JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-00868-y OPEN

Cross-tissue integration of genetic and epigenetic data offers insight into autism spectrum disorder

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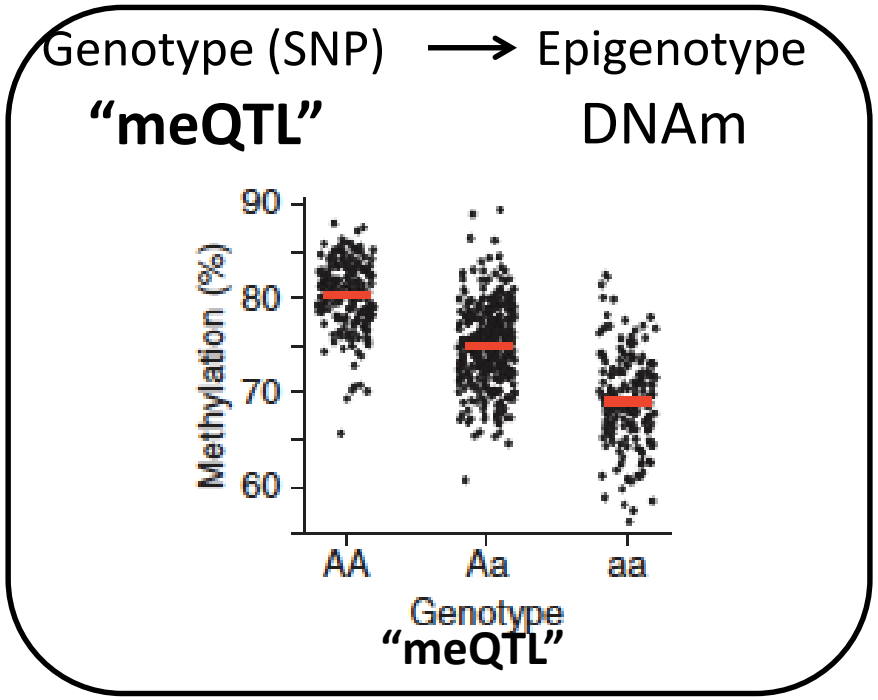
Inter-Agency Autism Coordinating Committee Meeting

October 24, 2017

What can we learn by integrating ASD genetic and epigenetic information?

Background:

- Epigenetic variation contributes to gene regulation/expression
- Epigenetic variation is tissue and timing dependent
- Epigenetic variation is in part controlled by genetic variation



Epigenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis

Yun Liu[1,2,12], Martin J Aryee[1,3,12], Leonid Padyukov[4,5,12], M Daniele Fallin[1,6,7,12], Espen Hesselberg[4,5], Arni Runarsson[1,2], Lovisa Reinius[8], Nathalie Acevedo[9], Margaret Taub[1,6], Marcus Ronninger[4,5], Klementy Shchetynsky[4,5], Annika Scheynius[9], Juha Kere[8], Lars Alfredsson[10], Lars Klareskog[4,5], Tomas J Ekström[5,11] & Andrew P Feinberg[1,2,6]

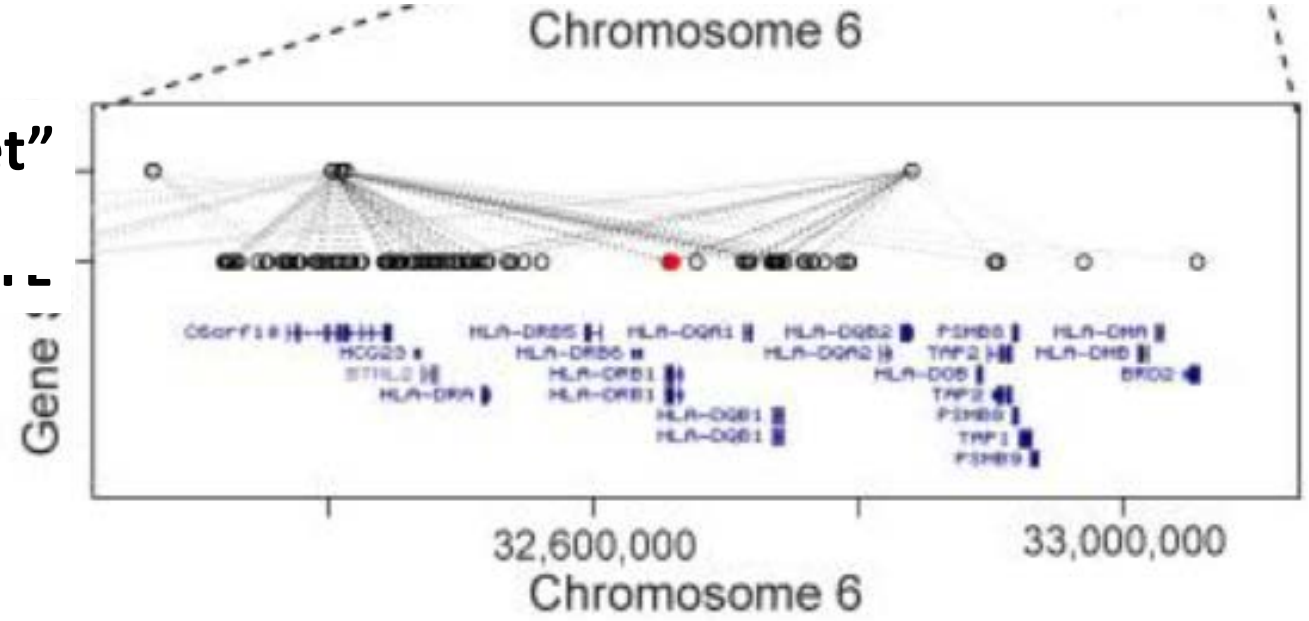
nature biotechnology

What can we learn by integrating ASD genetic and epigenetic information?

Background:

- Epigenetic variation contributes to gene regulation/expression
- Epigenetic variation is tissue and timing dependent
- Epigenetic variation is in part controlled by genetic variation
  - **Genetic-epigenetic "maps"** can be created, by tissue

meQTL "target"

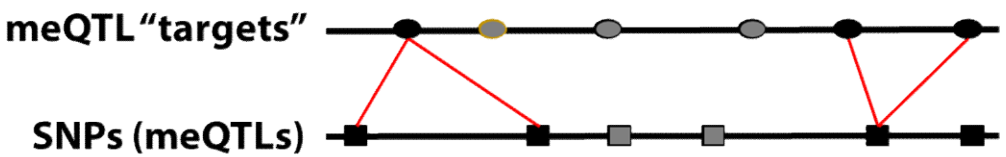


meQTL "Maps" Across Tissues

- From joint genotype and methylation data of
  - Peripheral blood (discovery in **SEED**, 2-5 yo)
  - Cord blood (discovery in **EARLI**, birth)
  - Fetal Brain (Mill, published list)

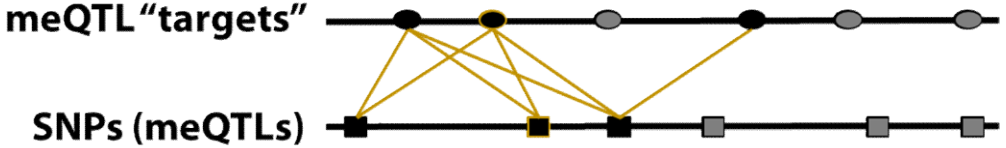
Child blood

Genotype → Epigenotype



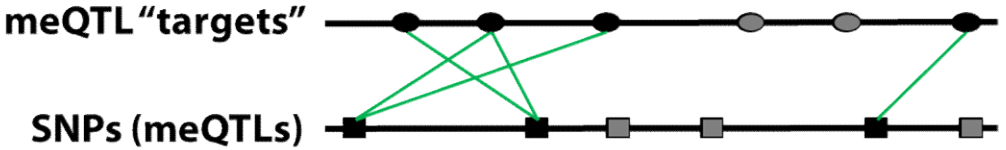
Cord (infant) blood

Genotype → Epigenotype



Fetal brain tissue

Genotype → Epigenotype



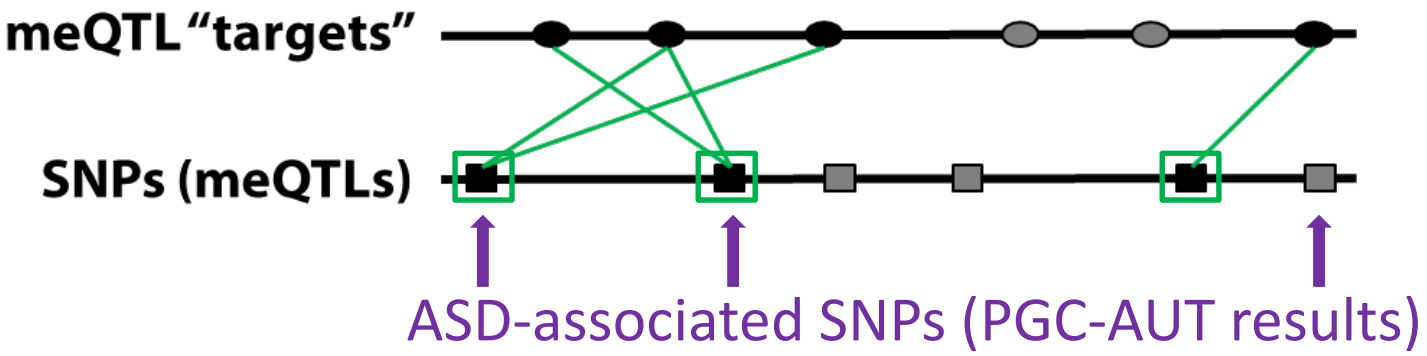
What can we learn by integrating ASD genetic and epigenetic information?

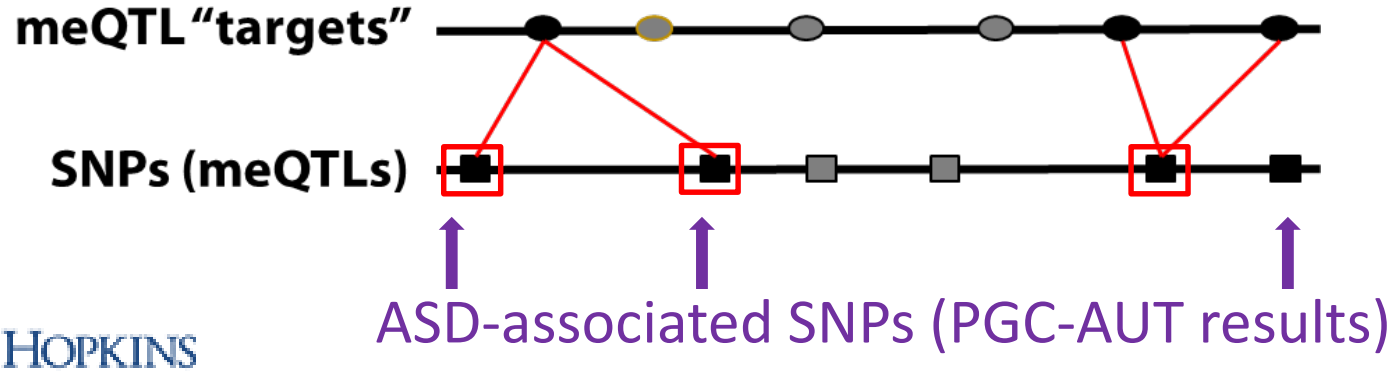
What can we learn using meQTL information?

1. Are ASD-associated SNPs enriched for meQTLs for particular tissues including blood?
2. Do ASD-associated SNP meQTL targets (CpGs) point to particular biology?
3. Do ASD-associated SNP meQTL targets point to genes not previously implicated?

What can we learn using meQTL information?

1. **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?**





What can we learn using meQTL information?

1. **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?**
   - ✓ YES

	ASD *P* value = 1e-03		
	meQTL *P*-value = 1e-08		
Fetal brain[a]		1.70 (<0.001)	
	meQTL FDR = 10%	meQTL FDR = 5%	meQTL FDR = 1%
Peripheral blood[b]	1.22 (<0.001)	1.20 (<0.001)	1.23 (<0.001)
Cord blood[b]	1.14 (0.032)	1.21 (0.011)	1.20 (0.023)
Lung[a]	—	1.09 (0.343)	—

Enrichment fold statistics and *P* values based on 1000 permutations
[a]LD pruning performed with 1000 Genomes CEU samples
[b]LD pruning performed with the study-specific genotype data. See Methods for additional details

What can we learn in autism using meQTL information?

1. Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?
   - ✓ YES

Table 2 Enrichment statistics for meQTLs derived from 4 tissue types in ASD GWAS SNPs

	ASD *P* value = 1e-03			ASD *P* value = 1e-04		
	meQTL *P*-value = 1e-08			meQTL *P* value = 1e-08		
Fetal brain[a]		1.70 (<0.001)			3.55 (<0.001)	
	meQTL FDR = 10%	meQTL FDR = 5%	meQTL FDR = 1%	meQTL FDR = 10%	meQTL FDR = 5%	meQTL FDR = 1%
Peripheral blood[b]	1.22 (<0.001)	1.20 (<0.001)	1.23 (<0.001)	1.31 (0.001)	1.40 (<0.001)	1.58 (<0.001)
Cord blood[b]	1.14 (0.032)	1.21 (0.011)	1.20 (0.023)	1.13 (0.299)	1.10 (0.392)	1.10 (0.406)
Lung[a]	—	1.09 (0.343)	—	—	0.80 (0.301)	—

Enrichment fold statistics and *P* values based on 1000 permutations
[a]LD pruning performed with 1000 Genomes CEU samples
[b]LD pruning performed with the study-specific genotype data. See Methods for additional details

What can we learn using meQTL information?

- ✓ **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?** YES
2. **Do ASD-associated SNP meQTL targets (CpGs) point to particular biology?**

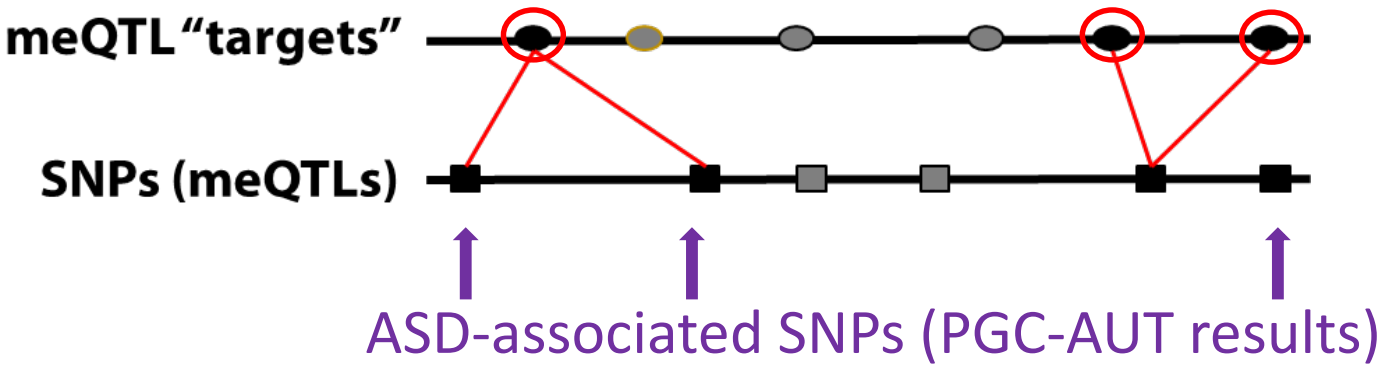


Table 3 Gene Ontology terms significantly enriched in multiple tissue types in comparison of ASD-related meQTL targets to meQTL targets generally

Term	Peripheral blood scaled rank[a]	Cord blood scaled rank[a]	Fetal brain scaled rank[a]
Response to interferon-gamma	0.14	0.11	0.11
Positive regulation of relaxation of cardiac muscle	0.20	0.46	0.30
Production of molecular mediator of immune response	0.65	0.22	0.28
Cellular response to interferon-gamma	NA	0.07	0.09
Detection of bacterium	NA	0.18	0.06
Detection of biotic stimulus	NA	0.26	0.04
T-helper 1 type immune response	NA	0.08	0.34
Regulation of interleukin-10 secretion	NA	0.09	0.43
Interferon-gamma production	NA	0.57	0.19
Regulation of interleukin-4 production	NA	0.24	0.62
Interleukin-4 production	NA	0.29	0.60
Interleukin-10 production	NA	0.25	0.74
Tongue development	NA	0.68	0.32
Inflammatory response to antigenic stimulus	NA	0.32	0.81
Endochondral bone growth	NA	0.71	0.53
Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II	0.01	0.05	NA
T-cell costimulation	0.05	0.01	NA
Positive regulation of hormone secretion	0.09	0.04	NA
Antigen receptor-mediated signaling pathway	0.08	0.13	NA
Immunoglobulin production involved in immunoglobulin mediated immune response	0.24	0.03	NA
Single organismal cell-cell adhesion	0.23	0.12	NA
Single organism cell adhesion	0.34	0.16	NA
Negative regulation of nonmotile primary cilium assembly	0.16	0.39	NA
Antigen processing and presentation of polysaccharide antigen via MHC class II	0.02	0.58	NA

What can we learn using meQTL information?

- ✓ **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?** YES
- 2. **Do ASD-associated SNP meQTL targets (CpGs) point to particular biology?**
  - ✓ YES - Blood, Cord blood, and Fetal Brain ASD meQTL targets implicate the <u>immune system</u>
  - Consistent with ASD findings to date:
    - Genetic variation does not (generally) point to immune system
    - Expression (and now methylation) results do, as well as many epidemiologic findings

Immune System Implicated by Expression and Methylation

Brain Studies

Blood Studies

Gene Expression

ARTICLE

Received 28 Sep 2014 | Accepted 3 Nov 2014 | Published 10 Dec 2014 DOI: 10.1038/ncomms6748 OPEN

Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism

Simone Gupta[1], Shannon E. Ellis[1], Foram N. Ashar[1], Anna Moes[1], Joel S. Bader[1,2], Jianan Zhan[2], Andrew B. West[3] & Dan E. Arking[1]

Transcriptomic analysis of autistic brain reveals convergent molecular pathology

Irina Voineagu[1], Xinchen Wang[2], Patrick Johnston[3], Jennifer K. Lowe[1], Yuan Tian[1], Steve Horvath[4], Jonathan Mill[3], Rita M. Cantor[4], Benjamin J. Blencowe[2] & Daniel H. Geschwind[1,4]

Peripheral blood gene expression signature differentiates children with autism from unaffected siblings

S. W. Kong · Y. Shimizu-Motohashi · M. G. Campbell · I. H. Lee · C. D. Collins · S. J. Brewster · I. A. Holm · L. Rappaport · I. S. Kohane · L. M. Kunkel

RESEARCH ARTICLE

Transcriptome Profiling of Peripheral Blood in 22q11.2 Deletion Syndrome Reveals Functional Pathways Related to Psychosis and Autism Spectrum Disorder

Maria Jalbrzikowski[1], Maria T. Lazaro[2], Fuying Gao[1], Alden Huang[2], Carolyn Chow[1], Daniel H. Geschwind[1,3], Giovanni Coppola[1,3☯], Carrie E. Bearden[1,4☯*]

DNA Methylation

ORIGINAL ARTICLE

DNA methylation analysis of the autistic brain reveals multiple dysregulated biological pathways

S Nardone, D Sharan Sams, E Reuveni, D Getselter, O Oron, M Karpuj and E Elliott

What can we learn using meQTL information?

- ✓ **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?** YES
- ✓ **Do ASD-associated SNP meQTL targets (CpGs) point to particular biology?** Immune system
3. **Do ASD-associated SNP meQTL targets point to genes not previously implicated?**

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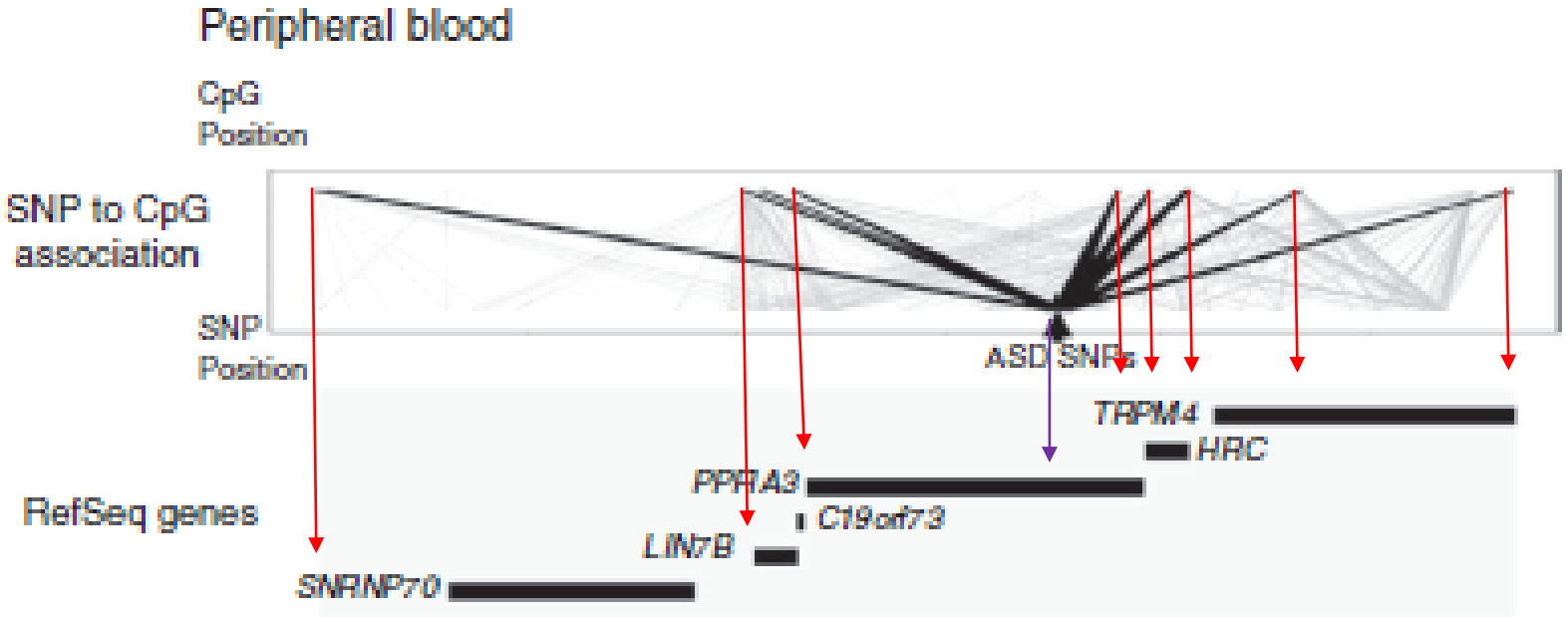

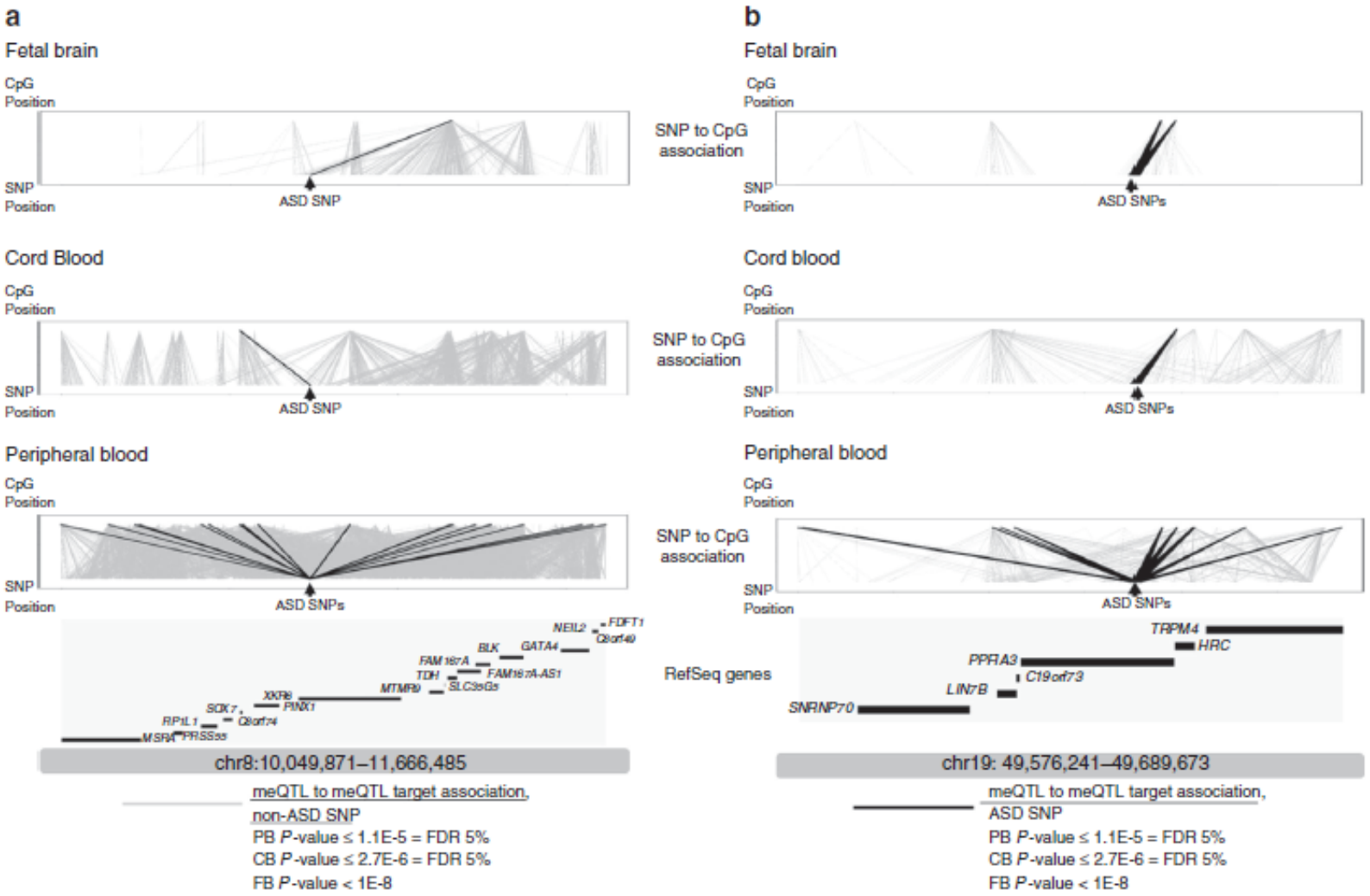

Fig. 1 'Expansion' of ASD loci through meQTL mapping in peripheral blood, cord blood, and fetal brain. Each tissue-specific panel presents, from bottom to top: genomic location, gene annotations, SNP locations, SNP–CpG associations, CpG locations. *Light gray* meQTL association lines denote all SNP to CpG associations in that tissue type; *Dark* meQTL association lines denote SNP–CpG associations for ASD-associated SNPs in PGC (*P* value < = 1e–04). **a** Locus at chr8; **b** Locus at chr19. Data are presented for meQTL maps for fetal brain (*top*); cord blood meQTLs (*middle*), and peripheral blood meQTLs (*bottom*). Please note locus coordinates differ from those in Supplementary Data 6 because in this context they encompass the locations of meQTL target CpG sites

What can we learn using meQTL information?

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- ✓ **ASD-associated SNP meQTL targets point to genes not previously implicated**

- ➢ **Blood–based meQTL information pointed to similar conclusions!**
- ❖ *Some important limitations regarding meQTL lists and ASD SNP list*

Summary of SEED I "Omic" Data

SEED 1 Genotype Data							
		# SEED 1 – child			# SEED 1 – mom		
Platform	**# SNPs***	**ASD****	**POP**	**DD**	**ASD**	**POP**	**DD**
Omni-Quad	>1M	419	555	193	0	0	0
Affy axiom KP	>700K	173	176	7	0	0	0
Omni-5M+ exome	>4.5M	13	19	1	301	0	0
Illumina MEGA	>1.4M	0	0	0		1269***	0
		605	**750**	**201**			

SEED 1 Methylation Data				
Platform	**# CpGs**	**ASD****	**POP**	**DD**
Illumina 450K	455,664	455	515	0

* measured. Imputed SNP ~ 8M

** includes possible low functioning cases (n=6)

*** genotype cleaning in-progress; numbers could change slightly

Collaborative Projects To Date

3 ASD GWAS contributions (meta-analysis and replication)
3 ASD EWAS contributions (meta-analysis)
2 non-ASD EWAS contributions (meta-analysis, PACE)
2 multi-omic collaborative projects

SEED-only methods contributions (not ASD focused):
2 EWAS / meQTL methodologic contributions
1 smoking environmental biomarker paper

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Acknowledge:
Eilis Hannon
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Funding:
CDC, NIEHS, Autism Speaks, NICHD, NIMH, NINDS, HRSA

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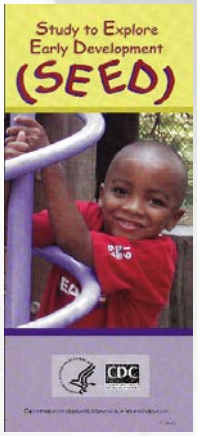

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