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ERBB2 transcriptome: From biology to genomics to biology

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In recent years, Kumar's lab has used high-throughput whole genome sequencing to gain genomic insights of the estrogen receptor positive, *HER2* positive and triple-negative breast cancer (TNBC). Results from these, and those from other laboratories have provided unprecedented insights into the pathobiology of breast cancer as well an inter- and intra-tumor genomic heterogeneity due to differential expression of transcripts, splicing and promoter switching. However, these studies provided very little details of the influence of transcriptome as affected by the lost receptors. To address this research question, the laboratory decided to generate isogenic clones of TNBC breast cancer cells, MDA-MB231 and MDA-MB468, stably expressing *ERBB2*. These TNBC and *ERBB2*-positive non-TNBC clones also offered an opportunity to study the nature of *ERBB2*-transcriptome in an isogenic background. The clones were initially characterized through a microarray based platform as a part of Master's dissertation project. This led to identification of *ERBB2*-modulated genes with some degree of overlap in gene expression profiles of *ERBB2*-positive human tumors through microarray analysis. To gain a deeper insight of *ERBB2*-transcriptome and to study the influence of *ERBB2* on TNBC biology, the project was advanced to a Doctoral degree dissertation project and isogenic clones were subjected to RNA-sequencing analysis. A large volume of work over the years led to identification of differential expressed genes, alternative spliced transcripts, predicted transcription and splicing factors which we presumed to be responsible, at-least, in-part, for the noted transcriptome of breast cancer cells as affected by *ERBB2*. RNA-sequencing analysis of isogenic clones identified *933 ERBB2*-regulated genes shared between two model systems. Mining of the RNA-seq data identified differentially spliced transcripts as affected by *ERBB2* overexpression in two isogenic systems. Analysis of differential exon usage between TNBC and non-TNBC cells also identified 416 deregulated exons. Next analysis of the flanking regions of deregulated exons for splicing factors motifs recognized shared motifs for a set of splicing factors including, SF2/SRSF1. Because of the lab research interests, follow up studies independently verified that *ERBB2*-overexpression is accompanied by up-regulation of ABCC3 as well as SF2 proteins as new targets of *ERBB2*. This is particularly exciting as ABCC3 has been implicated in multidrug resistance associated with *HER2* overexpression. On-going collaborative studies are designed to understand the role of *ERBB2* in the regulation of ABCC3 and SF2, and potential cross-talk among all three molecules-all residing on the same chromosome 17.

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The politics of approximation: An epistemological and mathematical critique of the Hardy-Weinberg equilibrium

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In the emergent field of population genomics, increasing attention has been paid to the role of admixed DNA in generating knowledge about human difference, disease susceptibility, and migration history. In this talk, I draw attention to the Hardy–Weinberg Equilibrium (HWE), a widely used but little-analyzed mathematical concept upon which much of the necessary calculations in these studies is based. The mathematical elegance and simplicity of the HWE is dependent upon six idealistic preconditions, among them panmixia, or random mating, that are rarely found in the natural world, let alone in human societies. I demonstrate the surprising, seemingly paradoxical way in which the HWE is employed in these studies as exclusionary criterion for candidate genes. Specifically, SNPs which do not fall within a certain margin of the ideal HWE proportions are excluded from further analysis. As a result, a set of highly specific, unlikely, and possibly nonexistent patterns of human mating are reflected in the genes and subsequent published studies. I argue that the implications of this have been obscured by the equation's own elegance and ubiquity, and recommend that contemporary admixture genomicists acknowledge more explicitly the mathematical limitations of this simplified model. Additionally, I assert the special importance of methodological rigor and careful reflection in studies that bear heavily upon issues of race, resource distribution, health and identity.

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