Identification Of Some Genetic Markers In Familial Breast Cancer In Egyptian Patients

Thesis

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In Clinical and Chemical Pathology

By

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Abstract

Background:

The Her- 2/neu gene encodes a receptor related to breast carcinogenesis and topoisomerase IIalpha (TOP2A) gene is located adjacent to Her-2/neu oncogene on chromosome 17 and encodes an enzyme plays a key role in DNA replication and is a target for multiple chemotherapeutic agents like anthracyclines.

The aim of the present study: was to evaluate cases of familial breast cancer (FBC) and compare them with sporadic cases (SBC) through hormonal status, immunostaining for Her-2/neu and TOP2A and Her-2/neu copy number alterations by FISH, and investigate the prevalence of alteration of TOP2A gene copy number in familial breast cancer.

Material and methods: 22 cases of invasive breast carcinomas: 12 cases with criteria that define familial breast cancer (FBC), and 10 cases of sporadic breast cancer (SBC) were involved in this study. Archival blocks of formalin fixed-paraffin embedded sections of these cases were used, these sections were subjected to immunostaining with Her-2/neu (Hercep test), ER (estrogen receptors) and PR (progesterone receptors), and Fluorescence in situ hybridization (FISH) was performed to evaluate TOP2A and Her-2/neu genes copy number alterations.

Results: revealed that the FBC tumors were more aggressive than SBCs regarding; pathological parameters (larger tumor size, and higher grade), and immunohistochemical markers (lower ER, and PR expression among FBCs), but the rate of Her-2/neu gene amplification and protein over-expression was equally likely between both groups. The rate of TOP2A gene amplification was 22.7%, co-amplification of Her-2/neu and TOP2A

genes was found in one case of the FBS patients (8.3%) and in two cases of the SBCs (20%). In contrast, Her-2/neu amplification alone was found in three patients of the FBCs (25%), compared to one case among the sporadic breast cancers (10%). Importantly, TOP2A amplification with normal Her-2/neu gene status was found in two of the FBCs (16.7%), but in none of the sporadic tumors (0%).

Our findings have potential therapeutic implications. Her-2/neu assessment is routinely used to select breast cancer patients for trastuzumab but also dose intensive anthracycline therapy. Our data suggest that FBCs also need to be tested for TOP2A amplification.

Conclusion: The clinical, pathological, and immunohistochemical characteristics of tumors should be of value in evaluating the genetic basis of breast cancer among families, as FBC tumors were more aggressive than SBCs. Identifying biological characteristics that can predict genetic background among breast cancer families and as a clinical consequence, we suggest that patients with suspected FBCs need more intensive therapy and careful follow up.

TOP2A gene amplification is more frequent in FBC than SBC and it may occur independent of Her-2/neu gene amplification, this finding together with the fact that TOP2A is the therapeutic target of anthracyclines suggests that this parameter should be determined on a routine basis in BC and especially in FBC.

Key Words :

Breast Cencar – TOP2A – Her-2/neu .

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Sally Gharib

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LIST OF ABREVIATIONS

(ER) α: Estrogen receptor alpha

(ER) β: Estrogen receptor beta

ACMG: American College of Medical Genetics.

ACOG: American College of Obstetricians and Gynecologists.

AJCC: American Joint Committee of Cancer.

ASCO: American society of clinical oncology

ATM: Ataxia telangiectasia mutation

BFB: Breakage Fusion Bridge

BRCA1: Breast Cancer susceptibility gene 1

BRCA2: Breast Cancer susceptibility gene 2

BRCT: Breast cancer gene 1(BRCA1) carboxyl terminal domain

CAP: College of American pathologist

CD: Cathpesin D

CGH: Comparative genomic hybridization

CHEK2: Cell cycle checkpoint kinase 2.

CI: Confidence interval.

CIN: Chromosomal instability.

CIS: Carcinoma in situ

DCIS: Duct carcinoma in situ.

DFS: Disease free survival.

DNA: Deoxy Nucleic Acid.

EGFR: Epidermal growth factor receptor.

ELISA: Enzyme linked immunosorbent assay

ER: Estrogen receptors

FBC: Familial breast cancer.

FDA: Food and drug administration in USA

FFPE: Formalin fixed paraffin embedded.

FGF: Fibroblast growth factor.

FISH: Fluorescent In Situ Hybridization

FISH: Fluorescnt insitu hybridization.

Her-2/neu: Human epidermal growth factor receptor 2.

HRT: Hormone replacement therapy

HSR: Homogenously stained regions

IHC: Immunohistochemistry

Kb: Kilo base

kDa: Kilo Dalton

LFS: Li- Fraumeni syndrome

LN: Lymph node.

LOH: Loss of heterozygosity

MIs: Mitotic indices

mRNA: Messenger ribonucleic acid.

NCCN: National Comprehensive Cancer Network.

NCI: National Cancer Institute.

OS: Overall Survival

PCBs: Polychlorinated biphenyls

PCR: Polymerase chain reaction

PGF: Platelet derived growth factor

PR: Progesterone receptors

PR-A: Progesterone receptor alpha.

PR-B: Progesterone receptor beta.

Rb1: Retinoblastoma gene.

RFS: Recurrence free survival

ROMA: Representational Oligonucleotide Microarray Analysis

SBC: Sporadic breast cancer.

SPF: S phase fraction.

TDLU: Terminal duct lobular unit

TKRs: Tyrosine kinase receptor

TLIs: Thymidine labeling indices

TOP2A: Topoisomerase II alpha.

TOP2A: TopoisomeraseII alpha.

uPA: Urokinase plasminogen activator

u-PA: urokinase plasminogen activator.

VEGF: Vascular endothelial growth factor

Vs: versus

List Of Errata

Chapter of results:

P.127, table 12; Menopausal status of FBC:

6 Cases premenopausal = 75%.

2 Cases post menopausal =25%.

The same in P.119, table 16 and figure 30.

P130: table29: ER+&PR+ in FBC: 16.7%.

Chapter of discussion:

P.157: line 11; ASCO, 2003&2011.

P.157: line 16; premenopausal cases (75%) and two postmenopausal cases (25%).

P.166: line 10; lost word: these contributing results could be also

Chapter of summary and conclusion:

P.175: line 15: through hormonal receptor status, and

P176: line 14: (75% Vs 20%).

P.176: line 18: and lower PR expression.

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