Towards precision medicine: The importance of clinical phenotypes and patient stratification in autism research

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PCORI Educational Workshop for the Autism Research Community:
Incorporating Genetic Information into Patient-Centered Outcomes Research
Kansas City, MO
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Learning objectives

- Understand the multiple factors that cause or affect risk for autism spectrum disorders (ASD)
- Understand the challenges associated with clinical heterogeneity of individuals with ASD
- Understand the importance of incorporating ASD phenotypes and patient stratification in biological and genetics research on ASD

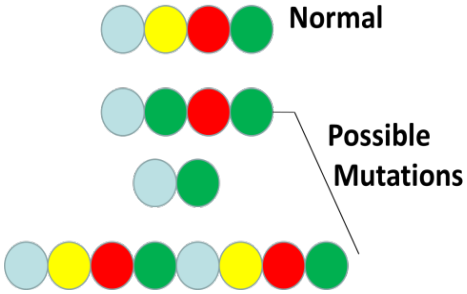
What Causes Autism?

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

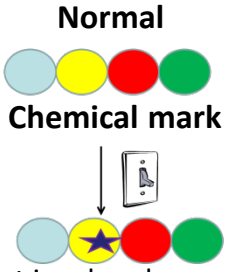
Experimental strategy: <u>Reduce phenotypic heterogeneity</u> by subgrouping individuals according to similarity of scores reflecting severity of behavioral symptoms

Genetic mechanisms for disrupting genes

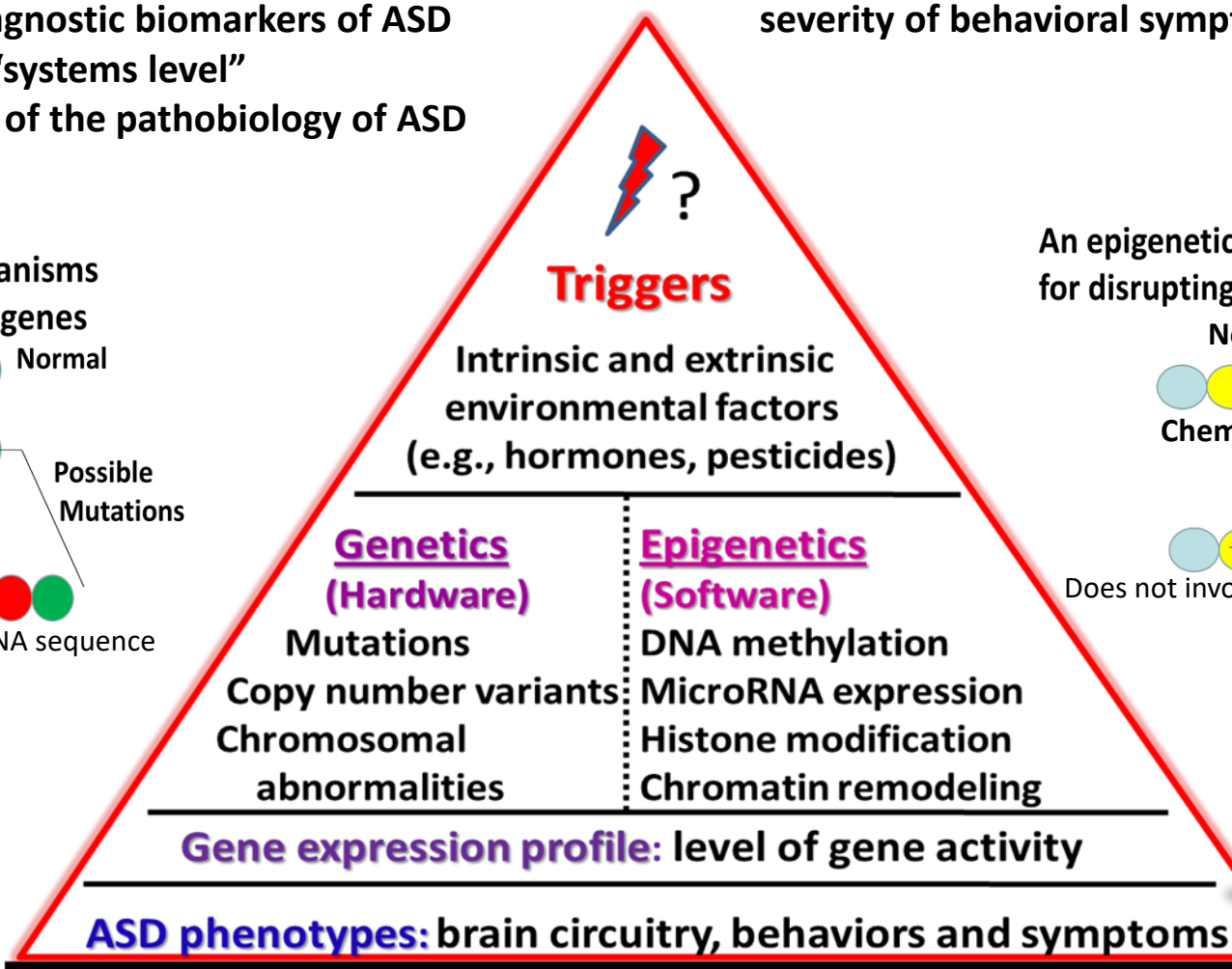


Involve changes in DNA sequence

An epigenetic mechanism for disrupting genes



Does not involve change in sequence



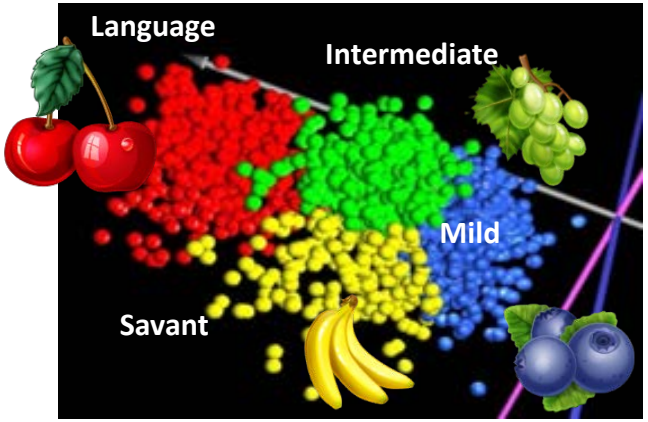
An integrated genomics approach to autism spectrum disorders

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.

Phenotypic subgrouping

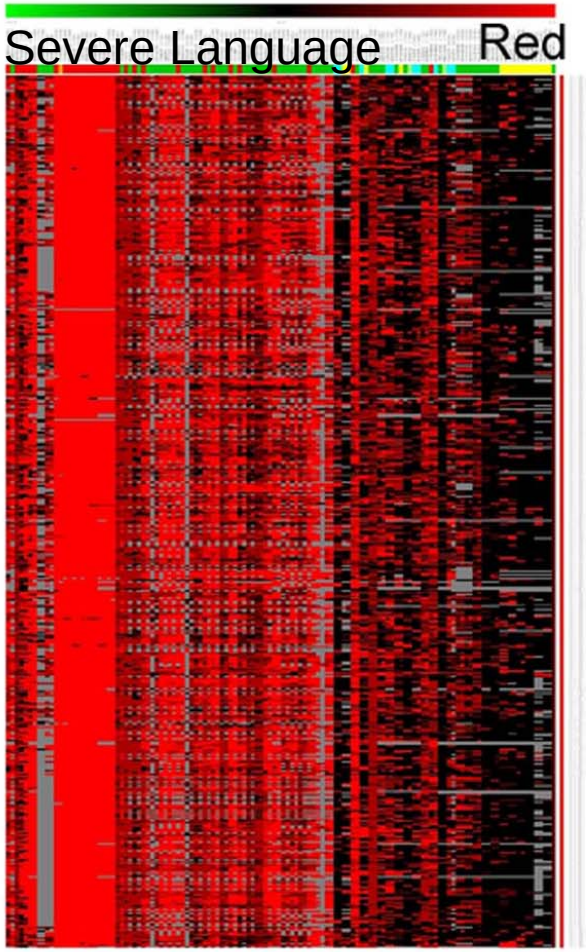
Cluster analyses of 123 severity scores from ADI-R clinical diagnostic screen reveal 4 distinguishable phenotypes of individuals with ASD

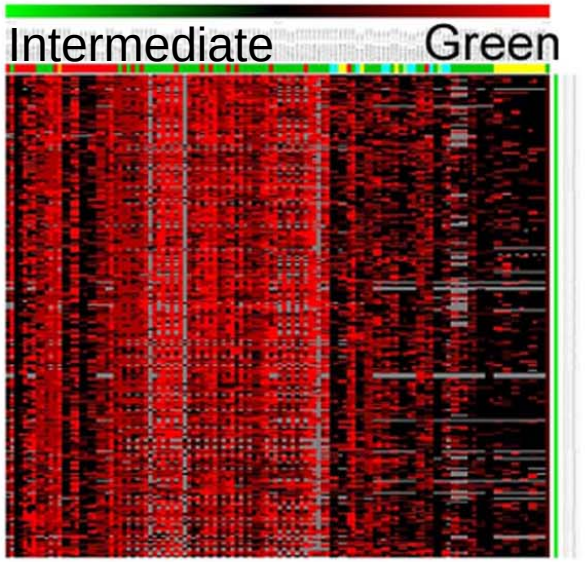
Rows: Individuals
Columns: ADIR "items"
Severity scores: 0-3
Bright red: 3
Black: 0 (normal)
Gray: no data

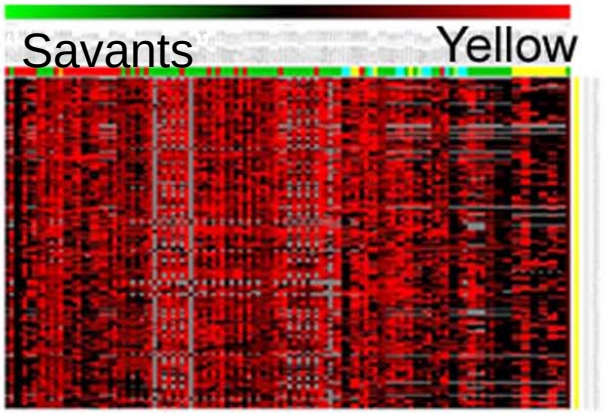


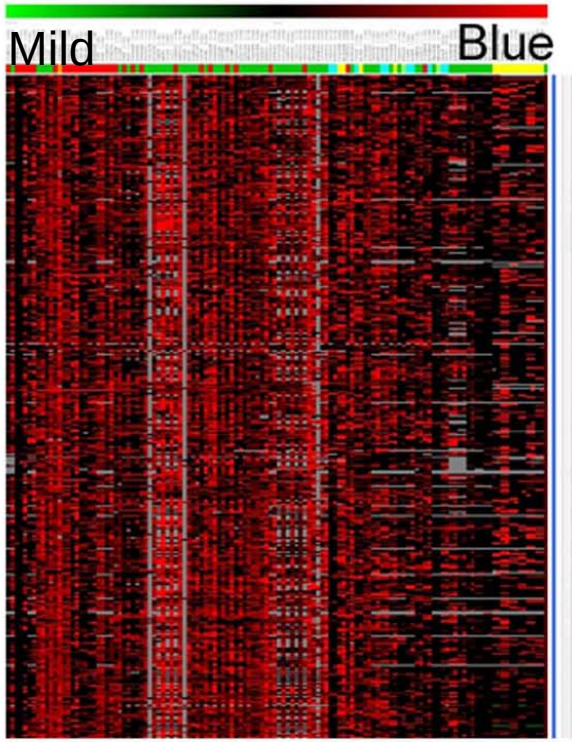
Principal components analysis

Autism Research 2:67-77, 2009; PLoS ONE 4(6):e5775, 2009

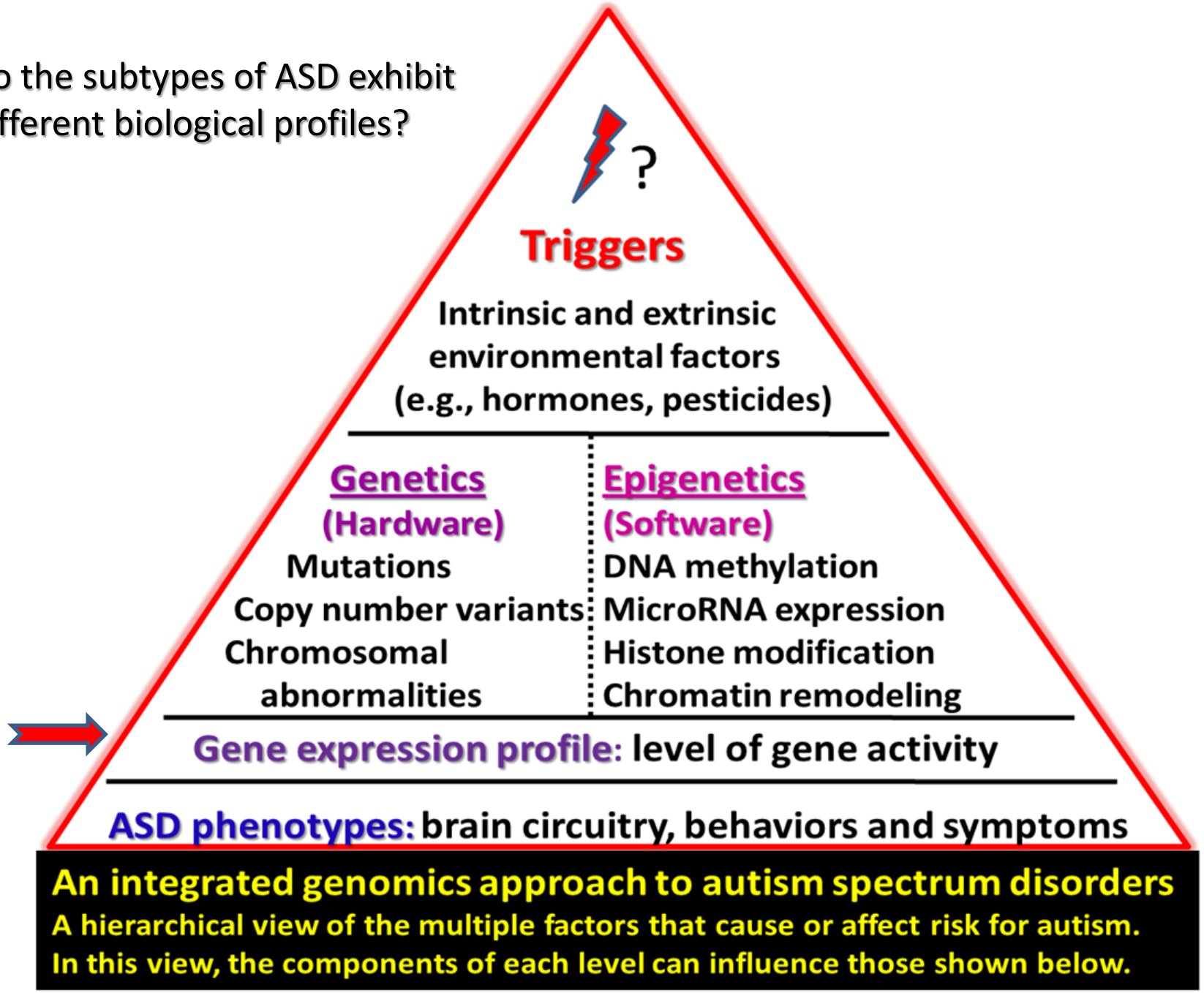








Do the subtypes of ASD exhibit different biological profiles?



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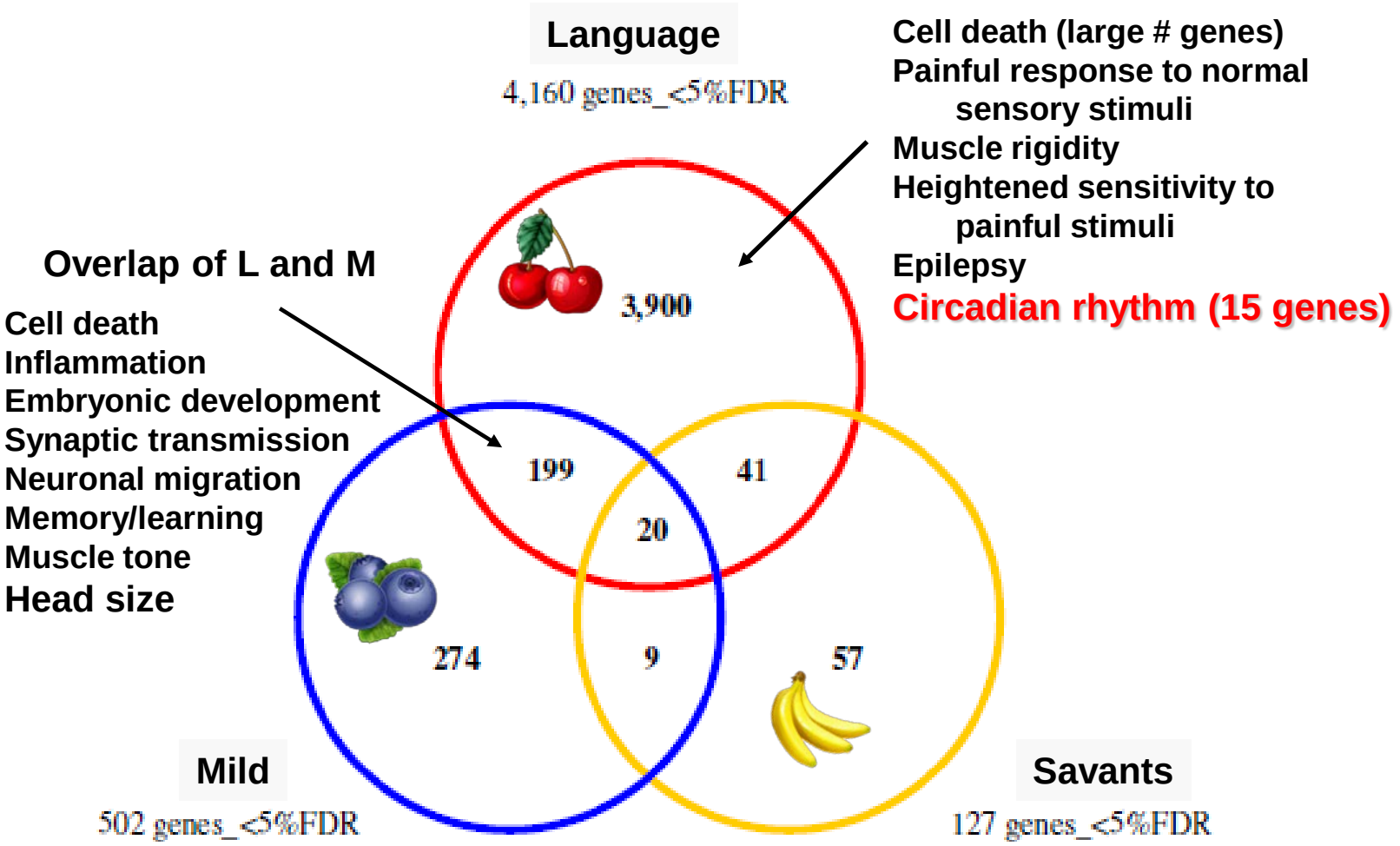
Genome-wide gene expression analyses of over 40,000 transcripts

⇒ Overlapping as well as unique genes are associated with each subgroup of ASD



Autism Res. 2(2):78-97, 2009

Functional analysis of 15 circadian "clock" genes associated with severely language-impaired phenotype of ASD

Associated functions and disorders

- Sleep-wake cycle
- Memory
- Learning
- Cell proliferation
- Steroid biosynthesis
- Digestive disorders
- Inflammation
- Muscle dysfunction
- Neuron toxicity

Novel target genes for subtype-specific treatment

- **AA-NAT**: controls melatonin biosynthesis ⇒ melatonin supplements?
- **DPYD**: genetic mutation predisposes to epilepsy, mental retardation, motor retardation, and ASD ⇒ suggests anticonvulsant medications as first line of treatment
- ⇒ Precision medicine

Diagnostic potential?

Gene expression differences can separate autistic cases and controls with <u>up to 94% accuracy</u>

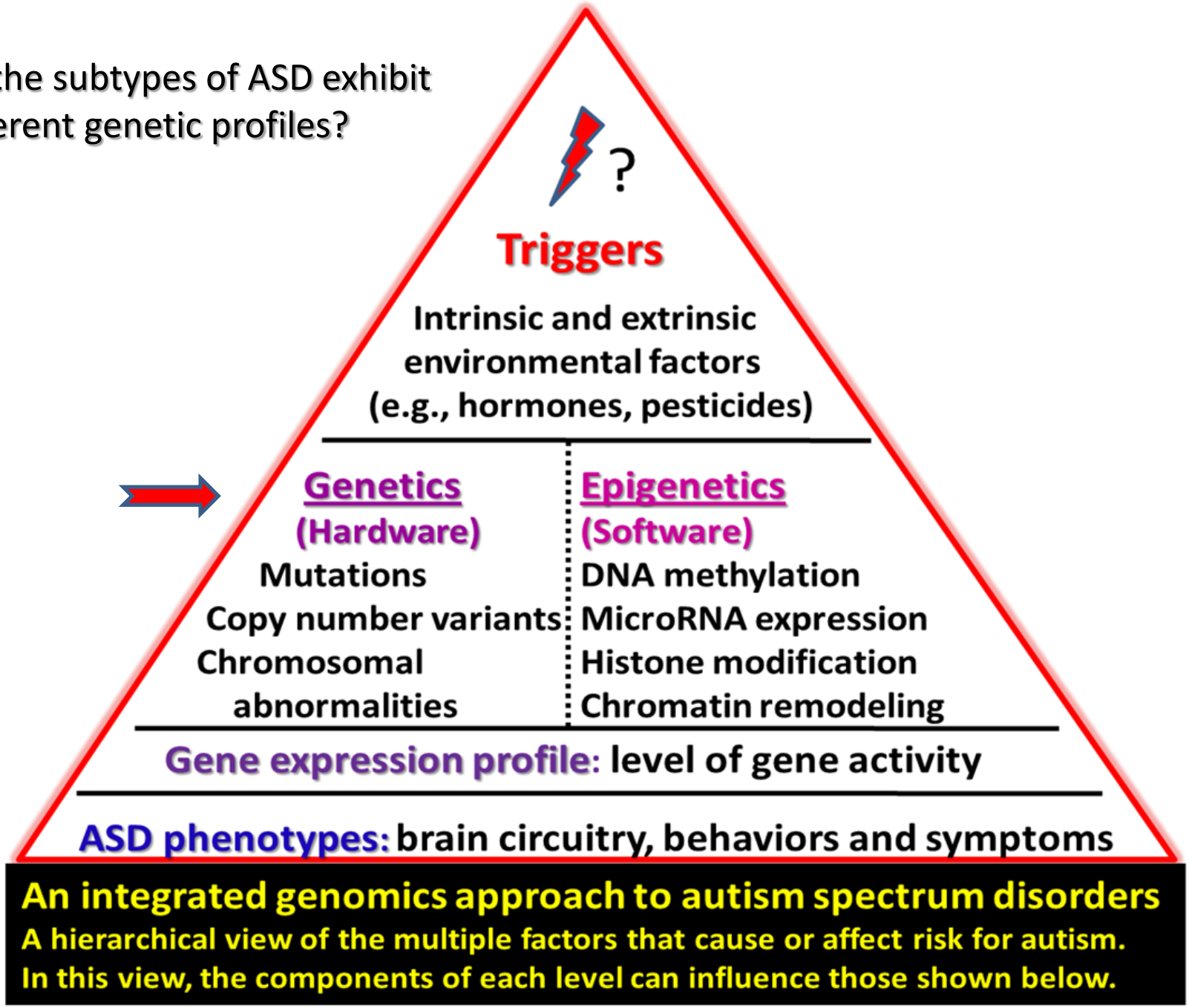
Case-control	% Accuracy (# genes)	% Sensitivity	% Specificity
L vs C 	93.3 (29)	96.6	90.3
M vs C 	94.5 (26)	96.0	93.3
S vs C 	94.0 (18)	96.6	90.5
A vs C 	81.8 (74)	91.2	61.1

A – all groups; L – language; M – mild; S = savant

Validation: 14 genes for the language-impaired subgroup (L) were shown to separate cases from controls in a new set of samples ⇒ potential for biomarker screen.

N A J Med Sci 6(3):107-116, 2013

Do the subtypes of ASD exhibit different genetic profiles?



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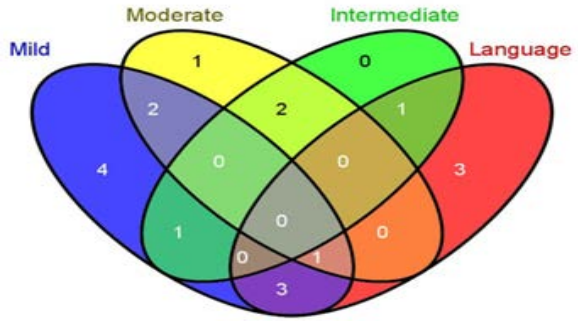
Grouping individuals by ASD subtypes also reveals subtype-dependent genetic loci

Genome-wide association study

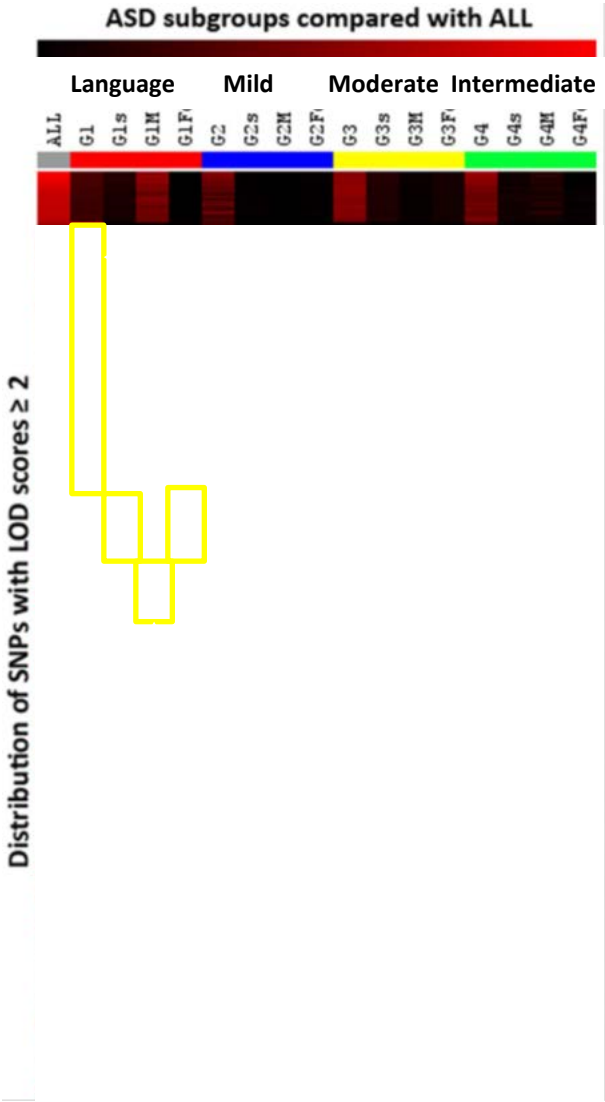


18 novel subtype-dependent genetic differences (SNPs)
Diagnostic potential?

Genes: **HTR4, CCL20, CCL25** (implicated in gut disorders)
GCH1 (involved in folate metabolism)
CDH6, LDHD, NSUN6, PTAR1, TRIM68
Functions: Axonogenesis, neurogenesis, long-term potentiation, memory, learning, steroid metabolism

Novel autism subtype-dependent genetic variants are revealed by quantitative trait and subphenotype association analyses of published GWAS data.
Hu et al. (2011) PLoS ONE 6(4):e19067

Genome-wide linkage analyses



A novel stratification method in linkage studies to address inter- and intra-family heterogeneity in autism.
Talebizadeh et al. (2013) PLoS ONE 8(6):e67569

Summary

- Heterogeneity of clinical manifestations of ASD are related to both genetic and biological heterogeneity of individuals on the autism spectrum.

- Dividing individuals with ASD into phenotypic subgroups reveals subtype-dependent differentially expressed genes and dysfunctional pathways that may lead to the development of novel subgroup-targeted therapies.

- Subtype-dependent genetic variants help to link genotype to phenotype and may be useful for diagnostic screening as well as for predicting response to specific medications (that is, pharmacogenomics).

- Incorporation of clinical phenotypes and patient stratification into biological and genetics research on ASD will lead to “precision medicine” approaches in treatment of ASD.

Acknowledgements

Mara Steinberg
ASD phenotyping

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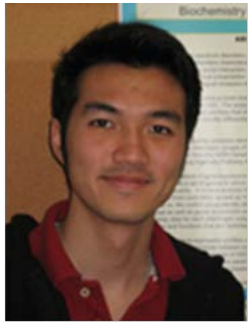
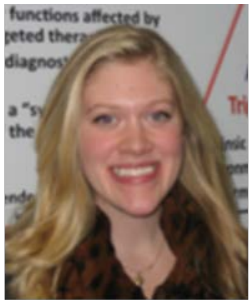
Gene expression



Tewarit Sarachana, Ph.D.
Gene and miRNA expression; Regulation of *RORA* and target gene analyses

AnhThu Nguyen
Global methylation analysis

Minyi Xu, M.S.
Sex hormone effects on *RORA*



Kristen Kocher, M.S.
Impact of EDCs on *RORA*

Collaborators

- John Quackenbush, Ph.D.: Formerly of TIGR
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- Yinglei Lai, Ph.D.: Dept. of Statistics, GWU
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