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Substantial Enhancer Activity Of Non-coding Regions in *ABCG2* (Breast Cancer Resistance Protein, BCRP)

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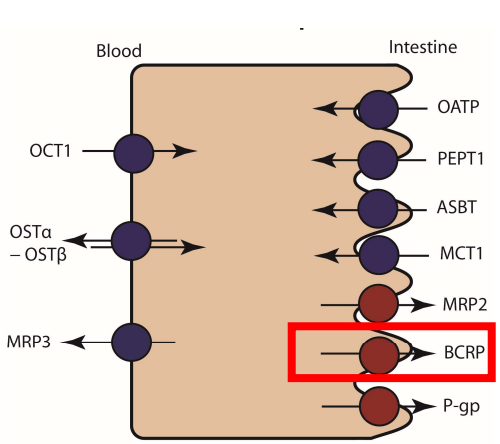
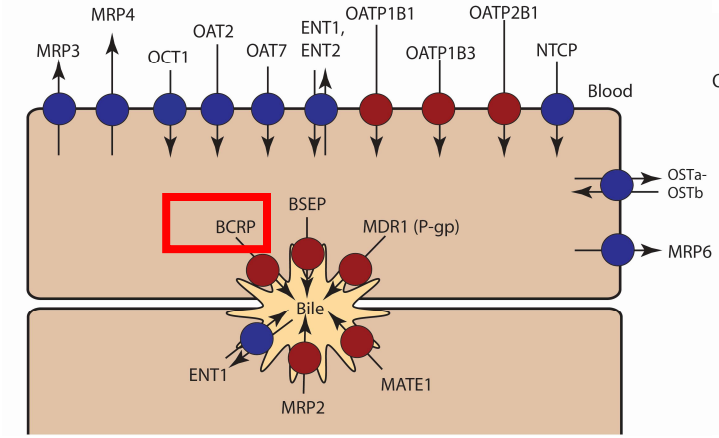
Principal Investigator: Kathleen Giacomini, Ph.D.

Department of Bioengineering and Therapeutic Sciences

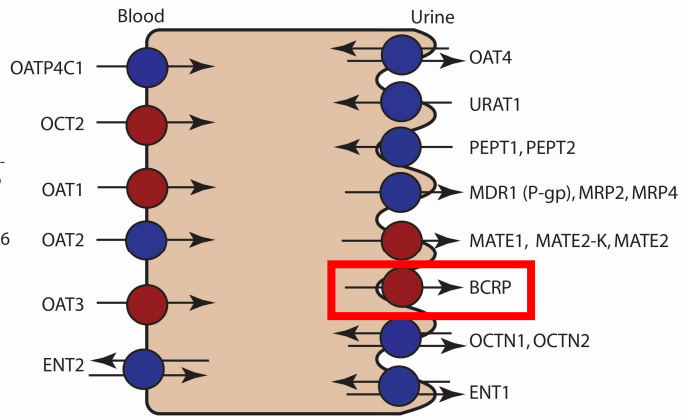
Genetic Variants in *ABCG2* are Associated with Variation in Drug Response



Intestinal Epithelia

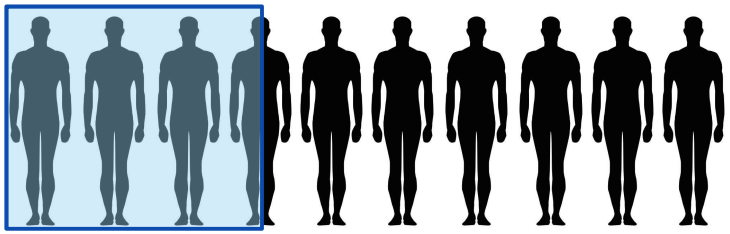


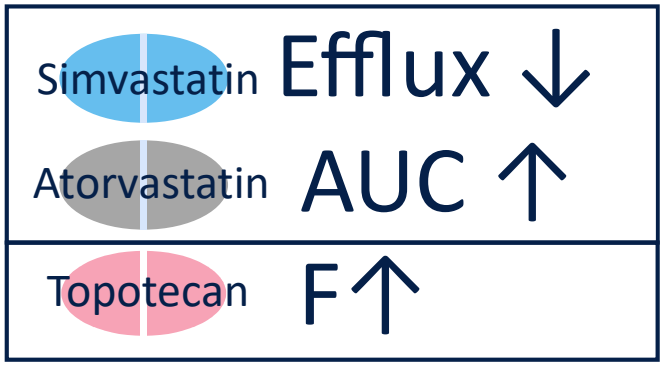
Hepatocytes



Kidney Proximal Tubules

ABCG2 421C>A, BCRP Q141K





Figures adopted from Giacomini et al

Giacomini KM et al. Nat Rev Drug Discov. 2010 Mar; 9(3): 215–236.. Keskitalo JE et al. Clin Pharmacol Ther.. 2009; 86:197-203; Keskitalo et al. Pharmacogenomics. 2009;10:1617-24. Sparreboom A et al. . Cancer Biology & Therapy. 2005; 4: 650–658.

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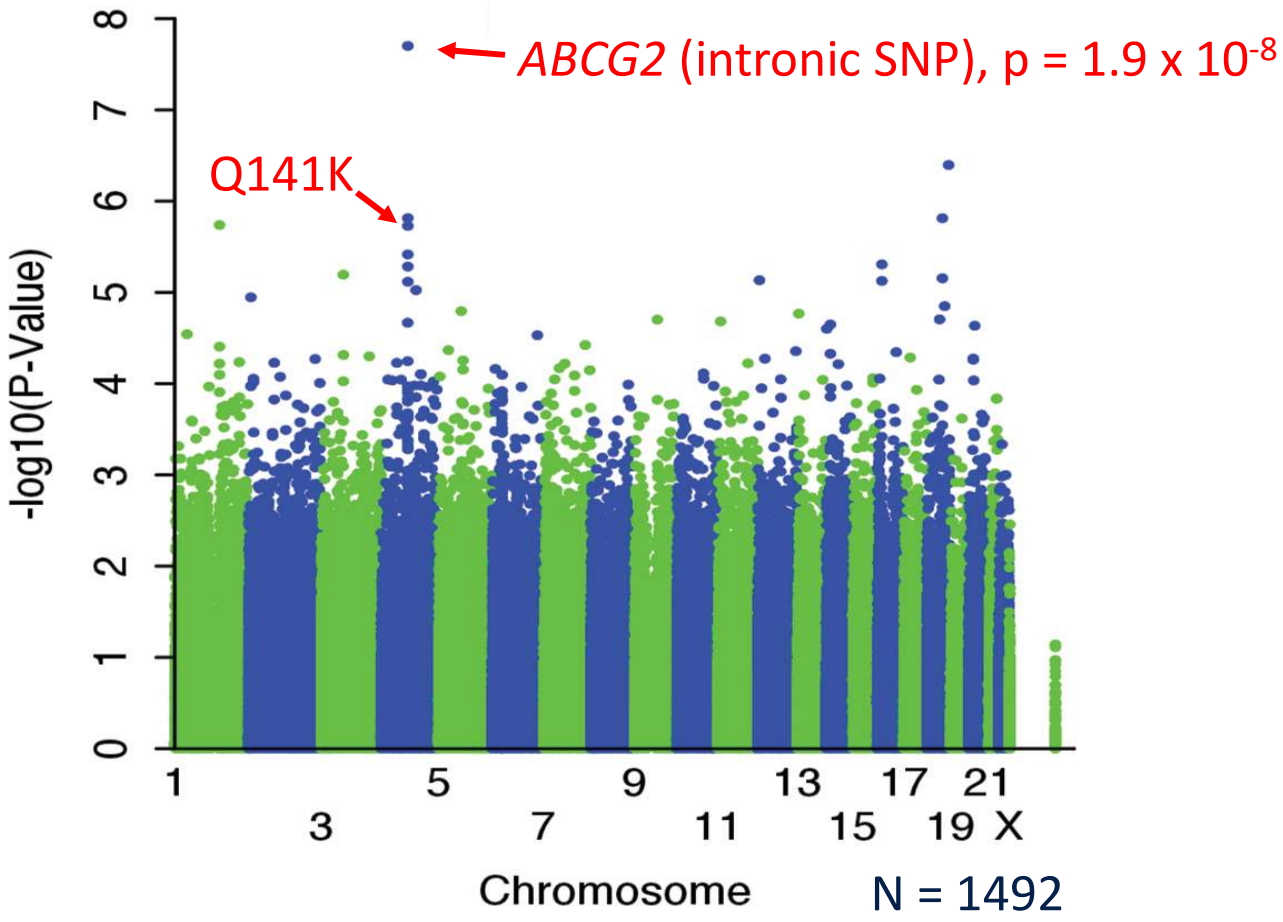
Variants of ABCG2 are Associated with Reduced Allopurinol Response



Wen C, et al. Clin Pharmacol Ther. 2015; 97(5): 518-25.

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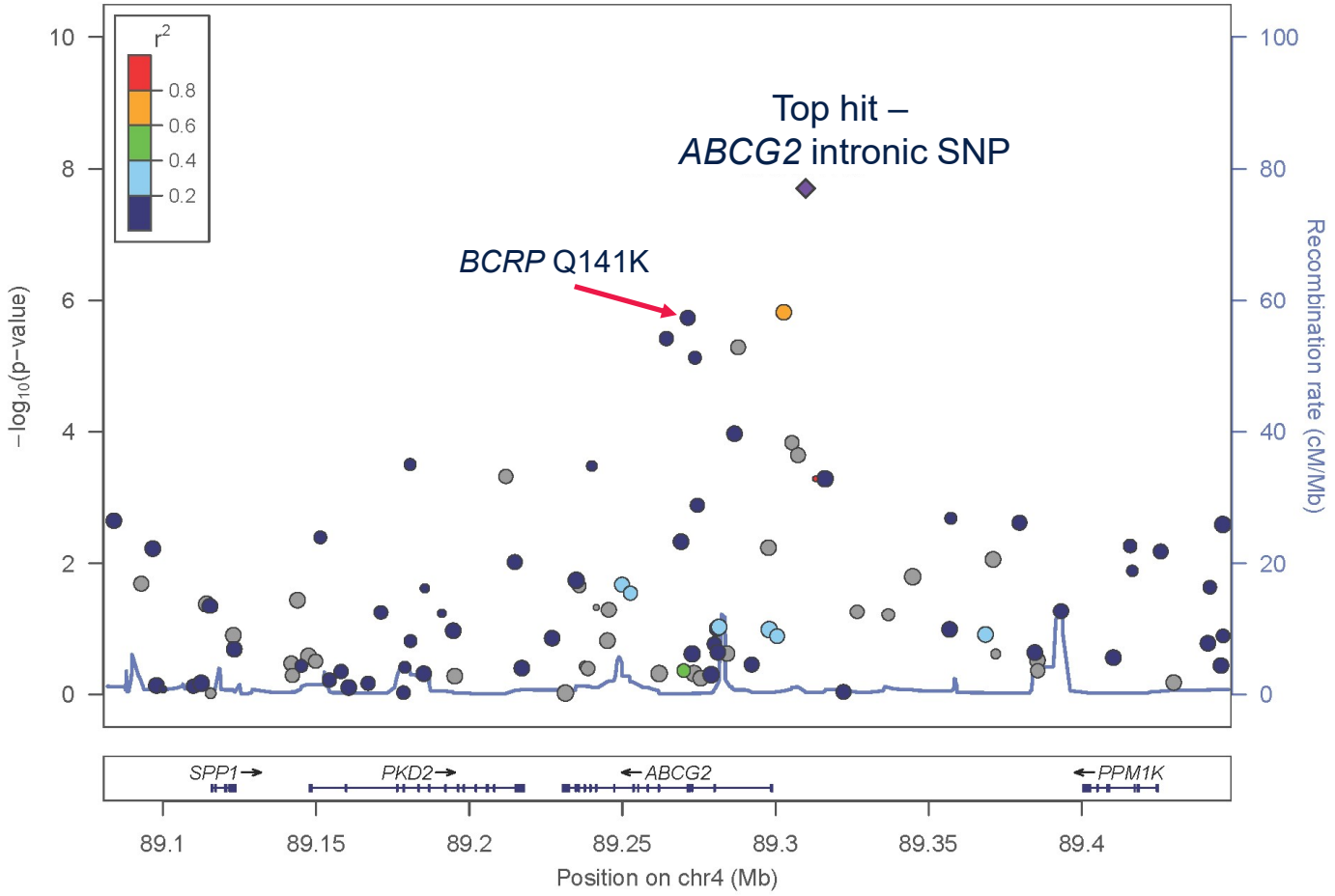
Intronic SNPs Identified in GWAS Act Independently of BCRP Q141K



Top intronic SNPs are not in linkage disequilibrium with *BCRP* Q141K

Wen C, et al. Clin Pharmacol Ther. 2015; 97(5): 518-25.

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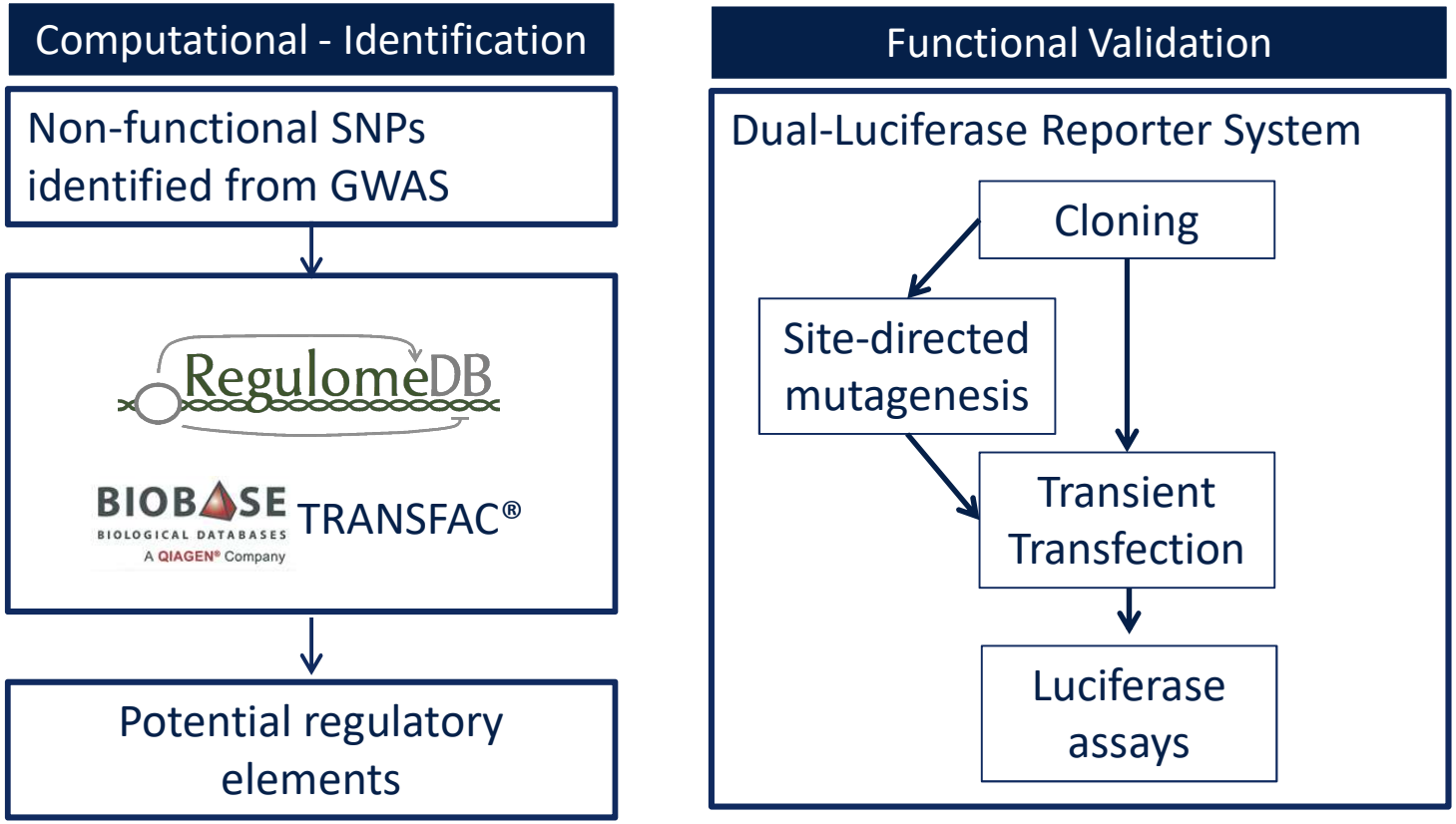
Goals of Study

1. Are the intronic SNPs identified from GWAS located in the known regulatory region of *ABCG2*?
2. What impact do these intronic SNPs have on enhancer activity *in vitro*?



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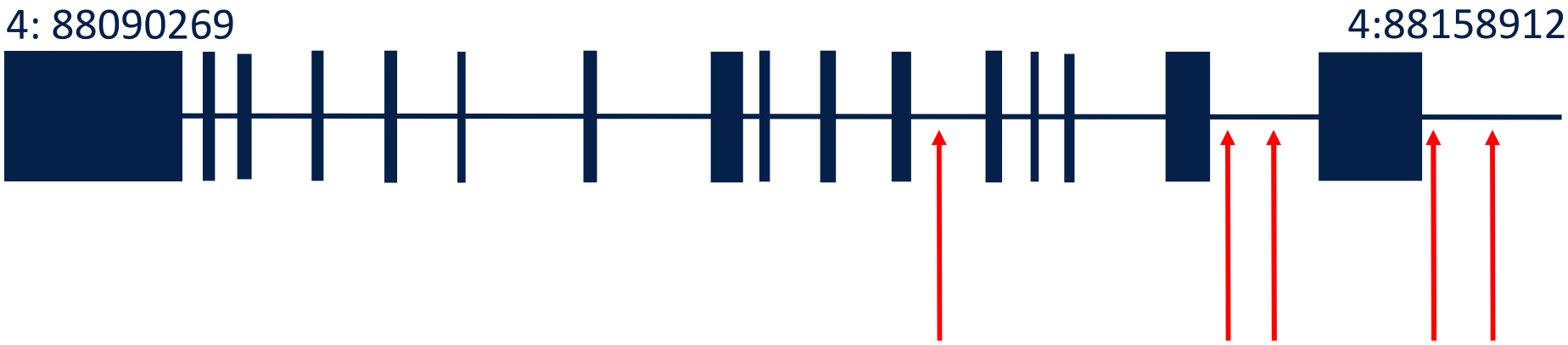
5 SNPs Selected for Functional Validation

SNPs selected for Functional Validation	
TRANSFAC	rs45499402 (4:88122482), rs2622627 (4:88144201)
Other Predictive Tools	rs3114020 (4:88162514), rs2622624 (4:88148254), rs4148162 (4:88159564)



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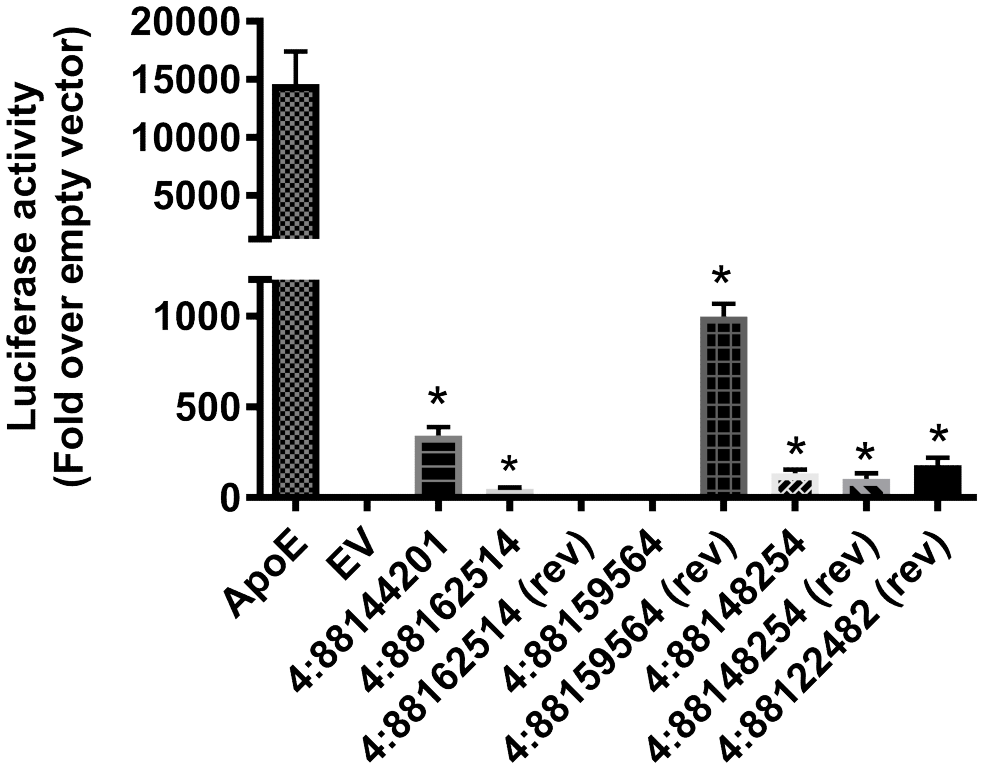
Intronic Regions Promoted Luciferase Activity in Liver Cells



* p <1x 10^{-6}
rev, reverse strand

1. Are these intronic SNPs identified from GWAS located in the known regulatory region of *ABCG2*?

2. What impact do these intronic SNPs have on enhancer activity *in vitro*?

Each bar represents mean of 6 data points

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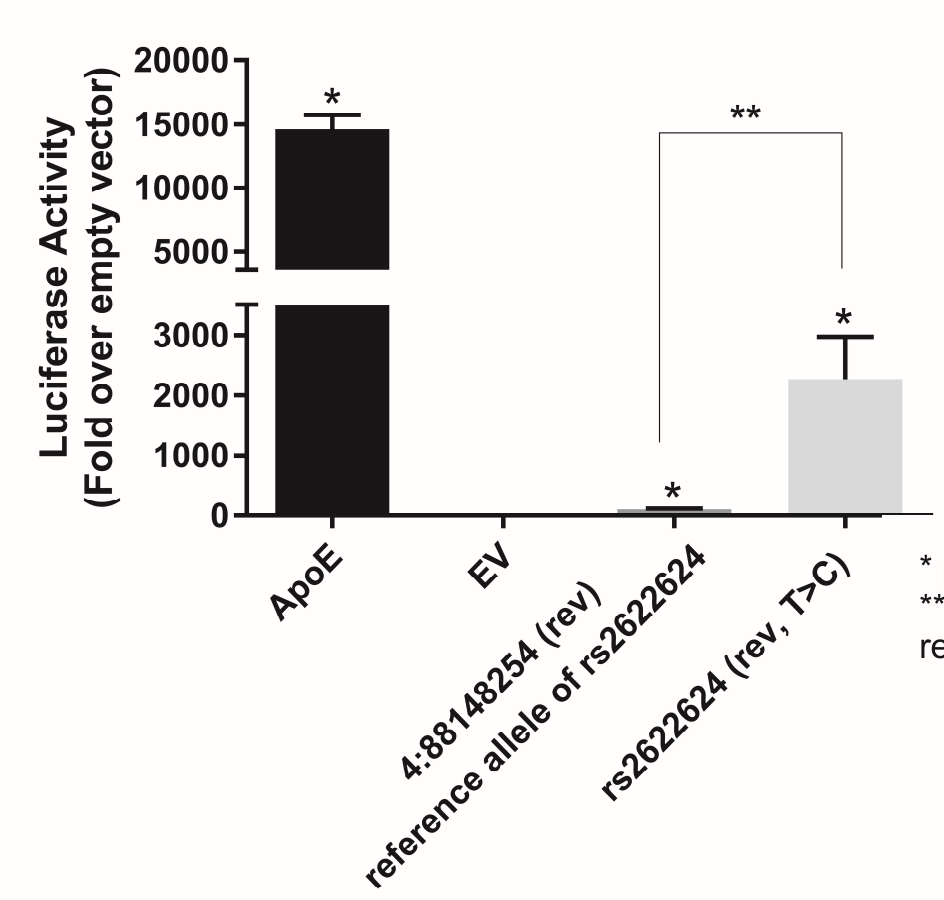
Intronic SNP Modulated Luciferase Activity in Liver Cells



* p < 0.01 vs EV
** p = 0.01
rev, reverse strand

1. Are these intronic SNPs identified from GWAS located in the known regulatory region of *ABCG2*?
2. **What impact do these intronic SNPs have on enhancer activity *in vitro*?**

Each bar represents mean of 6 data points

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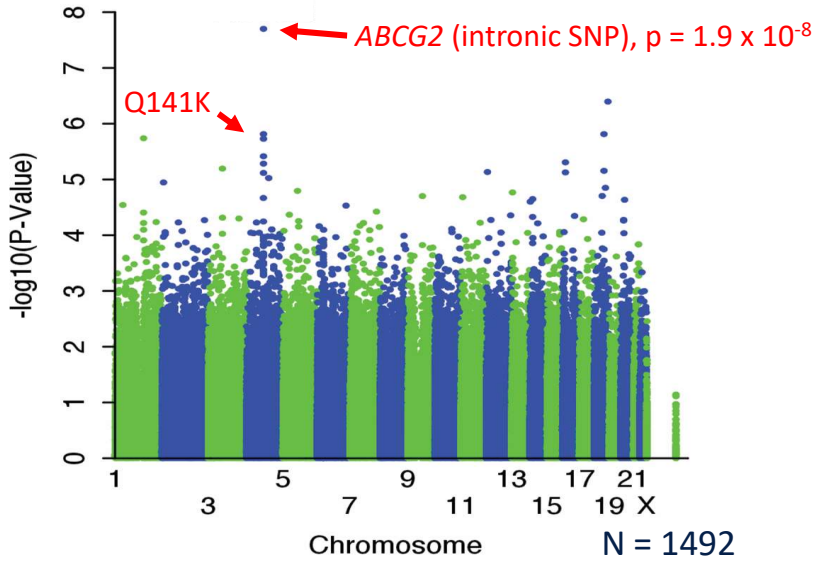
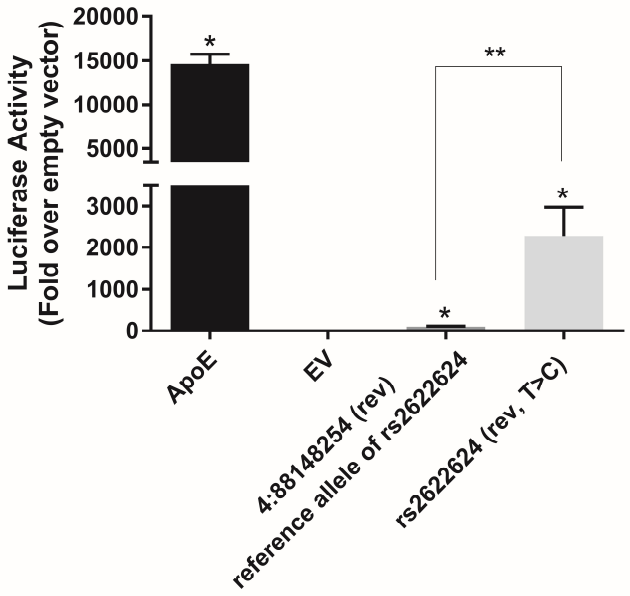
Conclusion

- The tested intronic regions in *ABCG2* had regulatory activity
- 1 intronic SNP drastically increased enhancer activity
- Intronic SNPs may act independently of Q141K to modulate *ABCG2*
- Precision medicine - Identification of these SNPs will inform future genotype assays that predict drug response





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Acknowledgement

- Kathleen Giacomini, PhD
- Giacomini Lab
  - Deanna Brackman
  - Sook Wah Yee, PhD
  - Huan-Chieh (James) Chien, PhD
  - Xiaomin Liang, PhD
- ASCPT

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Thank you!

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