BIOINFORMATION
Discovery at the interface of physical and biological sciences

open access www.bioinformation.net Editorial

Volume 8(11)

Single nucleotide polymorphisms (SNPs) for genome wide association studies (GWAS) and molecule of the month Nitric Oxide Synthase, multiple interactive pathways for three similar genes, Nitric Oxide Synthase-1, -2, -3 (NOS-1, -2, -3)

Paul Shapshak[1, 2*]

[1]Divsion of Infectious Disease and International Health, Department of Medicine and Department of Psychiatry and Behavioral Medicine, USF Morsani School of Medicine, Tampa General Hospital, 1 Tampa Gen Circle, Room G318, Tampa FL 33606; [2]Deputy Chief Editor, Bioinformation; Paul Shapshak - Email: pshapshak@gmail.com; *Corresponding author

Received June 06, 2012; Accepted June 08, 2012; Published June 16, 2012

This Editorial is divided into two parts. 1. Single nucleotide polymorphisms (SNPs) for genome wide association studies (GWAS) and 2. Molecule of the month, Nitric Oxide Synthase, multiple interactive pathways for three related genes, Nitric Oxide Synthase-1, -2, -3 (NOS-1, -2, -3).

Single nucleotide polymorphisms (SNPs) for genome wide association studies (GWAS):

Generally, genome wide association studies **(**GWAS) are done by analysis of DNA mutations including single nucleotide polymorphisms (SNPs) across the human genome. The DNA SNPs that occur in DNA coding regions are translated into cognate mRNAs and these mRNAs are translated into their cognate proteins. Therefore, the SNP information is carried through the different levels of information by transcription and translation. In addition to the sequence complexity caused by SNPs, are variations in mRNA splicing. Consequently, translation produces proteins that will reflect their corresponding mRNA variants that produced them (including both SNPs and splicing variants). When correlations are run against only the DNA then only one level of analysis is broached. However, from a gene functionality point of view or 'phenotype', knowledge may be required at the mRNA and protein levels as these are closer to phenotype than the DNA. Thus, the functionality of a gene product may vary not only depending on the SNPs that are transcribed into the mRNA but also will vary due to variations in splicing of different exons (when this occurs). This approach is of importance even if all of the variants are functional, because one or more such variants may be the ones actually associated with a disease or disease process. Therefore, at the protein level itself, such variations in sequence may occur due to the changes that occur at the amino acid sequence level due to the variants of mRNA as just mentioned. All three levels (DNA, RNA, and protein) may necessitate analysis to produce the sensitivity required to detect some gene associations. A naïve example follows. Let us assume two exons undergo splicing variation for a protein composed of 10 exons. Next, allow the proteins to be functional to varying degrees when they are produced from mRNAs with these variations.

exon1-exon2-exon3-…exon10
exon1-exon3-…exon10
exon2-exon3-…exon10

Therefore, even if there were only one SNP in exon1, three mRNA variants could be produced (for a gene that has this type of splice variation) and each of the proteins produced may exert different effects on the disease phenotype. This would be due to the differnet protein sequences due to splicing variations as well as the different placement of the SNPs in the protein tertiary and quaternary structure. The heterogeneousness of the

SNPs thus further affects the complexity calculations. In the world of GWAS studies, there are many levels of analysis relating the genetics findings with markers at the DNA, RNA and protein levels: SNPs, tandem repeats, copy number variations (CNVs), methylation at the DNA sequence level, and chromatin structural and biochemical changes. At the transcription level there are expression, miRNA, and various post-transcription modifications. Finally, at the translation level, the splice variants, isoforms, and even subtle tertiary/quaternary structural changes that occur via synonymous SNP variants affect the outcome as well (Personal communication, Prof. Andrew J Levine, UCLA School of Medicine, Westwood, CA).

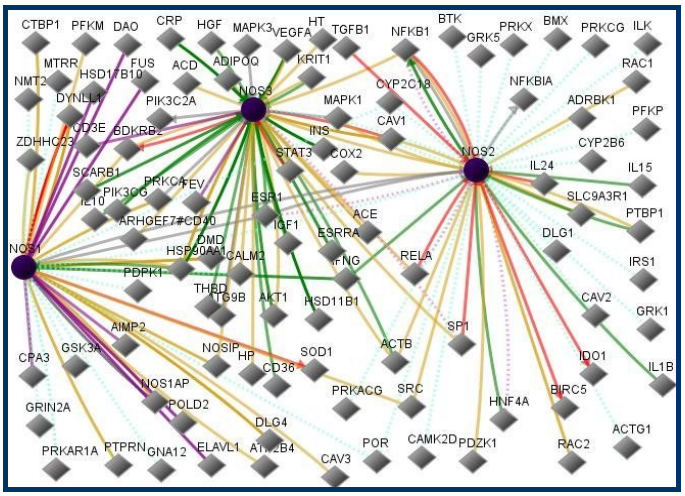

Figure 1: NOS interactions. In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted Transcription Factor Factor Regulation. (GenePro SA Biosciences, http://www.sabiosciences.com/).

Molecule of the month, Nitric Oxide Synthase, multiple interactive pathways for three similar genes, Nitric Oxide Synthase-1, -2, -3 (NOS-1, -2, -3):

Neuronal NOS (nNOS, NOS-1) is on chromosome 12 and expressed in neurons; Inducible NOS (iNOS, NOS-2) is on chromosome 17 and expressed in immune system cells; and Endothelial NOS (eNOS, cNOS, NOS-3) is on chromosome 7 and expressed in endothelial cells) **[1, 2]** There is also highly sophisticated technological evidence that the NOS-1 gene is in proximity to additional genes on chromosome 12 that are associated with brain hippocampus structure **[3].** (**Figure 1)** shows molecular interactions of various types as described in the figure legend for the three NOS gene products. Thus, there is a remarkable series of interactions that the proteins of the NOS-1, -2, and -3 genes exhibit that must be components in the function and effects of these genes.

Acknowledgment:
There are no financial conflicts.

References:

[1] Panda K *et al. J Biol Chem*. 2002 **277**: 31020 [PMID: 12048205]
[2] Kuljis RO *et al. J NeuroAIDS*. 2003 **2**: 19
[3] Stein JL *et al. Nature Genetics*. 2012. doi:10.1038/ng.2250

Citation: **Shapshak,** Bioinformation 8(11): 496-497 (2012)