

Genetics of Chemotherapy Toxicity in Human Lymphoblastoid Cell Lines from Diverse Populations

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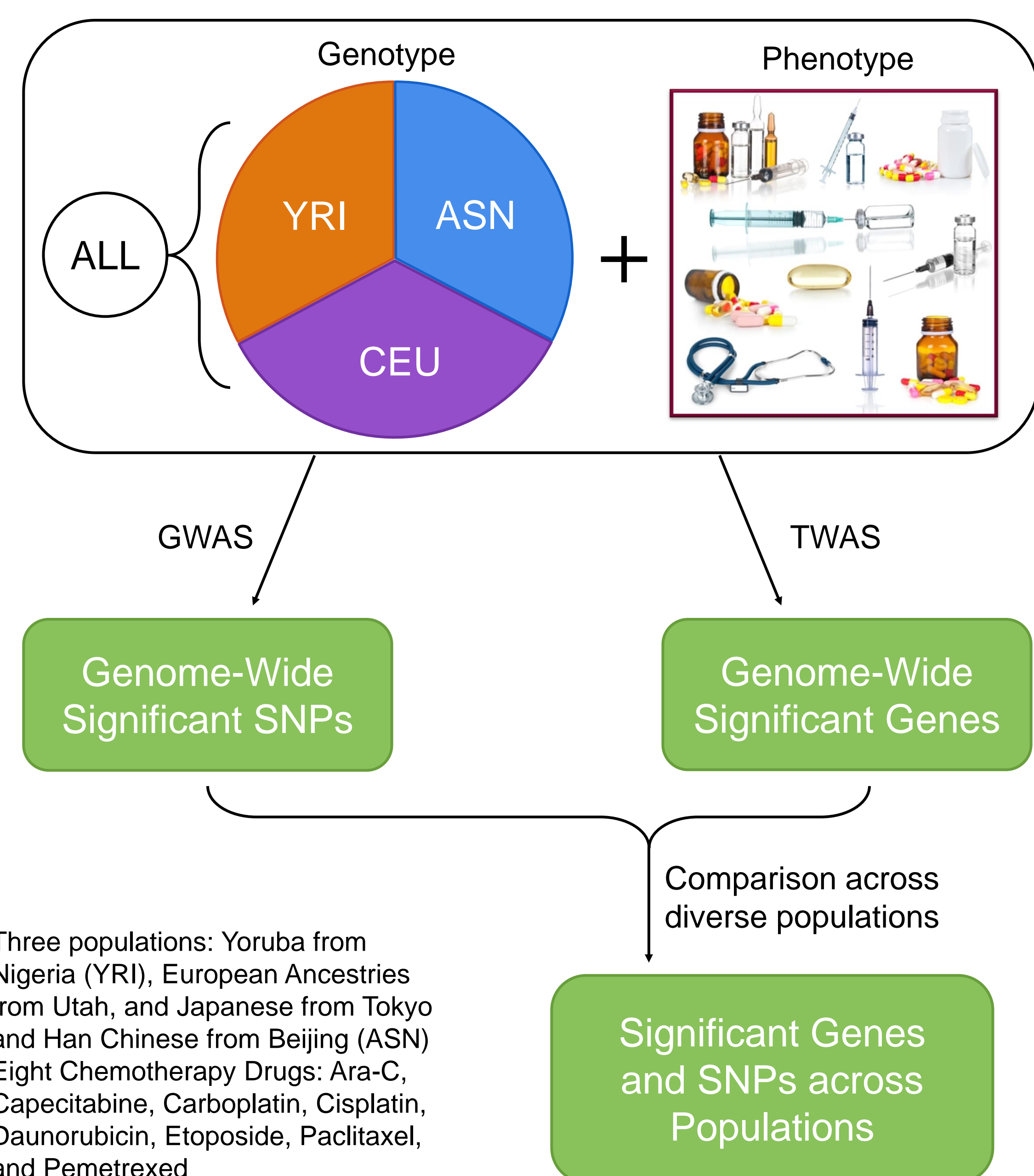
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Background

- Cancer is the second leading cause of death globally; therefore, the continuous development of new, more effective treatments is vital in the effort to reduce cancer deaths [1]
- The genetic makeup of an individual has been shown to affect the way in which their body responds to a given drug, meaning it is difficult to create a single treatment that will work for every patient [2]
- Lymphoblastoid cell lines (LCLs) are widely available across ethnic cohorts and constitute an effective model for measuring drug response in an individual [2]
- Genome-wide association studies (GWAS) can identify relationships between single nucleotide polymorphisms (SNPs) and phenotypes [3, 4]
- The majority of GWAS have been on individuals with European ancestries, but in order to develop personalized treatments other ancestries must be represented [5]
- Transcriptome-wide association studies (TWAS) aid in contextualizing the SNPs identified in GWAS as they estimate the level to which a gene is expressed, something not computed in GWAS [6]

Methods

Figure 1: Overview of methods.



Results

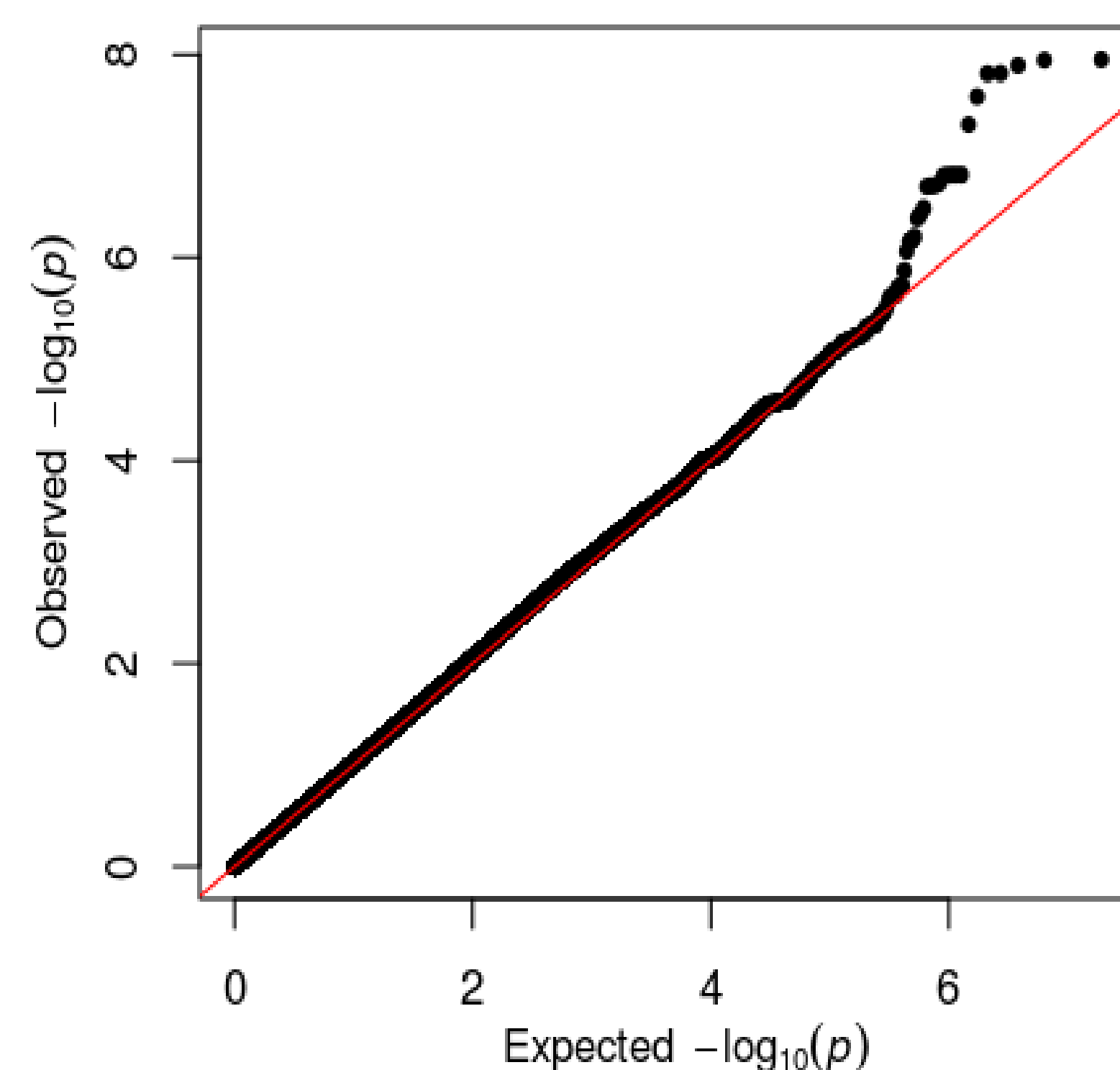


Figure 2: QQ plot of GWAS results for Etoposide in YRI. Six genome-wide significant SNPs were identified:

- rs7971310
- rs7960974
- rs7979399
- rs2711729
- rs2711728
- rs11183699

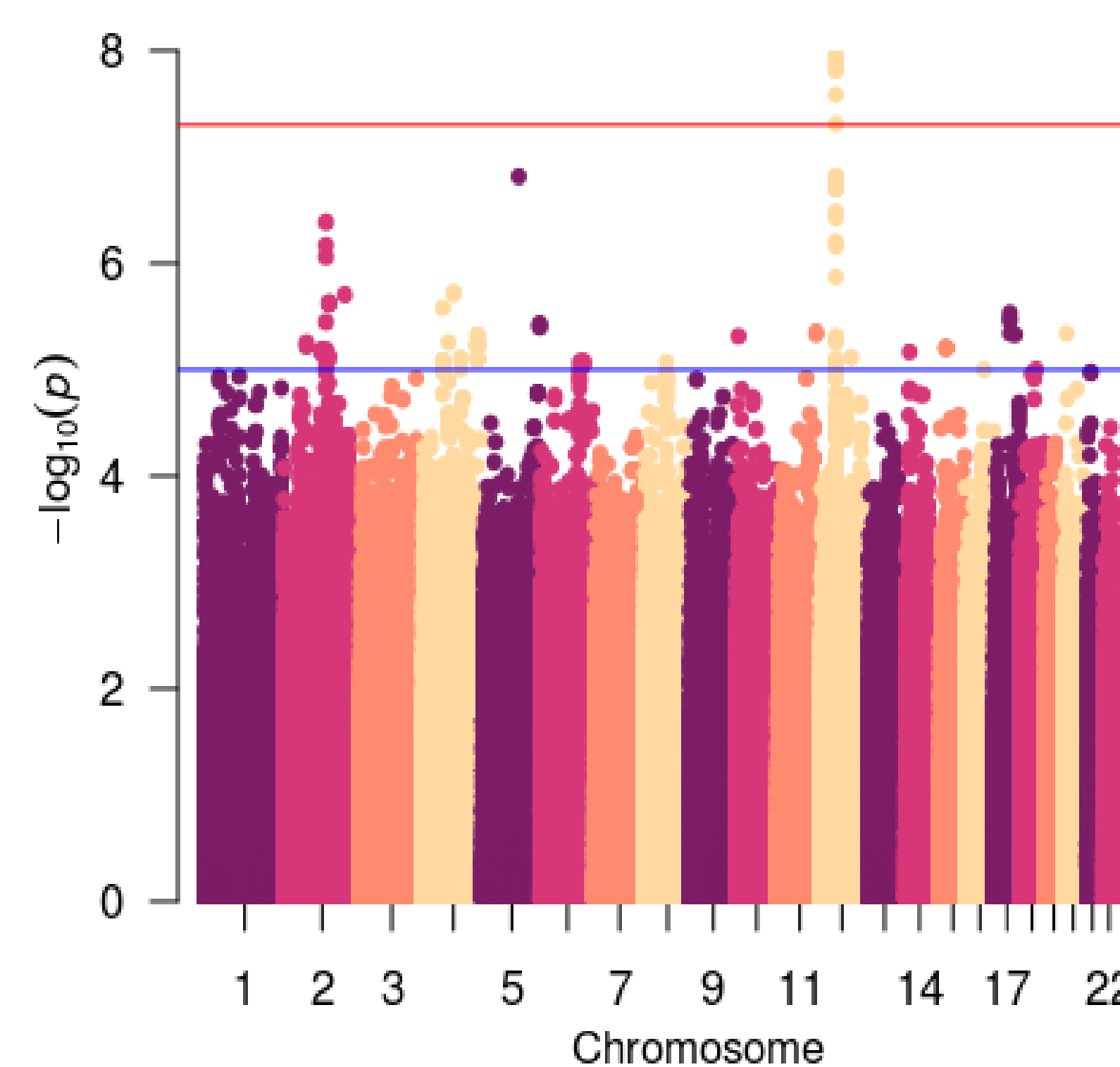


Figure 3: Manhattan plot of GWAS results for Etoposide in YRI. The red line indicates the genome-wide significance threshold. Six SNPs located on chromosome twelve met this threshold: ($p < 5e-08$)

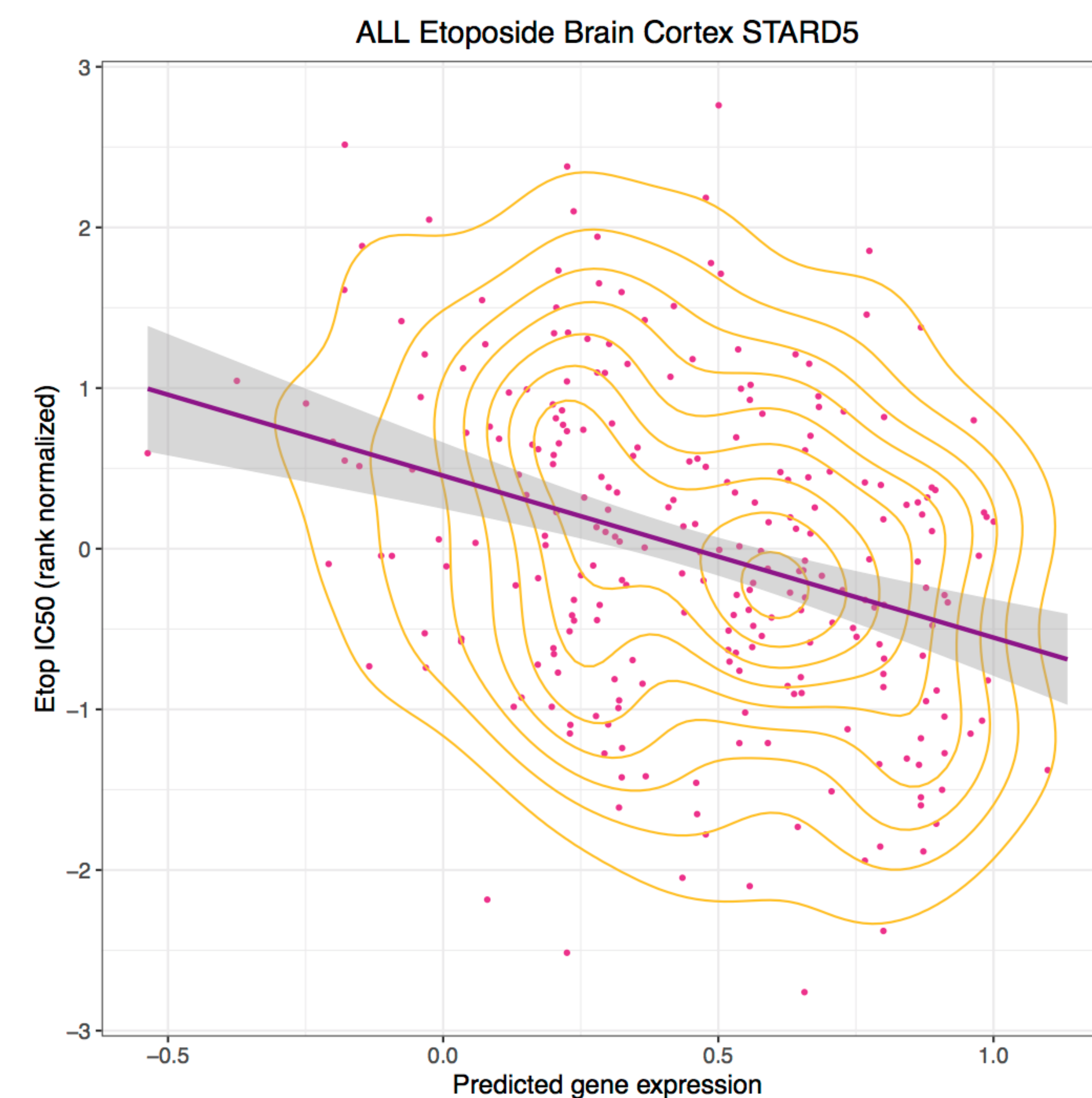


Figure 4: Predicted expression plot of *STARD5* predicted expression in the Brain Cortex vs Etoposide concentration in ALL. As *STARD5* expression decreases, the concentration of Etoposide needed for cytotoxicity increases.

Conclusions

- Six genome-wide significant SNPs on chromosome 12 were found to be associated with Etoposide cytotoxicity in YRI
- Two genome-wide significant SNPs on chromosome 4 were found to be associated with Daunorubicin cytotoxicity in YRI
- Three genome-wide significant SNPs on chromosome 9 were found to be significantly associated with Carboplatin in ASN
- Two genome-wide significant SNPs on chromosome 12 were found to be significantly associated with Etoposide in ALL
- High predicted expression of *STARD5* in the Brain Cortex was found to be significantly associated with cellular sensitivity to Etoposide in ALL ($p = 8.5e-08$)
- High predicted expression of *USF1* in the Liver was found to be significantly associated with cellular resistance to Capecitabine in ALL ($p = 8.7e-08$)

References

- [1] "Cancer." World Health Organization, World Health Organization, 12 Sept. 2018, www.who.int/news-room/fact-sheets/detail/cancer.
- [2] Wheeler, Heather E and M Eileen Dolan. "Lymphoblastoid cell lines in pharmacogenomic discovery and clinical translation" *Pharmacogenomics* vol. 13,1 (2012): 55-70.
- [3] Ikegawa, Shiro. "A short history of the genome-wide association study: where we were and where we are going" *Genomics & informatics* vol. 10,4 (2012): 220-5.
- [4] Sul, Jae Hoon et al. "Population structure in genetic studies: Confounding factors and mixed models" *PLoS genetics* vol. 14,12 e1007309. 27 Dec. 2018, doi:10.1371/journal.pgen.1007309.
- [5] Hindorf, L. A. et al. "Prioritizing diversity in human genomics research," *Nature Reviews Genetics*, November 2017.
- [6] Mogil, Lauren S et al. "Genetic architecture of gene expression traits across diverse populations." *PLoS genetics* vol. 14,8 e1007586. 10 Aug. 2018, doi:10.1371/journal.pgen.1007586.

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