Southern Illinois University Edwardsville School of Pharmacy

Meta-Analysis of Exogenous Food Metabolites Contributing to Polymorphic Change in CYP2D6

Mark Nogalo Pharm.D. Candidate. Dr. Ronald Worthington Ph.D.

Introduction/Background

- CYP2D6 has been identified as the largest polymorphic cytochrome P450 enzyme in the human body. Slightly 55% of each ethnic population subtype is considered a Normal Metabolizer (NM). Star alleles associated with NM are diplotypes containing *1 or *2
- Most common star (*) alleles resulting in an impaired or non-functioning allele in CYP2D6 are *4, *10, *17, *29, and *41. Intermediate metabolizers (IM) or Poor Metabolizers (PM) will usually carry 1 or 2 of these alleles
- Human CYP2D6 substates include many exogenous substances found in fruits, oils, plants, and spices such as: alkaloids, polyphenols, tannins, terpenes, safrole, and methyleugenol
- Consumption of certain foods lead to the metabolism of exogenous compounds that may have altered CYP2D6 evolutionary pattern, resulting in many polymorphisms today

Methods

- Articles were hand selected through PubMed and Web of Science databases
- MeSH search criteria was utilized, key words such as: advantageous, Asian, African, Caucasian, CYP2D6, CYP2D, CYP450, exogenous, fruits herbs, mutation, negative, positive, spices, selection, safrole, tannins, terpenes, and selection
- Minimal research has been conducted on specific plant consumption on early era humans

Results

- Upon review, 5 articles were chosen where three different compounds were selected: flavonoids, methyleugenol, and safrole
- One study found safrole to have inhibitory effects on CYP2D6, along with CYP1A2, 2E1, 2A6, and 3A4. Inhibitory concentration for 2D6 were detected at 100 μM with a SD of 12 μM
- Methyleugenol was also found to have inhibitory effects on CYP2D6, having the highest Kcat, but since the Km was found to be at 1.5 mM, low concentrations of methyleugenol would not be able to induce inhibitory effects.

Discussion

- Each compound showed limited to no inhibition as a substrate of CYP2D6, with lack of inhibition, evolution would not be favored into positive selection and not allow genetic conservation
- Movement and trade of different spices, oils, herbs, and other luxurious foods between civilizations within the last couple of millennia do not suggest that it would be a proponent in influencing selection pressures within CYP2D6

Conclusion

- No link was found between exogenous compounds found in foods such as flavonoids, methyleugenol, and safrole in inducing polymorphic change within the CYP2D6 enzyme
- It may be more of interest and better outcomes to provide more insight on early human eras when agriculture and farming was scarce

Limitations

- Lack of articles and evidence for possible explanations of certain plants/foods which may have contributed to evolutionary shift
- More research would need to be done on analyzing diets in earlier human eras

References

1. Alvarado, Angel T et all. "Frequency of CYP2D6*3 and *4 and Metabolizer Phenotypes in Three Mestizo Peruvian Populations." *Pharmacia*, 8 Dec. 2021.
2. Bojić, M., Kondža, M., Rimac, H., Benković, G., & Malešˇ, Ž. (2019). The Effect of Flavonoid Aglycones on the CYP1A2, CYP2A6, CYP2C8 and CYP2D6 Enzymes Activity. *Molecules (Basel, Switzerland)*, *24*(17), 3174.
3. Chaney, M. E., Piontkivska, H., & Tosi, A. J. (2018). Retained duplications and deletions of CYP2C genes among primates. *Molecular phylogenetics and evolution*, *125*, 204–212.
4. Chaney, M. E., Romine, M. G., Piontkivska, H., & Tosi, A. J. (2020). Diversifying selection detected in only a minority of xenobiotic-metabolizing *CYP1-3* genes among primate species. *Xenobiotica; the fate of foreign compounds in biological systems*, *50*(12), 1406–1412.
5. Darney, K et al. "Human variability in polymorphic CYP2D6 metabolism: Implications for the risk assessment of chemicals in food and emerging designer drugs." *Environment international* vol. 156 (2021): 106760. doi:10.1016/j.envint.2021.106760
6. Dorji, Palden Wangyel et al. "CYP2C9, CYP2C19, CYP2D6 and CYP3A5 polymorphisms in South-East and East Asian populations: A systematic review." *Journal of clinical pharmacy and therapeutics* vol. 44,4 (2019): 508-524. doi:10.1111/jcpt.12835
7. Fuselli, Silvia et al. "Evolution of detoxifying systems: the role of environment and population history in shaping genetic diversity at human CYP2D6 locus." *Pharmacogenetics and genomics* vol. 20,8 (2010): 485-99. doi:10.1097/FPC.0b013e32833bba25
8. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J 2005; 5:6–13
9. Jeurissen, Suzanne M F et al. "Human cytochrome p450 enzymes of importance for the bioactivation of methyleugenol to the proximate carcinogen 1'-hydroxymethyleugenol." *Chemical research in toxicology* vol. 19,1 (2006): 111-6. doi:10.1021/tx050267h
10. Jorge LF, Eichelbaum M, Griese EU, Inaba T, Arias TD. Comparative evolutionary pharmacogenetics of CYP2D6 in Ngawbe and Embera Amerindians of Panama and Colombia: role of selection versus drift in world populations. Pharmacogenetics. 1999 Apr;9(2):217-28.
11. Luo, Huai-Rong et al. "Polymorphisms of CYP2C19 and CYP2D6 in Israeli ethnic groups." *American journal of pharmacogenomics : genomics-related research in drug development and clinical practice* vol. 4,6 (2004): 395-401. doi:10.2165/00129785-200404060-00006
12. Milosavljevic, F., Bukvic, N., Pavlovic, Z., Miljevic, C., Pešic, V., Molden, E., Ingelman-Sundberg, M., Leucht, S., & Jukic, M. M. (2021). Association of CYP2C19 and CYP2D6 Poor and Intermediate Metabolizer Status With Antidepressant and Antipsychotic Exposure: A Systematic Review and Meta-analysis. *JAMA psychiatry*, *78*(3), 270–280.
13. Sistonen, J., Sajantila, A., Lao, O., Corander, J., Barbujani, G., & Fuselli, S. (2007). CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. *Pharmacogenetics and genomics*, *17*(2), 93–101.
14. Thomas J. H. (2007). Rapid birth-death evolution specific to xenobiotic cytochrome P450 genes in vertebrates. *PLoS genetics*, *3*(5), e67.
15. Ueng, Yune-Fang et al. "Inhibition of human cytochrome P450 enzymes by the natural hepatotoxin safrole." *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* vol. 43,5 (2005): 707-12. doi:10.1016/j.fct.2005.01.008
16. Zhou, Q et al. "Genetic polymorphism, linkage disequilibrium, haplotype structure and novel allele analysis of CYP2C19 and CYP2D6 in Han Chinese." *The pharmacogenomics journal* vol. 9,6 (2009): 380-94. doi:10.1038/tpj.2009.31