotypes:

- *GSTM1*1/1* (present)
- *GSTM1*1/0* (heterozygous)
- *GSTM1*0/0* (null)

NRF2 35652124 and *KEAP1* rs1048290

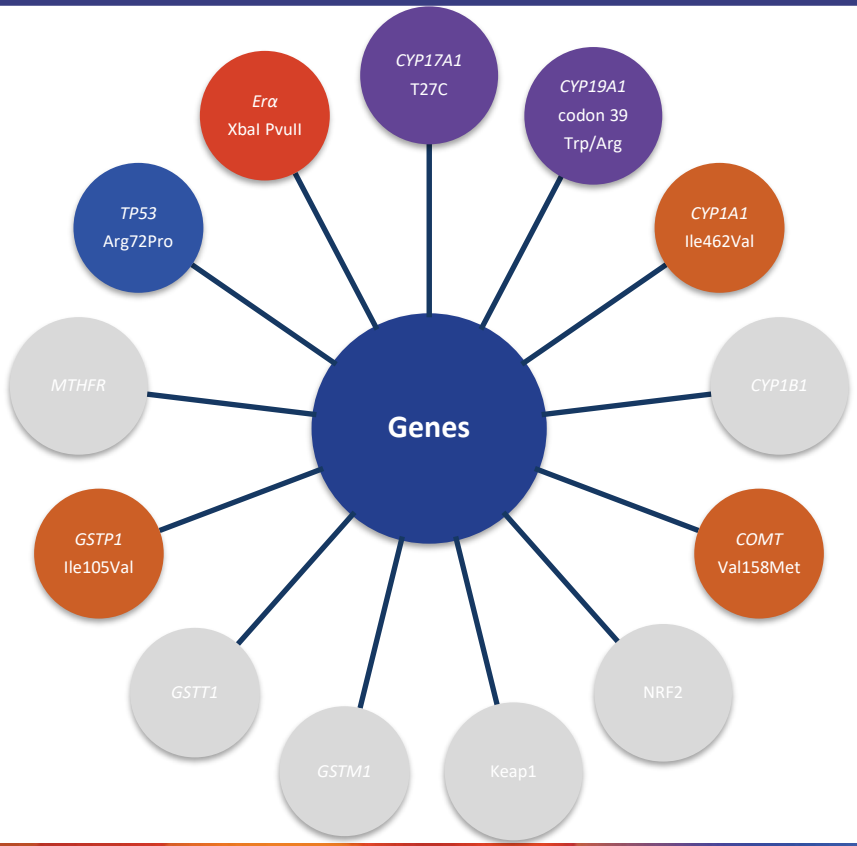
Clinical parameteres in order to evaluate breast cancer prognosis

GSTM1 and *GSTT1* null polymorphism with *CYP1B1* Val432Leu and *MTHFR* C677T.

Age at diagnosis of breast cancer

Introduction

Framework



Clinical parameteres in order to evaluate the breast cancer prognosis

Age at diagnosis

Results and discussion

Metabolism regulators, phase II enzymes and breast cancer prognosis

n=52
Women with hormone-dependent (ER+) breast cancer

GSTM1 present genotypes to withdraw the risk of *GSTM1* null genotype

*GSTM1*1/1*
*GSTM1*1/0*

KEAP1 and *NRF2* polymorphisms

KEAP1 rs1048290
NRF2 rs35652124 are related to ↑NRF2 levels in cytoplasm, might lead to resistance to therapeutic

HER2 status

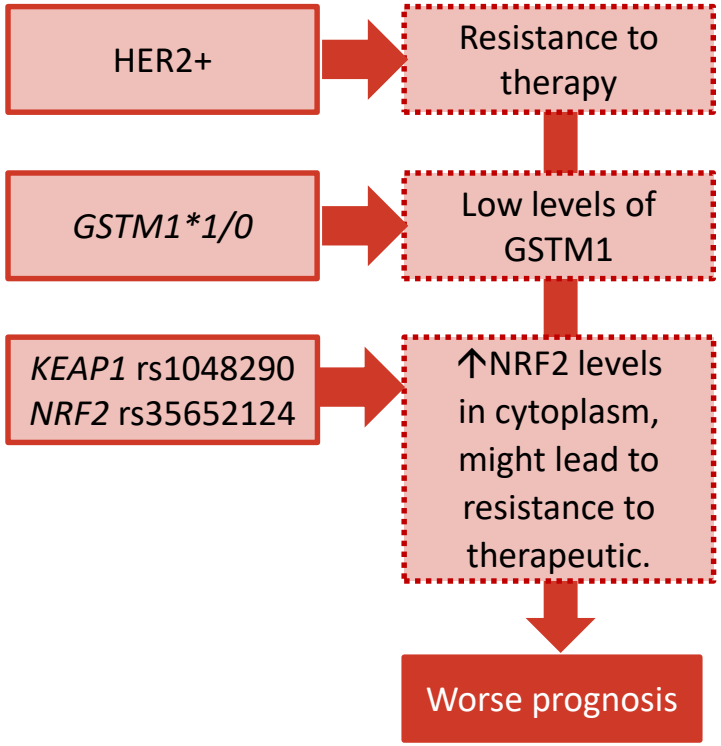
HER2+ breast cancers are related to chemotherapy resistance and worse prognosis

Results and discussion

Metabolism regulators, phase II enzymes and breast cancer prognosis

Association of *KEAP1* and *NRF2* polymorphisms in cases with *GSTM1* present genotype (*1/1 or *1/0) and correlation with HER2 status

Genotype		HER2 status n (%) +	HER2 status n (%) -	P value
KEAP1 rs1048290	*GSTM1*			
CC	1/1	0	0	
CC	1/0	4 (15.4)	0	
CG/GG	1/1	0	1 (3.8)	**0.044**
CG/GG	1/0	18 (69.2)	3 (11.5)	
NRF2 rs35652124	*GSTM1*			
AA	1/1	0	0	
AA	1/0	9 (34.6)	2 (7.7)	
AG/GG	1/1	0	1 (3.8)	**0.043**
AG/GG	1/0	13 (50)	1 (3.8)	



Results and discussion

Polymorphisms in estrogen metabolic pathway and age at diagnosis

n=157

GSTM1	*CYP1B1* Val432Leu	Age, n (%) <50	Age, n (%) ≥50	p-value
Present	Leu/Leu (WT)	8 (5.1)	10 (6.4)	1
Present	Leu/Val + Val/Val	9 (5.7)	38 (24.2)	0.038*
Null	Leu/Leu (WT)	2 (1.3)	19 (12.1)	0.013*
Null	Leu/Val + Val/Val	12 (7.6)	59 (37.6)	0.012*

GSTT1	*CYP1B1* Val432Leu	Age, n (%) <50	Age, n (%) ≥50	p-value
Present	Leu/Leu (WT)	10 (6.4)	21 (13.4)	1
Present	Leu/Val + Val/Val	17 (10.8)	62 (39.5)	0.239
Null	Leu/Leu (WT)	0	8 (5.1)	0.062
Null	Leu/Val + Val/Val	4 (2.5)	35 (22.3)	0.022*

GSTT1	*MTHFR* C677T	Age, n (%) <50	Age, n (%) ≥50	p-value
Present	CC (WT)	10 (6.4)	30 (19.1)	1
Present	CT+TT	17 (10.8)	53 (33.8)	0.933
Null	CC (WT)	2 (1.3)	13 (8.3)	0.351
Null	CT+TT	2 (1.3)	30 (19.1)	0.034*

GSTM1 null + *CYP1B1*Val

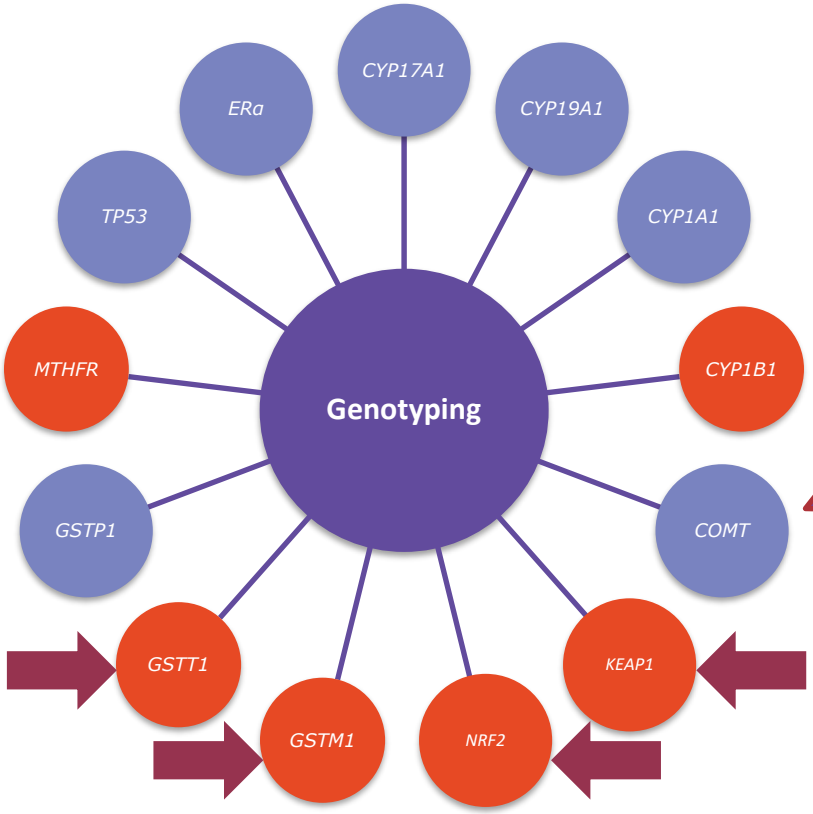
GSTT1 null + *CYP1B1*Val

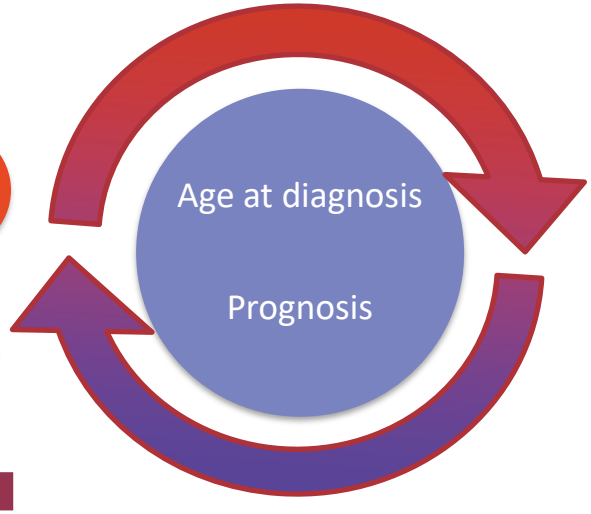
GSTT1 null + *MTHFR* T allele

Breast cancer diagnosis at ≥ 50 years old

Results and discussion

Polymorphisms in estrogen synthetic and metabolic pathway: age at diagnosis and prognosis

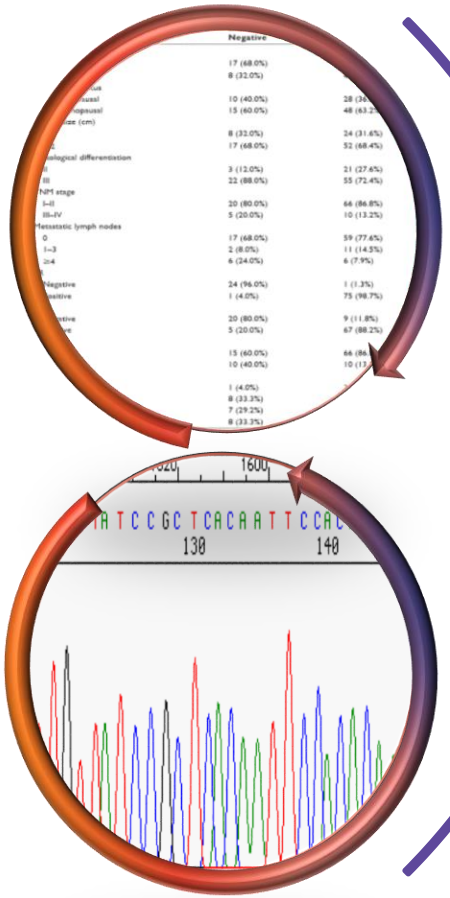




Signifcant results allows to emphasize

That polymorphisms in *NRF2/KEAP1* complex and the null polymorphisms of *GSTM1/GSTT1* should be consider prognostic markers for prognosis of the disease and of cancer therapy.

Conclusions



Cumulative presence of polymorphisms in *NRF2/KEAP1* and *GSTM1*1/0* genotype might be associated with worse prognosis in breast cancer patients and with resistance to therapy.

Cumulative presence of polymorphisms in genes related to estrogen metabolism and lifetime exposure to estrogens might lead to breast cancer development at later ages.

Polymorphisms in *NRF2* and *KEAP1*, also as the null polymorphisms of *GSTM1* and *GSTT1* should be further investigated as possible targets for breast cancer therapy.

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