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| I. Project Title |
| Epigenome-wide survival analysis based on integrating meQTL for non-small cell lung cancer | **Date:**09/30/2017 |
| **II. Project Group Investigators** |
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| III. Background |
| Lung cancer remains the leading cause of cancer-related mortality worldwide, with an estimated 224,390 new cases and 158,080 deaths in the USA in 2016. Improving survival is a major challenge, since the 5-year survival rate remains <15% across all stages of this disease [1]. DNA methylation, a reversible epigenetic modification, regulates gene expression and provides potential cancer biomarkers and therapeutic targets [2]. Epigenome-wide association studies (EWAS) have attempted to identify methylation biomarkers associated with survival status [3-5]. However, cancer studies that measure DNA methylation have been hampered by specimen availability and cost. Consequently, many DNA methylation-survival associations have not been detected, especially those with small effects. In this proposed study, we aim to predict DNA methylation through large scale TRICL SNP data and perform epigenome-wide association study based on those predicted DNA methylation data and survival information. |
| IV. Specific Aims |
| Aim: To discover novel DNA methylation loci that are associated with survival of non-small cell lung cancer (NSCLC) based on predicted DNA methylation data.  |
| **V. Methods** |
| Stage 1: By exploiting TCGA data, the association weights for DNA methylation level of each locus and its cis-SNPs will be calculated through multiple methods, including meQTL, LASSO, BLUP, BSLMM, or Elastic-net. Heritability of cis-SNP on each DNA methylation locus will be generated. Loci with low heritability will be screened out before calculating association weights.Stage 2: DNA methylation of each locus will be imputed by TRICL SNP data, based on association weights generated in Stage 1.Stage 3: Epigenome-wide survival analysis will be performed to detect DNA methylation loci that are associated with survival status, based on imputed DNA methylation data.  |
| **VI. Materials or variables needed from the study PIs** |
| We prefer to get the genotyping data from GAME-ON OncoArray study, as well as phenotype data with overall survival information. Summarized-level association results are also welcome.1. Demographic and clinical descriptions for study samples:Overall survival timeProgression-free survival timeCensoring status (Yes/No)Age GenderEthnic (White/Black/Hispanic/Asian/Others)Smoking status (never/former/current)Tumor stage (I/II/III/IV)Histology (LUAD/LUSC/Others)Surgery (Yes/No)Chemotherapy (Yes/No)Radiotherapy (Yes/No)Adjuvant therapy (Chemotherapy or Radiotherapy: Yes/No)Other treatment details2. Association results for SNP with NSCLC overall survival:HR, SE of log(HR), z of log(HR) and P of log(HR) |
| **VII. Time line** |
| Stage 1-2: 3 months Stage 3-4: 2 monthsManuscript drafting: 3 months  |
| **VIII. Other remarks** (e.g. publication plan, etc) |
| We aim to publish our results in high quality journal. |

Reference

1. Crino, L., et al., *Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2010. **21 Suppl 5**: p. v103-15.

2. Hojfeldt, J.W., K. Agger, and K. Helin, *Histone lysine demethylases as targets for anticancer therapy.* Nat Rev Drug Discov, 2013. **12**(12): p. 917-30.

3. Sandoval, J., et al., *A prognostic DNA methylation signature for stage I non-small-cell lung cancer.* J Clin Oncol, 2013. **31**(32): p. 4140-7.

4. Bjaanaes, M.M., et al., *Genome-wide DNA methylation analyses in lung adenocarcinomas: Association with EGFR, KRAS and TP53 mutation status, gene expression and prognosis.* Mol Oncol, 2016. **10**(2): p. 330-43.

5. Karlsson, A., et al., *Genome-wide DNA methylation analysis of lung carcinoma reveals one neuroendocrine and four adenocarcinoma epitypes associated with patient outcome.* Clin Cancer Res, 2014. **20**(23): p. 6127-40.