Relationship Between NOS Gene Methylation and Heart Failure Outcomes

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Introduction

- Heart disease is a leading cause of death worldwide, with heart failure patients having some of the worst outcomes.
- DNA methylation, a transcription regulation mechanism involving the addition of a methyl group without changing the base sequence, might offer insight on contributors to severe outcomes in those patients.
- Our area of interest is the nitric oxide synthase (NOS) genes, responsible for the synthases that produce nitric oxide, an important signaling molecule.
- The goal of this project was to identify associations between DNA methylation patterns and risk of severe cardiovascular outcomes in patients with heart failure.

Methods

- Clinical data was obtained from the University of Illinois at Chicago Heart Failure Database, and all patients provided informed written consent before being included in the database.
- DNA methylation data (in M-values) were obtained using the Illumina Human Methylation 450K array.
- Cox proportional hazard tests were performed to assess the risk of death, hospitalization, and total combined risk of both.
- Three analyses were performed, one on global methylation, one on individual NOS gene mean methylations, and one on the methylation of CpG sites within the NOS region.

Results

- Increased global methylation trended towards a decreased mortality risk (HR: 3.402e-135).
- In NOS gene region, increased mean methylation in the NOS3 region trended with a decrease in combined hospitalization and mortality risk (HR:0.0001743) as well as the hospitalization risk alone (HR: 0.0001406)
- Two probes, cg00963113 (Gene: TMEM176B) and cg13666659 (Gene: NLK), were highly significantly associated (p-value ≤ 0.001).

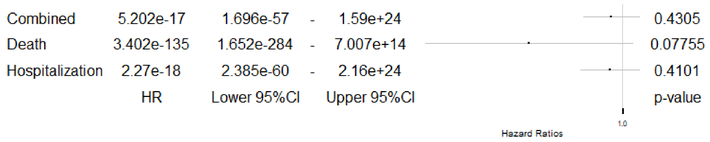

Figure 1. Associations between global methylation and clinical outcomes in HF patients

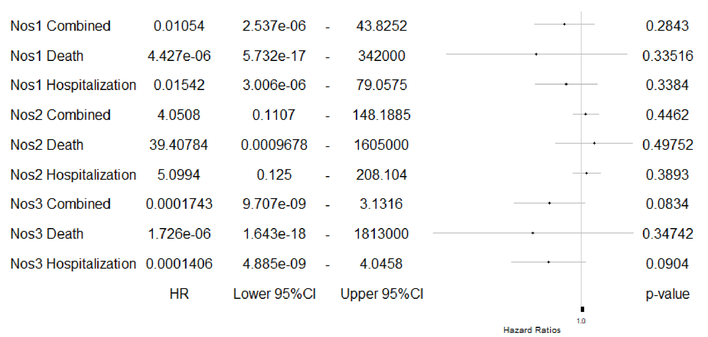

Figure 2. Associations between mean NOS methylation and clinical outcomes in HF patients

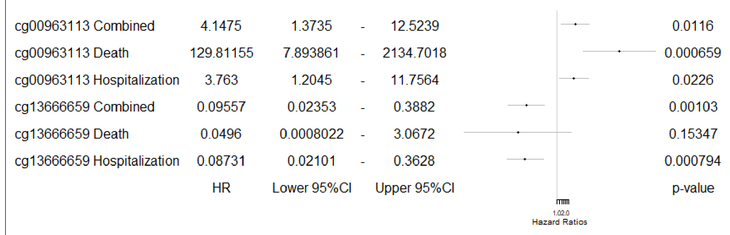

Figure 3. Associations between individual methylation sites within NOS gene regions and clinical outcomes in HF patients

Conclusions

- Global methylation shows a possible protective trend towards mortality risk; however, the number of deaths in the sample was very low – only 9 out the 118 patients.
- Mean methylation within the NOS3 gene region seems to show a protective trend towards combined mortality and hospitalization risk as well as hospitalization risk alone.
- Methylation at the cg00963113 CpG site seems to show a trend towards increased mortality risk, the site itself is part of a transmembrane protein of unknown function.
- Methylation at the cg13666659 CpG seems to show a trend towards decreased hospitalization risk.
- The methylation data in our analyses was obtained from blood cells, a future analysis with methylation data from cardiomyocytes could offer more insight.
- The roles of genes that the CpG sites are found in could also be explored.