



Gene Regulatory Region Variations Potentially Modulating the Drug Metabolism Response

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Motivation

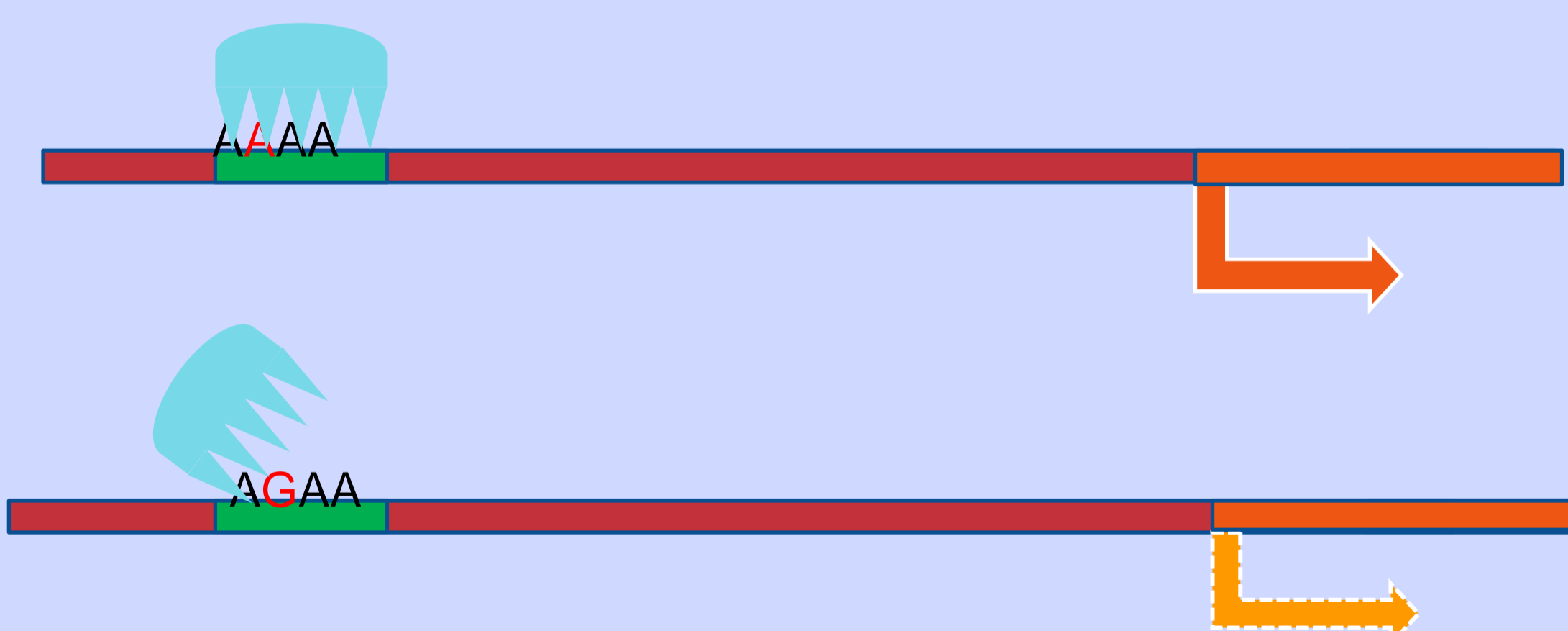
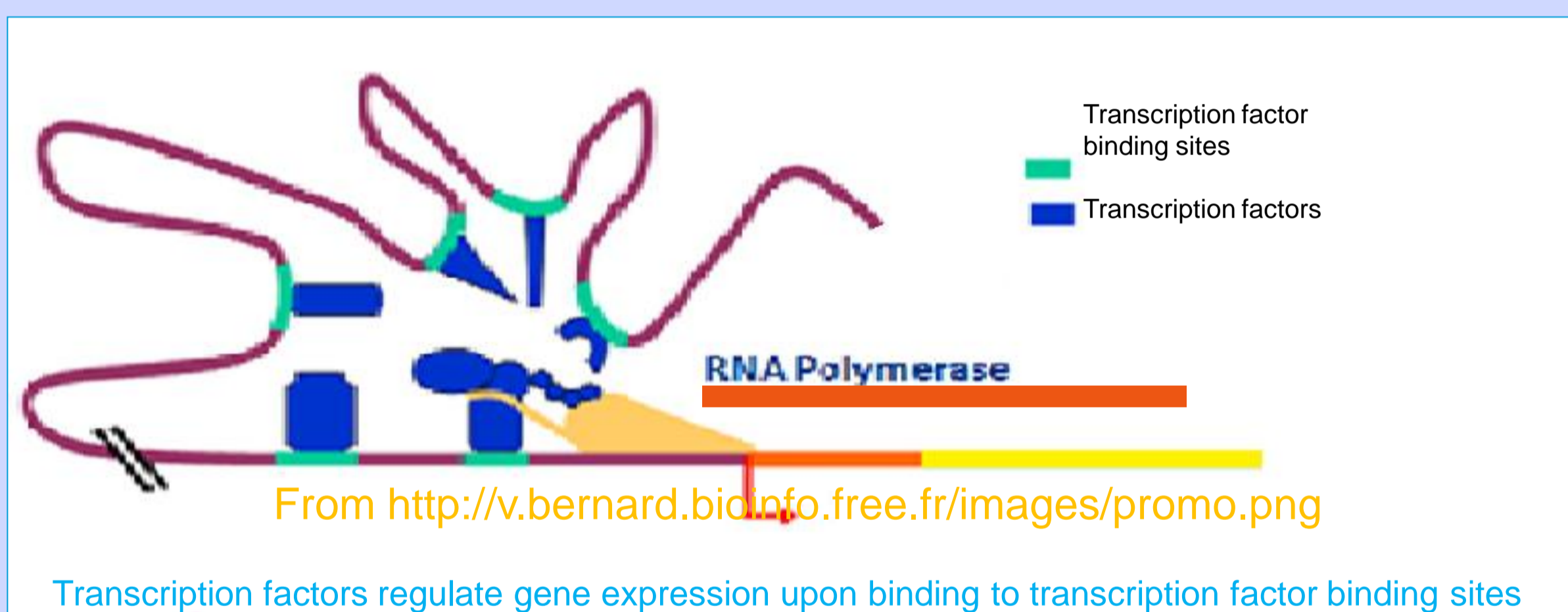
Adverse drug reactions (ADRs) are among the most common causes of hospitalization in paediatric patients. Genetic factors account for 20% to 95% of ADRs.



From www.surrythai.acth/node/1238

Hypothesis

Individual differences in gene regulatory regions can lead to drug metabolism differences



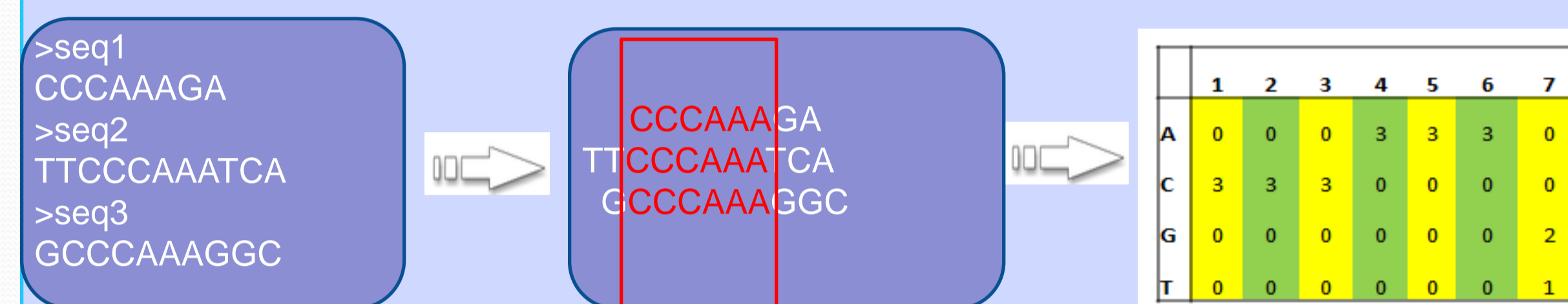
Focus

3 transcription factors (TFs) are known to have regulated the expression of a whole range of drug metabolizing genes.

- AHR**: Responses to aryl hydrocarbon compounds
- HIF1A**: Responses to hypoxia
- NFE2L2**: Responses to antioxidant and xenobiotics

Methods & Results

Building a transcription factor binding site (TFBS) profile for each of the 3 transcription factors

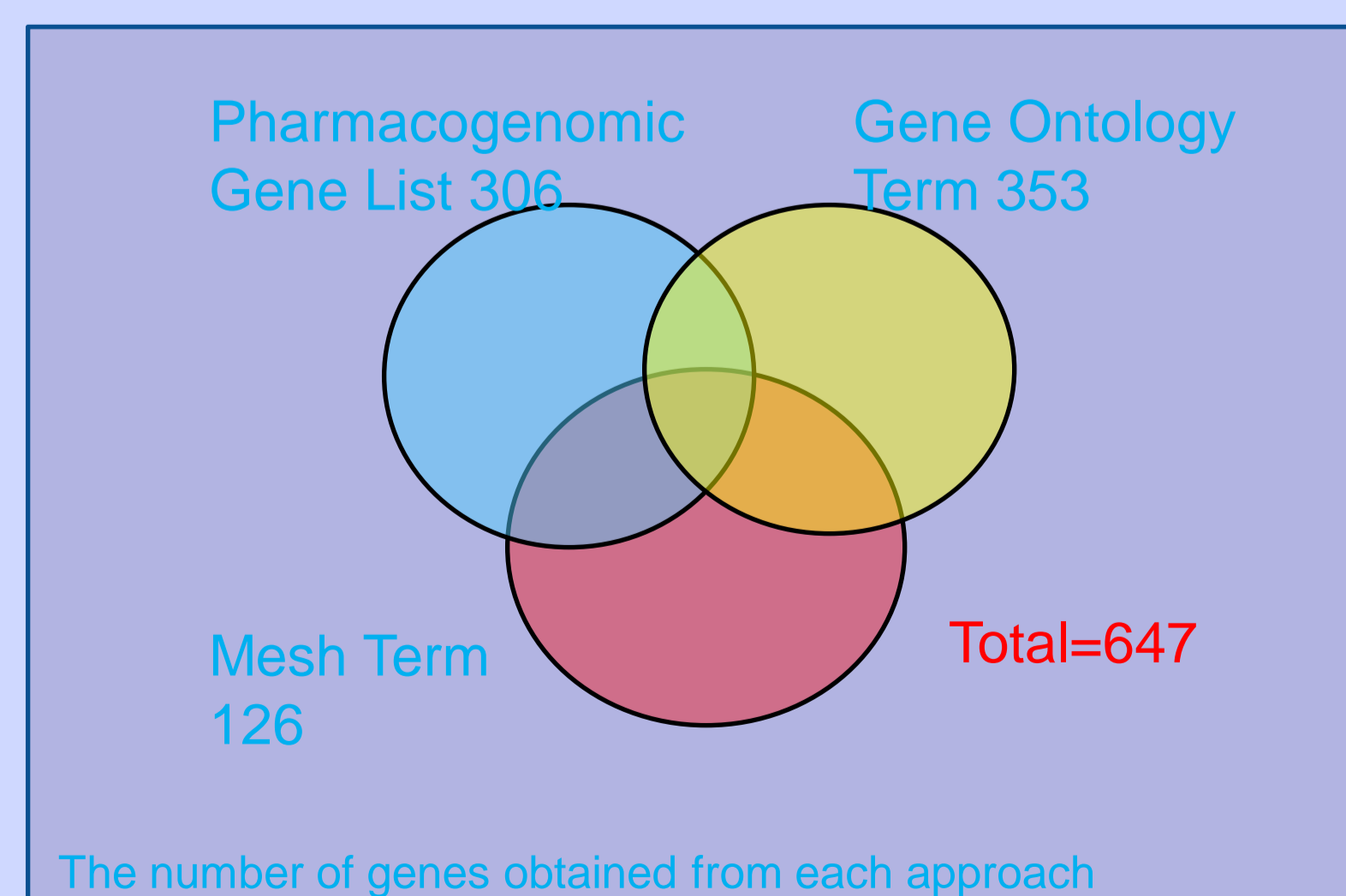


| Transcription factors | Gene Set Size | Position Frequency Matrices |
|-----------------------|----------------|-----------------------------|
| NFE2L2 ₃ | 627 sequences | |
| HIF1A ¹ | 2077 sequences | |
| AHR ² | ? sequences | |

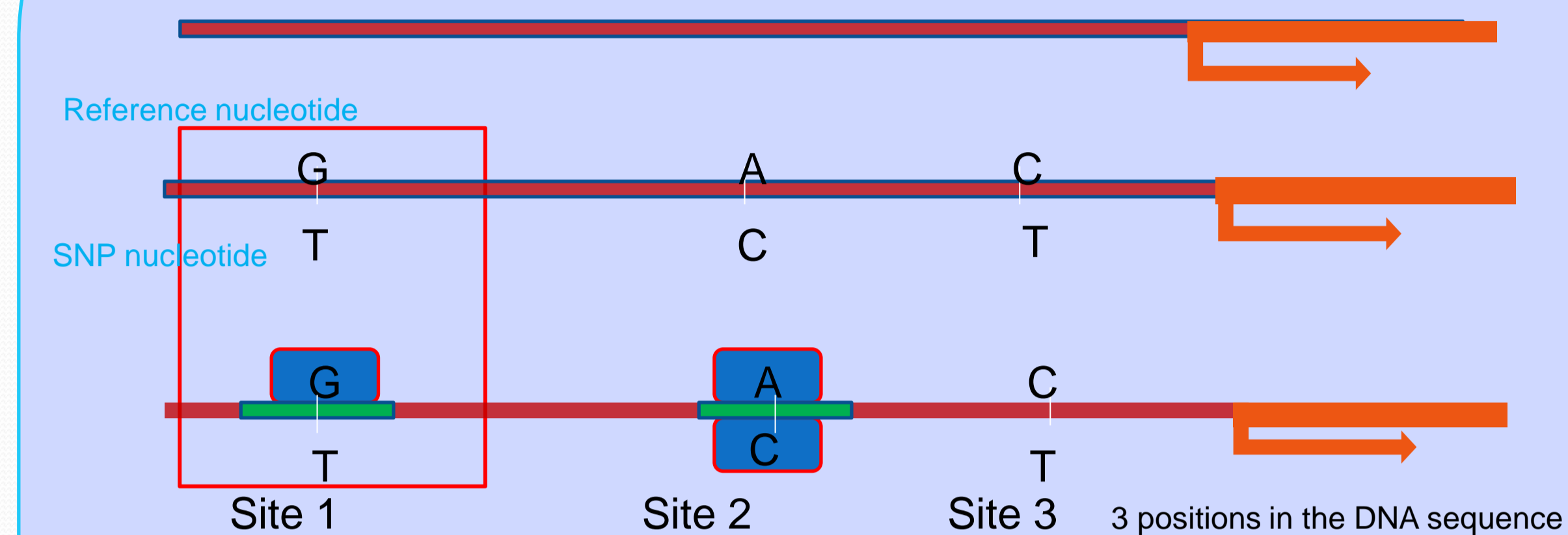
Prediction of over-represented transcription factor binding sites based on position frequency matrices (PFM)

Compiling a list of drug-metabolizing genes

- Pharmacogenomic Gene List obtained from Dr. Colin Ross, Hayden Lab, CMMT
- Gene Ontology term search using BioMart <http://www.ensembl.org/biomart>
- Finding genes relating to drug metabolism using Mesh term search tool developed by Warren Cheung, Wasserman Lab http://dgene.oicr.on.ca/digenei/gene_browse.html#



Finding the transcription factor binding sites overlapping Nucleotide Polymorphisms (SNPs)



Search for SNP sites or reference sites that match the TFBS exclusively. The unique form of nucleotide at the specific position which may be able to account for drug metabolism differences.

Conclusion

Produced a prioritized list of regulatory region variations that may be responsible for individual differences in drug metabolism



Clinical Implications

http://i.ehow.com/images/a05/d1/bg/safe-tylenol-infant-drops-acetaminophen_-200X200.jpg

- Highlight potential regulatory sequences in the drug metabolizing genes for personalized genome analysis
- Predict and therein prevent adverse drug reactions based on individual genome scan
- "Ideal" drug design tailored to individual drug metabolizing system.

Reference

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- Pansoy A. et al. 3-Methylcholanthrene Induces Differential Recruitment of Aryl Hydrocarbon Receptor to Human Promoters. *Toxicological Sciences*, 1-32 (2010);
- Portales-Casamar E. et al. PAZAR: a Framework for Collection and Dissemination of Cis-regulatory sequence Annotation. *Genome Biol* (2007)