

## **Title: Identifying New G protein Coupled Receptor Kinase 2 and 3 Substrates among Proteins Closely Linked to Breast Cancer with Positive Prognosis**

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### **Purpose**

In certain breast cancers, the protein expressions of G protein coupled receptor kinases (GRKs) 2 and 3 vary, suggesting that their roles in modulating breast cancer development could be important. Even though these kinases are highly homologous (~85% based on amino acid sequences), their functions may vary when it comes to phosphorylating various proteins. In this bioinformatics study, we explored their potential ability to phosphorylate proteins most associated with positive prognosis of breast cancer to decipher if their roles in mediating positive prognosis differ between the two.

### **Methods**

In this study, the phosphorylation site predictors Phosphonet and GPS (versions 3.0 and 5.0) were utilized to determine if GRK2 or GRK3 is predicted to phosphorylate the top 20 proteins found to be most associated with positive prognosis of breast cancer according to [proteinsatlas.org](http://proteinsatlas.org). For the top 6 proteins identified to be the most likely proteins phosphorylated by GRK2 or GRK3 by these predictors, their biological functions were sorted into a variety of biological processes associated with cancer.

### **Results**

Overall, among the top 20 proteins, we found some are predicted to be best phosphorylated by both GRK2 and GRK3, along with some that are predicted to be best phosphorylated by either GRK2 or GRK3. This suggests some shared and different functions associated with these kinases in breast cancer with positive prognosis. Exploring the top 6 proteins, we found that those most likely to be phosphorylated by GRK2 and GRK3 share similar functions like effects on cell proliferation, cell metabolism and inflammation, and are linked to cell signaling processes. GRK2 may have a minor role in modulating cell death unlike GRK3.

### **Conclusion**

In this study, we compared the potential effects of GRK2 and GRK3 in breast cancer that have a positive prognosis using a bioinformatic approach. Among proteins associated with positive prognosis, GRK2 and GRK3 can phosphorylate the same proteins and, surprisingly, different proteins as well despite their high degree of homology. This study also shows that they may have both similar, like signaling transduction, and different functions, like in cell death, in breast cancer. Collectively, this suggests that GRK2 and GRK3, if they play a role in the development of breast cancer with positive prognosis, may do this through both similar and different proteins. This could also suggest that treatments may be chosen that are more targeted to select signaling systems depending on the level of GRK2 or GRK3 expression in these breast cancers.