allied academies

J Clin Exp Tox, Volume 3
DOI: 10.4066/2630-4570-C1-006

International Conference on

Environmental Toxicology and Pharmacology

February 21-22, 2019 | Paris, France

Computational integration of Human genetic data to evaluate AOP- specific susceptibility

Holly M Mortensen
National Health and Environmental Effects Research Laboratory, USA

There is a need for approaches to define human variability and susceptibility in response to environmental chemical exposure. Direct estimation of the genetic contribution to variability in susceptibility to environmental chemicals is only possible in special cases where there is an observed association between exposure and effect (e.g. genotype and phenotype information). The availability of genetic data sources makes it possible to indirectly estimate the relative contribution of genetic variability to differential human susceptibility. We developed a computational workflow that integrates genetic and toxicological resources. This approach implements the Adverse Outcome Pathway (AOP) framework in order to integrate molecular targets associated with AOPs with functional genomic annotations and population allele frequencies. Resources include the EPA internal Adverse Outcome Database (AOP-DB), and publicly available resources, such as the AOP-wiki, Ensembl genomic annotations, expression Quantitative Trait loci identified by the GTEx consortium, and 1000 Genomes Project. With this information it is possible to formulate predictions of genetic susceptibility built upon established toxicological and genetic knowledge that are specific to an adverse outcome.

The computational workflow was developed in R and built around the Ensembl database interfaces (REST API and biomaRt R package). It downloads, integrates, and analyzes the available data sources when an AOP is given as input. Data is processed in four steps: 1. Genetic identities of AOP key events are extracted from the AOP-DB; 2. Nearby regulatory annotations are downloaded from the Ensembl regulatory build; 3. GTEx Expression quantitative trait loci are imported for AOP-relevant tissue types; and 4. Allele and haplotype frequency information is retrieved from the 1000 Genomes Project stage 3 dataset. The analysis provides an estimate of the degree of genetic variation at functionally relevant loci. With ongoing AOP development, this automated workflow will allow rapid assessment of outcome specific human genetic susceptibility. This abstract does not reflect EPA Policy.

e: mortensen.holly@epa.gov

Notes: