Mutational Pathways Analysis

Mutations are a critical factor in the development of cancer. We will predict the functional effect of SNVs through the Ensembl Variant Effect Predictor (VEP), which will provide information regarding status in coding and non-coding regions, as well as protein translation effect (missense, splice-site variation, frameshift, deletion) [27268795]. Mutations found in non-coding regions will be considered in the transcription factor analysis by the method described in [28333948], while those that lie within a gene will be filtered by their effect. A literature curation will be done to explore the importance of damaging mutations in triple negative breast cancer tumorigenesis. For mutations without information in the literature, we will conduct in-silico perturbation experiments via Igenuity Molecule Activity Predictor and compare to gene expression data to try to determine its effect [citation does not exist for function].

SNVs have the capability to inactivate, activate, or modify the specificity of a protein’s kinase domain which may cause profound signaling changes within a cell. We will use the ReKINect software to predict and classify kinase modifying mutations in our SNV data [26388441]. ReKINect employs a database of all known human kinase domains, 111 SH2 domains, and 149,838 phosphorylation sites and will predict the functional impact of the SNV. If mutations affecting protein kinase function are identified, KINSpect, using the ReKINect database, will be used to determine the downstream targets of the mutated kinase [26388442]. KinomeXplorer will be used to investigate upstream kinase specificity changes for mutated proteins [24874572]. The identified mutated pathways will be added to the network manually, as they are not included in signaling databases.