European Journal of Human Genetics

Volume 23 Supplement 1 June 2015 www.nature.com/ejhg

European Human Genetics Conference 2015

June 6 - 9, 2015
Glasgow, Scotland, United Kingdom

Abstracts

nature publishing group npg

PM12.026

Panel next-generation sequencing reveals a high prevalence of deleterious ATM mutations in BRCA1/2-negative breast and ovarian cancer families

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Approximately 24% of familial breast cancer (BC) and/or ovarian cancer (OC) cases analyzed within the framework of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) are due to pathogenic *BRCA1/2* mutations. However, the mutation frequencies of non-*BRCA1/2* genes associated with familial BC and/or BC/OC are largely unknown. Here, we present the NGS analysis (TruRisk™ gene panel) of a cohort of 574 *BRCA1/2*-negative index cases which comprises 256 unselected patients with triple negative breast cancer (TNBC) and 318 cases from high-risk BC and BC/OC families. By focusing on 21 BC/OC associated genes (*ATM, BARD1, BRIP1, CDH1, CHEK2, FANCM, MLH1, MSH2, MSH6, MRE11A, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMARCA4, STK11, TP53*, *XRCC2*), we identified 40 different pathogenic variants in 38 unrelated mutation carriers derived from 318 high risk BC and BC/OC families (12%). In contrast, only 9 mutation carriers (3.5%) were discovered among the unselected TNBC cases. Interestingly, we identified a high frequency of pathogenic *ATM* mutations *(n=10, 3.1%)* in the familial cases whereas no *ATM* mutations were found in the TNBC cohort. Additionally, we found a high frequency of mutations in *CHEK2*, *PALB2*, *RAD50* and confirm *FANCM* and *SMARCA4* as novel BC/OC predisposing genes. Due to the unexpectedly high mutation frequencies in familial cases, our study highlights the importance of these genes to be included in BC/OC routine diagnostics.

PS12.027

The Estrogen Receptor -α Gene rs1801132 variation and Breast Cancer risk in Iran

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Iranian breast cancer patients are relatively younger than their Western counterparts. Evidence suggests that alterations in estrogen signaling pathways, including ESR1(estrogen receptor-α), occur during breast cancer development in Caucasians. Epidemiologic studies have revealed that age-incidence patterns of breast cancer in Asians differ from those in Caucasians. Genomic data for ESR1in either population is therefore of value in the clinical setting for Iranian breast cancer.
A case-control study was conducted to establish a database of ESR1polymorphisms in Iranian women population in order to compare Western and Asian with Iranian (Asian-Caucasians) distributions and to evaluate ESR1-polymorphism as an indicator of clinical outcome. DNA was extracted from Iranian women with breast cancer referred to Imam Khomeini Hospital Complex clinical breast cancer group (150 patients) and in healthy individuals (147 healthy control individuals). PCR single-strand conformation polymorphism technology was performed.
A site of silent single nucleotide polymorphism (SNP) rs1801132 was found, The frequency of allele 1 in codon 325 (CCC→CCG) was significantly higher in breast cancer patients (39.6%) than in control individuals (28.9%; P = 0.007). The allele CCG had also significant association with the occurrence of lymph node metastasis.
Data suggest that ESR1polymorphisms in exon 4 codon 325 is correlated with various aspects of breast cancer in Iran. ESR1 genotype, as determined during presurgical evaluation, might represent a genetic marker for predicting breast cancer lymph node metastasis.

PM12.028

Nonsense mutation in FANCM confers risk for triple-negative breast cancer

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Inherited predisposition to breast cancer is known to be caused by loss-of-function mutations in *BRCA1, BRCA2, PALB2, CHEK2*, and other genes involved with DNA repair. However, most families severely affected by breast cancer do not harbor mutations in any of these genes.
In Finland, founder mutations have been observed in each of these genes, suggesting that the Finnish population may provide a unique resource for identification of additional breast/ovarian cancer alleles. We studied 24 breast cancer patients from 11 Finnish breast cancer families with exome sequencing and further genotyped selected DNA repair variants in 3166 familial and/or unselected breast cancer patients as well as 569 ovarian cancer patients and 2090 population controls. Of all genotyped variants, a nonsense mutation (c.5101C>T, rs147021911, p.Gln1701Ter) in Fanconi Anemia complementation gene M (*FANCM*) was significantly associated with breast cancer risk (OR = 1.86, 95% CI = 1.26-2.75, *P* = 0.0018). Further assessment based on tumor pathology identified a particularly strong effect in triple-negative breast cancer (OR = 3.56, 95% CI = 1.81-6.98, *P* = 0.0002). These findings identify *FANCM* as a novel breast cancer predisposition gene, with a moderate risk of especially triple negative breast cancer for mutation carriers.
The study has been supported by the Helsinki University Central Hospital Research Fund, the Academy of Finland, the Sigrid Juselius Foundation, Nordic Cancer Union, and the Finnish Cancer Society. FJC was supported by the Breast Cancer Research Foundation, and CA116201 NIH SPORE award in breast cancer to the Mayo Clinic.

PS12.029

Associations Between HER2/neu ,TOP2A ,Chromosome 17 Copy Numbers and TWIST , RARβ2 and ESR1 Gene Promotor Hypermethylations of Patients with Breast Cancer

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Introduction: Breast cancer is an important public health problem worldwide. The HER2 /neu protooncogene is amplified and overexpressed in approximately 25-30% of invasive breast carcinomas. DNA topoisomerase 2-alpha enzyme controls and alters the topologic states of DNA during transcription. TWIST expression in breast tumors correlate with increased disease recurrence and poor disease-free survival. Steroid receptor genes family members such as the RARβ2 and ESR1 genes are methylated and silenced in a fraction of breast cancer.
Method: In this study we analysed retrospective HER2/neu, TOP2A gene and Chromosome17 copy number alterations by fluorescence in situ hybridization (FISH) in primary tumor core biopsies from 100 high-risk primary breast cancer patients (tumors ≥2 cm and/or lenfatic metastase and/or distant metastases and/or under 40 years) . The methylation levels of the TWIST, RARβ2 and ESR1 gene promoters were assessed Methylation Sensitive High Resolution Melting Analysis (MS-HRM).
Results: In our study, HER2/neu amplifications were identified in 25% and TOP2A amplifications in 24% and deletions in 6% of patients. HER2/neu and TOP2A amplifications are found to be associated with IDC tumor type and high grade also HER2/neu amplifications is associated with PR(-), TOP2A amplifications is associated with ER(+). TOP2A deletions is associated with ER(-) and PR(-). Polysomy17 was present in 23% and monosomy 12% of patients. TWIST, RARβ2 and ESR1 methylation frequencies were 24%, 90% and 69% respectively.
Conclusions:. Our study is important as being the first study that analyzes association between HER2/neu, TOP2A gene copy numbers and TWIST, RARβ2 and ESR1 gene promotor methylation status in Turkish population.

PM12.030

Exome analysis of families with hereditary breast and ovarian cancer (HBOC) to identify new candidate genes related with breast cancer development

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