Use of Genetics to Inform Drug Development of a Novel Treatment for Schizophrenia

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Why Use Genetics to Guide Drug Development?

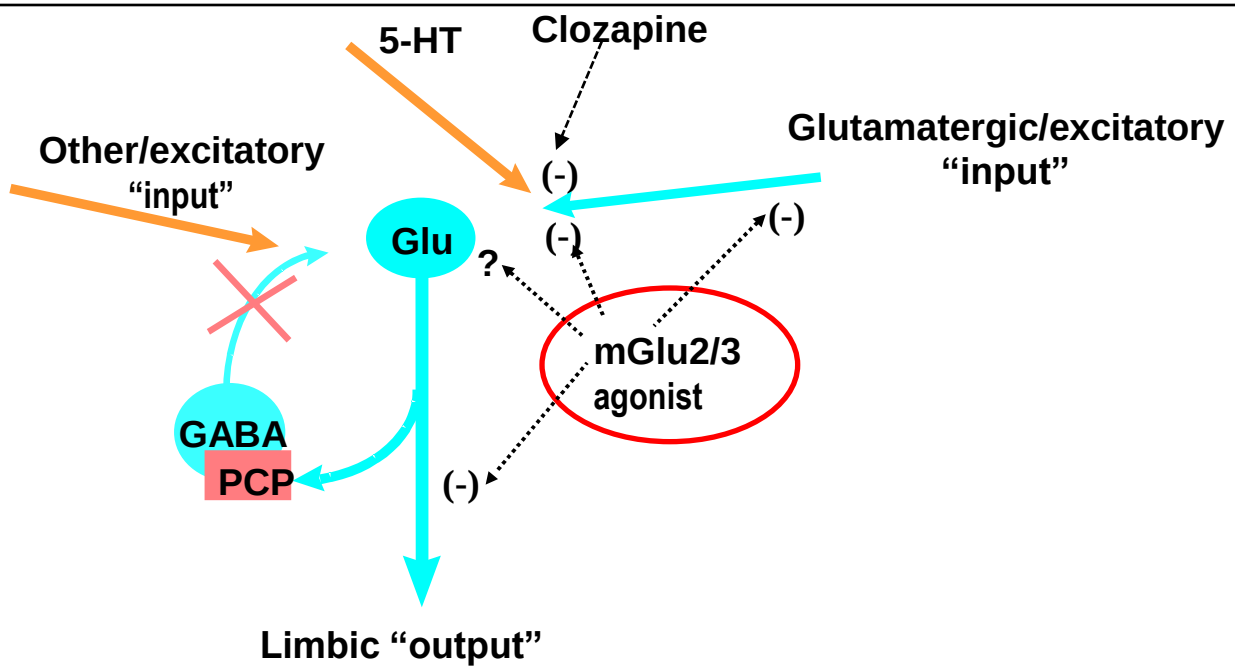
- The drug targets we study are polymorphic
- The pathways we target are complex
- The diseases we treat are polygenic & heritable
- Individual patients have differential response to treatments

Can Genetics Inform Drug Development for the Treatment of Schizophrenia?

- Chronic psychiatric illness with mortality rates that are 2 to 3 times higher than those observed in the general population
- Even after 5 decades of modern pharmacotherapy, the functional outcomes of schizophrenia remain poor
- New therapeutic approaches are needed
- Schizophrenia is highly heritable (~80%), but also highly complex
- While recent studies have shed light on common and rare variants associated with schizophrenia, a clear understanding of the biological mechanisms that contribute to neuropsychiatric disease does not exist

We used knowledge of the drug mechanism to formulate a strategy for discovery of drug-response markers

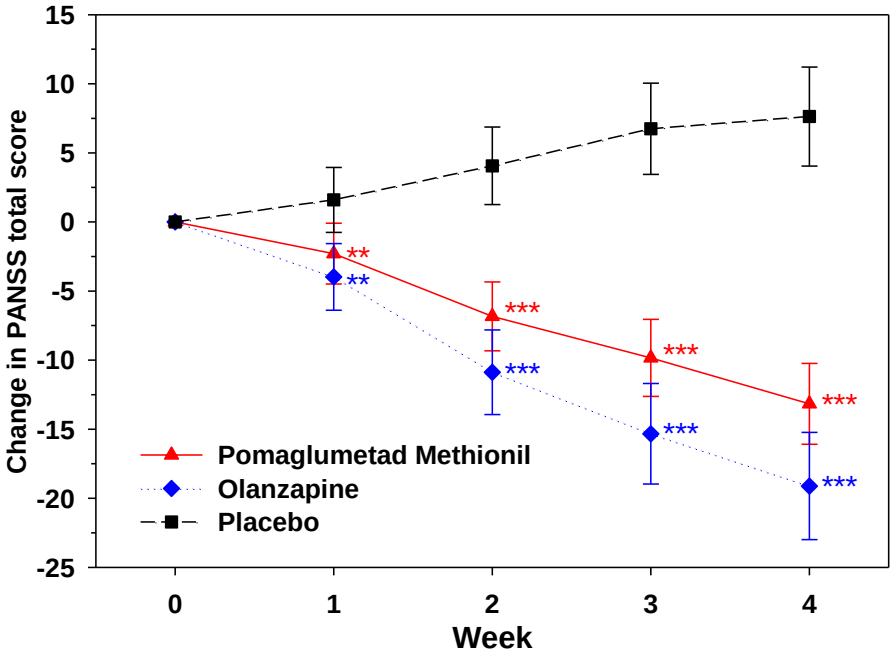
Pomaglumetad Methionil (Pomaglumetad) is an mGlu2/3 Agonist Being Developed as a Novel Treatment for Schizophrenia



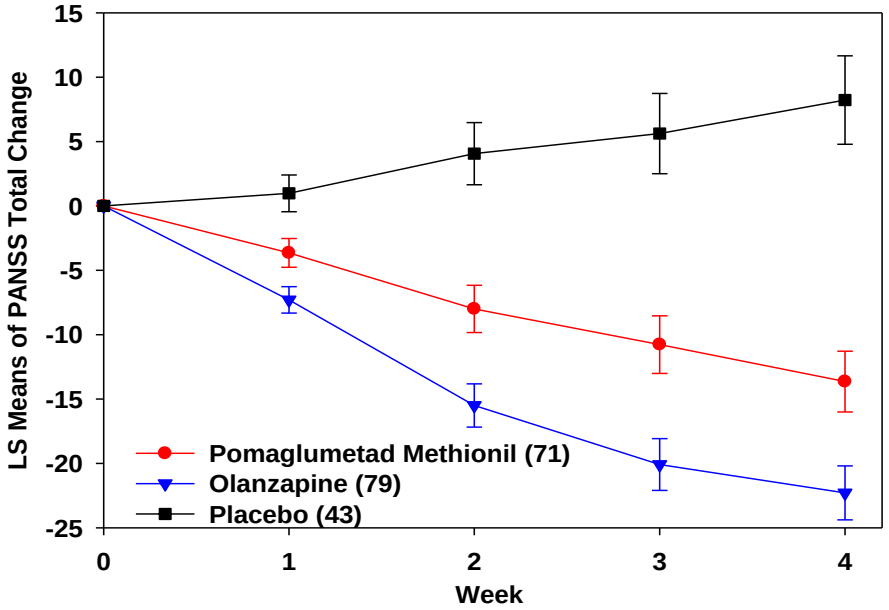
- There were no specific genetic data at the outset of the program to guide development
- Any new therapeutic would need to differentiate from available generic and branded competition
- Optional DNA banking was included in protocols

Pomaglumetad Methionil was Observed to be Superior to Placebo in a Proof of Concept Study, HBBD

HBBD Proof of Concept Study



HBBD DNA Cohort



Goals of Pharmacogenetic Program

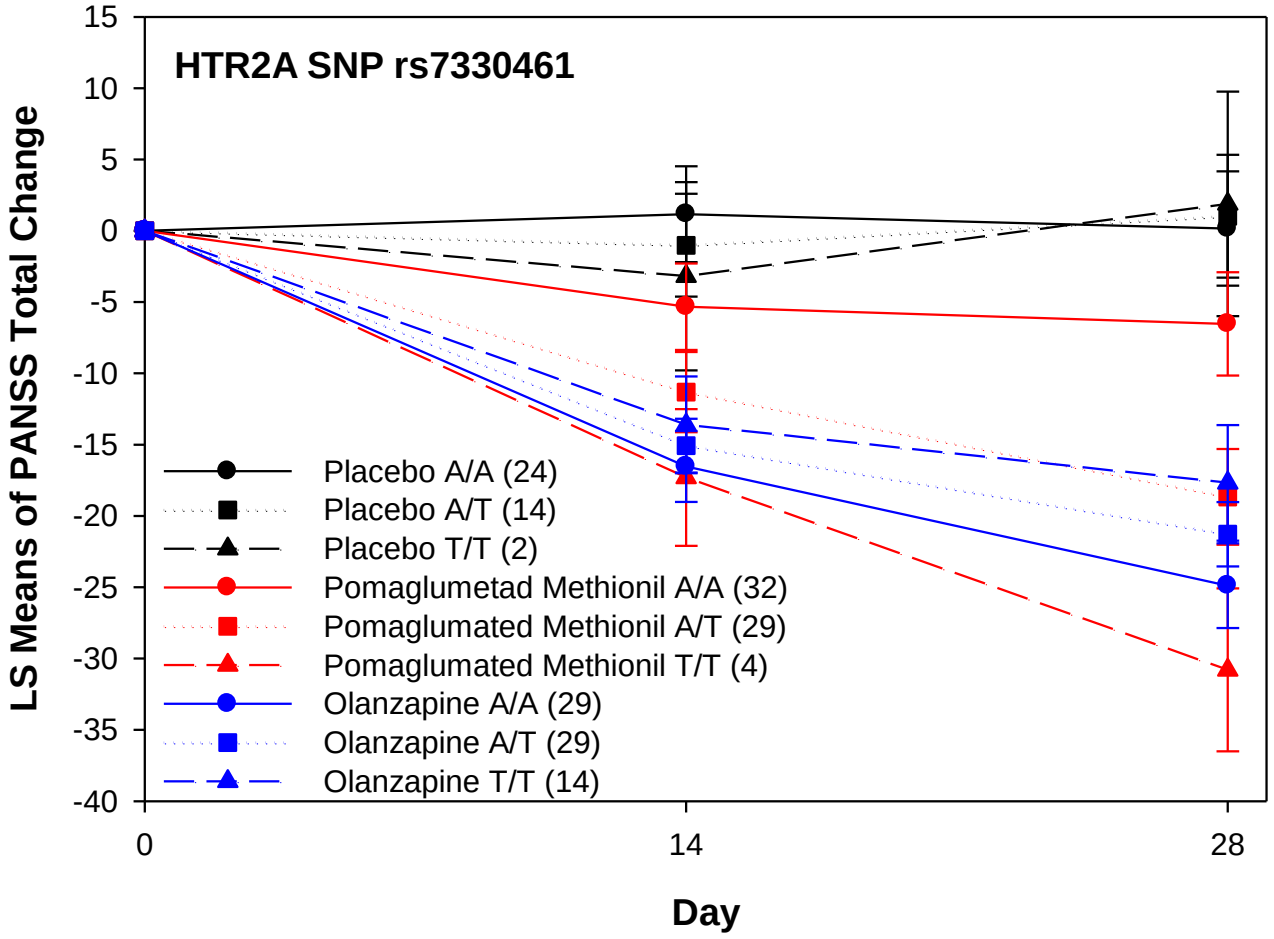
- Use candidate gene association study to identify genetic markers associated with treatment response
- Focus on target and pathway genes

NOTE: **LY2140023 monohydrate = pomaglumetad methionil**

Patil ST, et al. . *Nat Med* 2007;13(9):1102-7.

HBBD Candidate Gene Study *Discovered* Genetic Variants Associated with Pomaglumetad Methionil Response

16 SNPs in HTR2A Associated with Treatment Response in White Caucasians

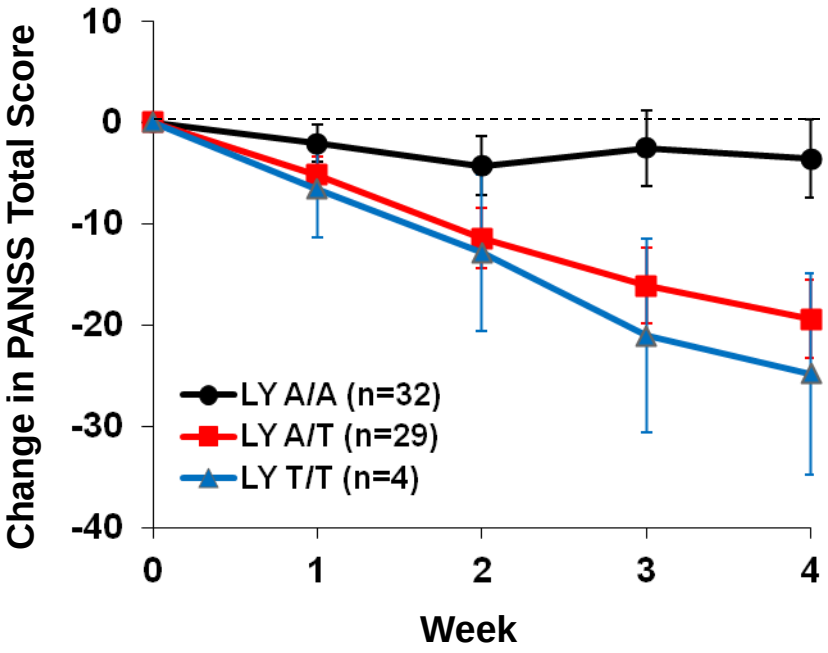


NOTE: **LY2140023 monohydrate = pomaglumetad methionil**

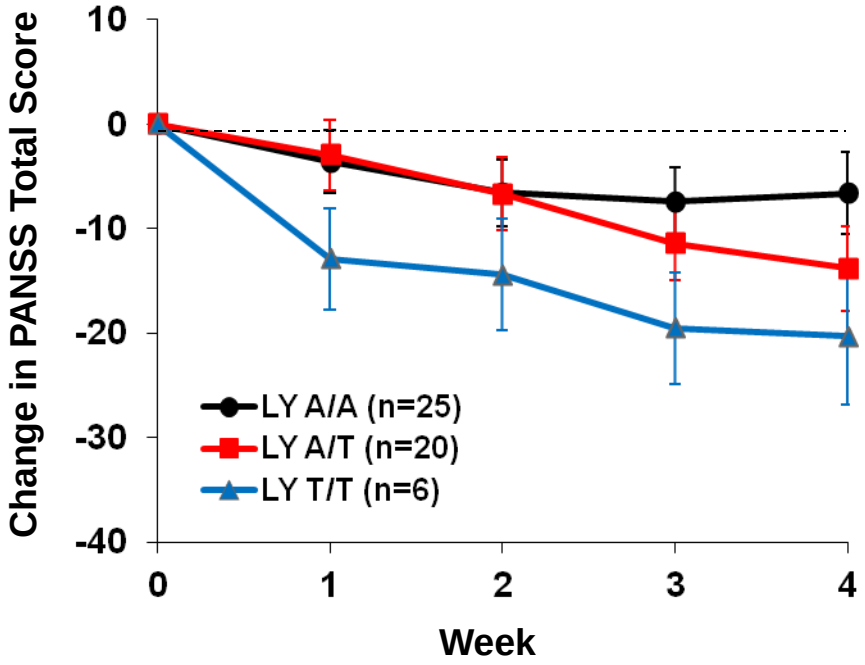
Genetic Effect of HTR2A SNP rs7330461 Was Also Observed in a Safety Study, HBBR

Change in PANSS Total Score in Pomaglumetad Methionil-Treated non-Hispanic Caucasians

HBBD Proof of Concept Study



HBBR Safety Study



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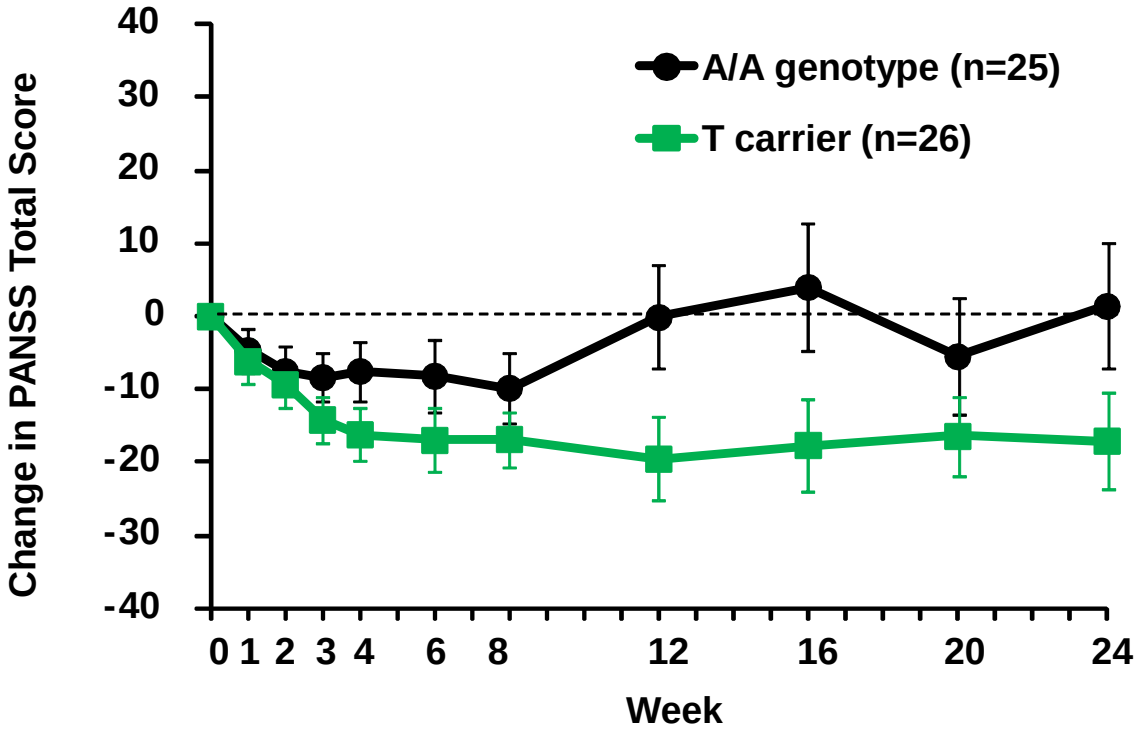
Comparison Between HTR2A SNP rs7330461 T-Carrier and A/A Genotype Groups in Study HBBR

Change in PANSS Total Score in Pomaglumetad Methionil-Treated non-Hispanic Caucasians



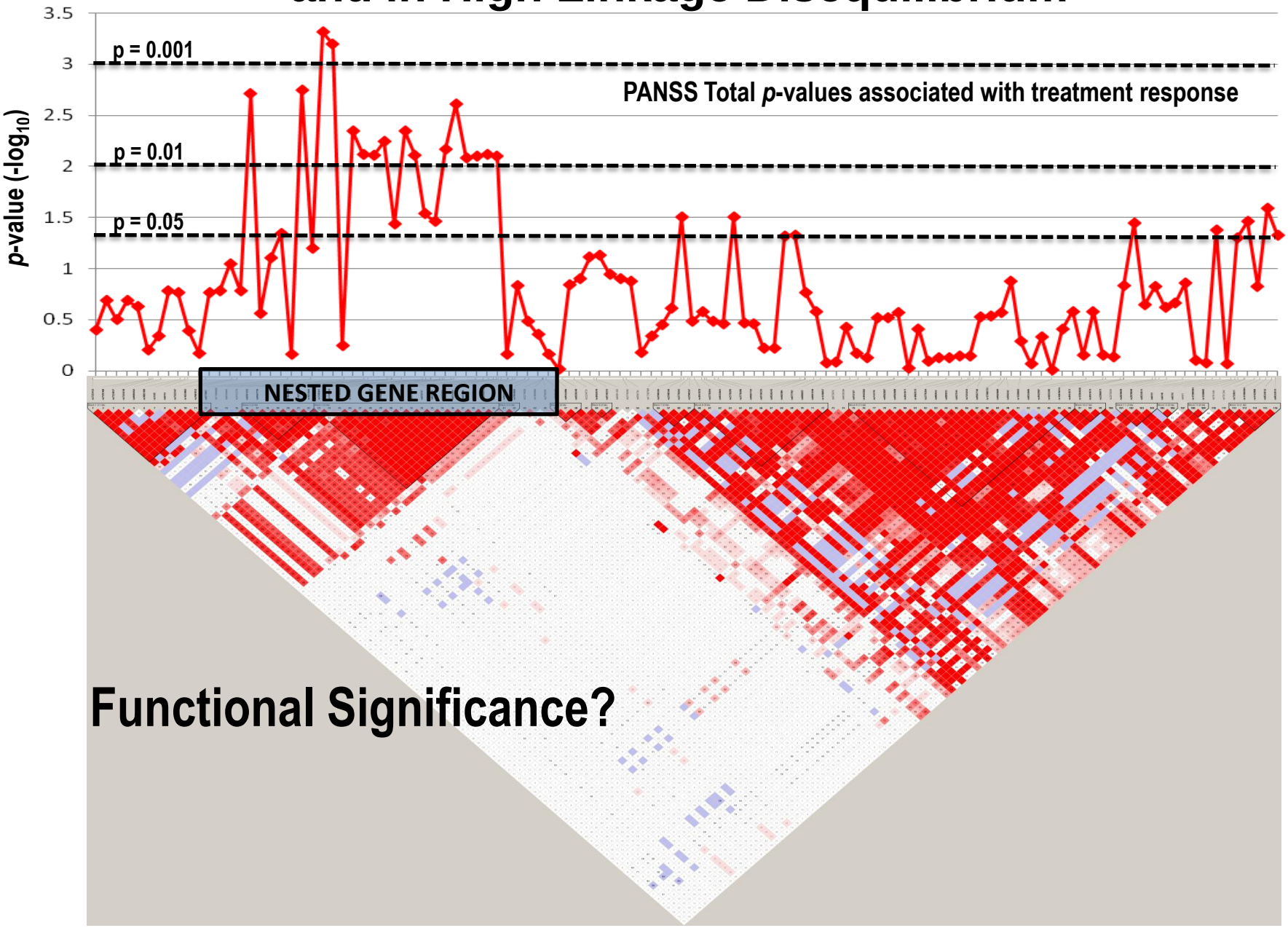
T Carrier – Better Response to Pomaglumetad Methionil

A/A – Reduced Response to Pomaglumetad Methionil

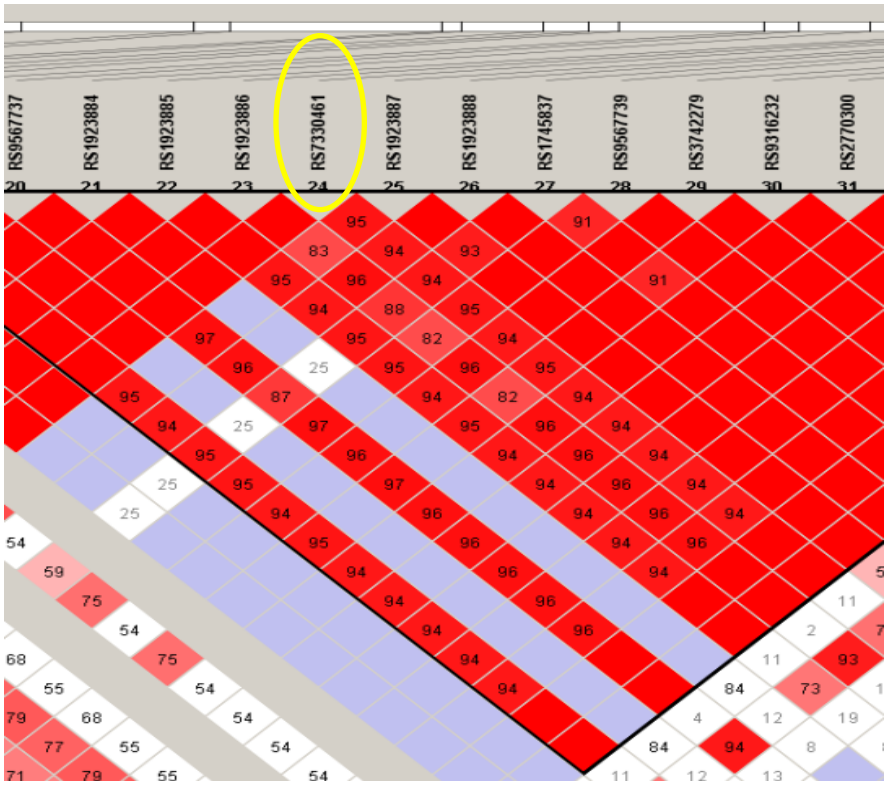
DISCOVER, REPLICATE AND VALIDATE

Next Step

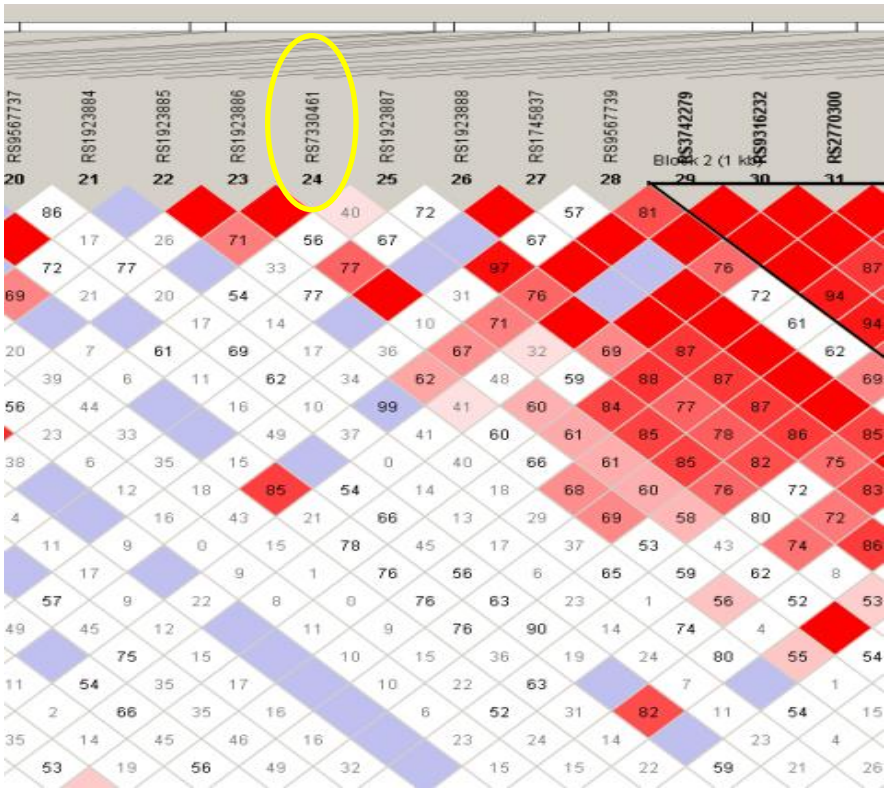
HTR2A SNPs Associated with Drug Response are Intronic and in High Linkage Disequilibrium



There are Differences in Linkage Disequilibrium in Distinct Populations



White Caucasian



African American

Access to sufficient samples in different populations is required to understand if the marker is causal or “tagging”

Summary

- Pomaglumetad Methionil has the potential to be a major advance in the treatment of schizophrenia
- HTR2A SNP rs7330461 is associated with response to antipsychotic treatment in non-Hispanic Caucasians
  - T Allele associated with enhanced response to LY2140023
- Future studies will be needed to assess these findings in a larger population and to determine whether similar results will be observed in non-Caucasian populations

Challenges

- Limited biological understanding of neuropsychiatric disease does not provide a prior hypothesis for genetic-based drug discovery/ development → leads to hypothesis generation in Phase 2
- Development of PGx hypothesis in Phase 2 necessitates replication ***and*** validation of hypothesis in Phase 3
- If genetic biomarker is not causative, underlying genetic structural differences across populations may prevent generalization of genetic marker to other populations
- If Phase 3 results support the need for a companion diagnostic, timing has the potential to become rate-limiting for drug approval