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Modeling ATP-Binding Cassette G2 (ABCG2) Substrate Specificity

Raghav D. Acharya  
*Virginia Commonwealth University, acharyard@vcu.edu*

Aurijit Sarkar  
*Virginia Commonwealth University*

Glen E. Kellogg  
*Virginia Commonwealth University*

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Modeling ATP-Binding Cassette G2 (ABCG2) Substrate Specificity

Raghav D. Acharya¹, Aurijit Sarkar¹, and Glen E. Kellogg²*
Department of Biology¹, and Department of Medicinal Chemistry², VCU, Richmond, VA

Abstract

- Cancer estimates for USA in 2015:
  - 1.6 million new cases,
  - half a million deaths [1]
  - majority of deaths due to resistance to chemotherapy [2]
- ATP-binding cassette (ABC) efflux transporters (e.g., ABCG2)
  - overexpressed in chemotherapy-resistant cancer cells
  - Anticancer drugs are prone to efflux
- What we need:
  - identify substrate and non-substrate chemotypes
  - gain a structural understanding of the efflux mechanism

Aim: Understand ABCG2 structure and function

Introduction

Why are certain compounds effluxed while others are not?

Method

Discrimination Analysis

Target property = ax + by + cz + k

Where:
- a, b & c are correlation coefficients
- x, y & z are independent properties

Non-Linear SVM method used for this study.

References

(3) Hazai, E. et al. BMC Bioinformatics 2013, 14, 130.
(B) Sugimoto et al Mol Cancer Ther 2003, 2(1): 105-112

Descriptors Used

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<th>Our Model</th>
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<td>Length (II)</td>
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<tr>
<td>Width (III)</td>
</tr>
<tr>
<td>Binding Energy (IV)</td>
</tr>
<tr>
<td>Atom Count (V)</td>
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<tr>
<td>Radius of Gyration (VI)</td>
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Results

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<td>58.9 ± 26.3%</td>
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Discussion

SVM model capable of discriminating between substrates and nonsubstrates with a median accuracy of 76.05% and an Interquartile range of 7.04%.

Accuracy highly dependent on composition of training, test and external validation sets.

Insights into efflux mechanism – role of Arg482 in substrate recognition suggested by significant difference in binding energy between substrates and non substrates.

Implications

- Discriminant models are noisy – understanding of the structural mechanism of efflux might lead to better models.
- More experimental data needed – might make for a better predictive model.

Future directions

- Glean structural information on ABCG2-mediated efflux to improve model.

Acknowledgements

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