2015

The Cancer Genome Atlas (TCGA): Breast and Ovarian Cancers

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Introduction to Genomics
A genome is the complete ordered sequence of DNA bases (A, C, G, T) which make up all of the protein- and RNA-coding genes, and regulatory sequences necessary for the construction of an organism. The field of genomics began in the 1970’s when Walter Fiers and his team in Ghent, Belgium sequenced the genome of the M2 bacteriophage.

Significant Genomic Sequencing Events from 1993-2005
- 1993: First bacterium sequenced (Mathanococcus jannaschii)
- 1995: First fungus sequenced (Arabidopsis thaliana)
- 1997: First animal sequenced (Caenorhabditis elegans)
- 2001: First human genome sequenced
- 2003: First egg-laying animal genome sequenced (Drosophila melanogaster)
- 2005: First mammal genome sequenced (Mus musculus)

Human Genome Project
HGP was an international, collaborative research program with the goal to sequence and map the full human genome of 3 billion base pairs to gain a better understanding of all of the genes that are present. It was initiated in 1990 and a draft sequence was published in 2003, paving the way for the development of new genomics-based research projects.

The Cancer Genome Atlas
The National Institutes of Health (NIH) and the National Human Genome Research Institute (NHGRI) initiated a pilot project called The Cancer Genome Atlas (TCGA) in 2006. The overall goal of TCGA is to catalog all of the significant genomic changes in the major types and subtypes of cancer. It is hoped that this catalog of information will serve as a critical resource for the prevention, diagnosis, and treatment of these cancers.

Key:
- ER: Estrogen receptor
- PR: Progesterone receptor
- HER2: Human epidermal growth factor receptor 2

Genes Mutated in HGS-OvCa
- TP53: Missense (n=302) 96%
- BRCA1: Germline, somatic (n=11) 3%
- CSMD2: Missense (n=19) 6%
- CDK12: Nonsense, indel, missense (n=9) 3%
- FAT3: Missense (n=19) 6%
- GABRA6: Missense (n=6) 2%
- BRCA2: Germline, somatic (n=10) 3%

Genes Mutated in Breast Cancer mRNA Subtypes
- PIK3CA: (n=225) 45% Basal-like (n=93) 9%
- MAP3K1: (n=126) 13% Luminal A (n=57) 9%
- TP53: (n=126) 12% Luminal B (n=69) 9%
- CDH1: (n=126) 9% HER2-enriched (n=57) 9%
- AKT1: (n=126) 4% HER2-enriched (n=57) 4%
- RB1: (n=126) 0.4% Basal-like (n=93) 0.4%
- ML3: (n=126) 8% Basal-like (n=93) 8%
- TBX3: (n=126) 3% Basal-like (n=93) 3%
- RUNX1: (n=126) 5% Basal-like (n=93) 5%
- FOXB: (n=126) 2% Basal-like (n=93) 2%
- AFF2: (n=126) 1% Basal-like (n=93) 1%
- PIK3R1: (n=126) 4% Basal-like (n=93) 4%
- PTPN22: (n=126) 4% Basal-like (n=93) 4%
- NF1: (n=126) 2% Basal-like (n=93) 2%
- CTCF: (n=126) 4% Basal-like (n=93) 4%
- FOXA1: (n=126) 2% Basal-like (n=93) 2%
- SF3B1: (n=126) 3% Basal-like (n=93) 3%
- MLL3: (n=126) 5% Basal-like (n=93) 5%
- CDKN1B: (n=126) 1% Basal-like (n=93) 1%

TCGA Breast & Ovarian Cancers
- 825 samples of breast cancer tumor & normal tissue
- 489 samples of stage II-IV high-grade serous ovarian cancer (HGS-OvCa) tumor & normal tissue
- Whole Genome/Exome Sequencing
- mRNA, miRNA, protein expression analysis
- DNA methylation analysis
- Chromosome copy-number variation analysis

What Has Evolved From This?
One of the most significant findings from TCGA was that basal-like breast cancer subtype is most similar to HGS-OvCa, containing similar types and frequencies of mutations. These results suggest that the two cancers may have a similar molecular origin, and may be responsive to similar therapies.

Predominant similarities:
- High frequency of TP53 mutations
- Inactivation of BRCA1
- Amplification and high expression of cMYC
- Loss of RB1

References