

What Causes Autism?

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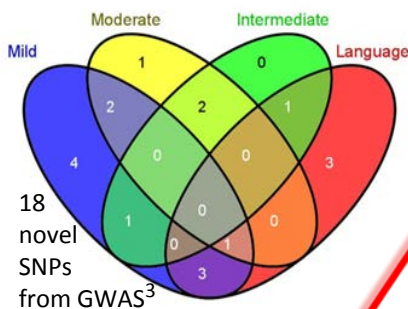
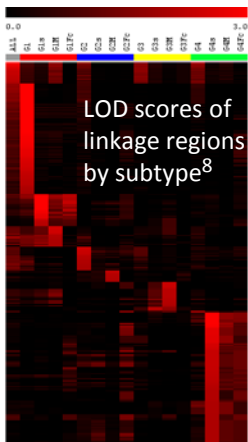
Goals:

- To identify genes and biological pathways or functions for targeted therapies
- To identify diagnostic biomarkers of ASD
- To develop a “systems level” understanding of the pathobiology of ASD



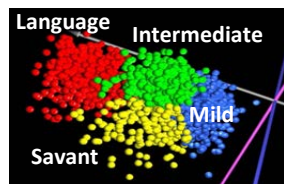
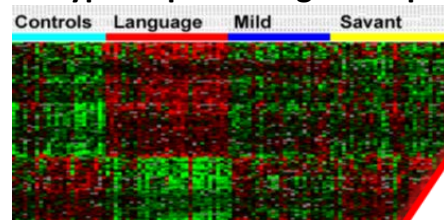
Problem

Strategy: Grouping individuals according to severity of behavioral symptoms (ADIR scores)
⇒ Subtype-dependent diagnosis & treatment⁷



Subtype-dependent genetic differences^{3,8}

Subtype-dependent gene expression²



ASD subtypes¹



Triggers

Intrinsic and extrinsic environmental factors
(e.g., hormones, pesticides)

Genetics
(Hardware)

Mutations
Copy number variants
Chromosomal abnormalities

Epigenetics
(Software)

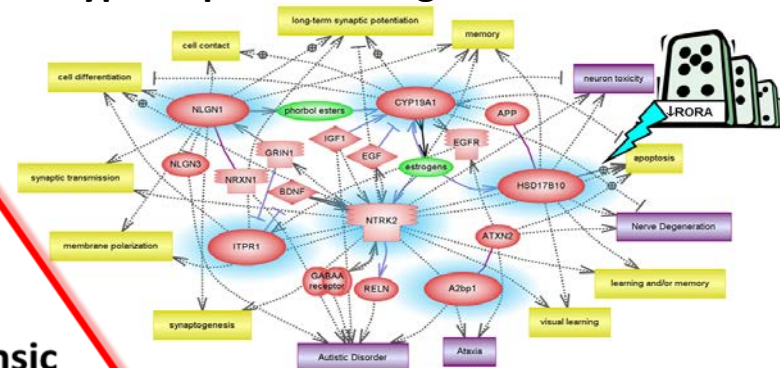
DNA methylation
MicroRNA expression
Histone modification
Chromatin remodeling

Gene expression profile: level of gene activity

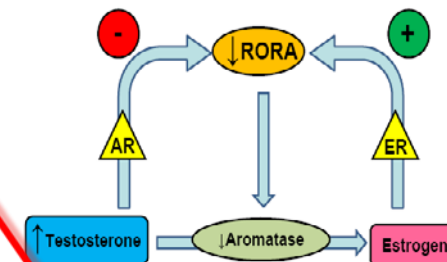
ASD phenotypes: brain circuitry, behaviors and symptoms

An integrated genomics approach to autism spectrum disorders⁶

A hierarchical view of the multiple factors that cause or affect risk for autism.
In this view, the components of each level can influence those shown below.



Deficiency in RORA impacts many autism susceptibility genes⁹



Effects of male and female hormones on RORA explain increased testosterone levels and why males may be more susceptible to ASD^{4,5}

Selected References

- 1) Hu, V.W. and Steinberg, M.E. (2009) Novel clustering of items from the Autism Diagnostic Interview-Revised to define phenotypes within autism spectrum disorders. *Autism Research* 2:67-77.
- 2) Hu, V.W., Sarachana, T., Kim, K.S., Nguyen, A., Kulkarni, S., Steinberg, M.E., Luu, T., Lai, Y., and Lee, N.H. (2009) Gene expression profiling differentiates autism case-controls and phenotypic variants of autism spectrum disorders: Evidence for circadian rhythm dysfunction in severe autism. *Autism Research* 2:78-97.
- 3) Hu, V.W., Addington, A., and Hyman, A. (2011) Novel Autism Subtype-dependent Genetic Variants are Revealed by Quantitative Trait and Subphenotype Association Analyses of Published GWAS Data. *PLoS ONE* 6(4):e19067.
- 4) Nguyen, A., Rauch, T.A., Pfeifer, G.P., and Hu, V.W. (2010) Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain. *FASEB J.*, 24(8):3036-51.
- 5) Sarachana, T., Xu, M., Wu, R.-C., and Hu, V.W. (2011) Sex hormones in autism: Androgens and estrogens differentially and reciprocally regulate RORA, a novel candidate gene for autism. *PLoS ONE*, 6(2): e17116.
- 6) Hu, V.W. (2012) From Genes to Environment: Using integrative genomics to build a “systems level” understanding of autism. Invited review, *Child Development*, 84(1):89-103.
- 7) Hu, V.W. (2012) Subphenotype-dependent disease markers for diagnosis and personalized treatment of autism spectrum disorders. Invited review, *Disease Markers*, 33(5):277-88.
- 8) Talebizadeh, Z., Arking, D.E., and Hu, V.W. (2013) A novel stratification method in linkage studies to address inter and intra family heterogeneity in autism. *PLoS ONE*, 8(6):e67569.
- 9) Sarachana, T. and Hu, V.W. (2013) Genome-wide identification of transcriptional targets of RORA reveals direct regulation of multiple genes associated with autism spectrum disorder. *Molecular Autism*, 4:14.

More at:

<http://www.gwumc.edu/smhs/facultydirectory/profile.cfm?empName=Valerie%20Hu&FacID=2046028605>