ASD Working Group – Molecular Target

Literature Review Topics

- Molecular Targets in the current pipeline – Access through Citeline
- Molecular targets from genetic risk variants – Linda Brady
- Role of neurotransmitter systems – Targets currently in development
- Role of Immune System - Celso Arango/Marion LeBoyer

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Molecular Targets from genetic risk variants- CNV

Sandres et al., 2015

•Analysis of de novo CNVs (dnCNVs) from the full Simons Simplex Collection (SSC) (N = 2,591 families) replicates prior findings of strong association with autism spectrum disorders (ASDs) and confirms six risk loci (1q21.1, 3q29, 7q11.23, 16p11.2, 15q11.2- 13, and 22q11.2).

•The addition of published CNV data from the Autism Genome Project (AGP) and exome sequencing data from the SSC and the Autism Sequencing Consortium (ASC) shows that genes within small de novo deletions, but not within large dnCNVs, significantly overlap the high-effect risk genes identified by sequencing. Alternatively, large dnCNVs are found likely to contain multiple modest-effect risk genes.

•Overall, we find strong evidence that de novo mutations are associated with ASD apart from the risk for intellectual disability.

•Extending the transmission and de novo association test (TADA) to include small de novo deletions reveals 71 ASD risk loci, including 6 CNV regions (noted above) and 65 risk genes (FDR % 0.1).

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Molecular Targets from genetic risk variants- CNV

Leppa et al. 2016. Families ascertained for having two or more children with ASD and simplex families from the SSC show distinct patterns of genetic risk: the rate of large, **rare de novo CNVs is lower in multiplex families, and there is an increased burden of large, rare inherited CNVs.**

- We identified a risk locus for ASD and language impairment at chromosomal region **2q24.1**
- The clinical manifestations in individuals with a **de novo 2q24.1 deletion**, including ASD or autism-like behavior and language delay, are quite similar, indicating that this CNV causes a distinct clinical syndrome.
- We also discovered one previous report of a single individual with a **hemizygous deletion overlapping NR4A2 and GPD2**; this proband displayed intellectual delay and pervasive developmental disorder
- Our observations, when combined with those of previous studies, provide strong statistical support for **2q24.1 deletions** as a cause of a highly penetrant form of syndromic ASD consisting of ID, language delay, and ASD-like behavioral and cognitive deficits.
- **Homozygous mutations in WWOX** cause an epileptic encephalopathy

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Molecular Targets from genetic risk variants

GWAS Analysis - Psychiatry Genomics Consortium

We observe a GWS **locus at 10q24.32** that overlaps several genes including **PITX3**, which encodes a transcription
factor identified as playing a role in neuronal differentiation and **CUEDC2** previously reported to be associated with social skills in an independent population cohort.
We also observe overlap with regions previously implicated in schizophrenia which was further supported by a strong genetic correlation between these disorders (Rg = 0.23; P=9 ×10−6). We further combined these Psychiatric Genomics Consortium (PGC) ASD GWAS data with the recent PGC schizophrenia GWAS to identify additional regions which may be important in a common neurodevelopmental phenotype and identified 12 novel GWS loci. These include loci previously implicated in ASD such as FOXP1 at 3p13, ATP2B2 at 3p25.3, and a ‘neurodevelopmental hub’ on chromosome 8p11.23.

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Role of Immune System

Meltzer, Van de Water 2016

•In the prenatal environment, a strong line of evidence is beginning to develop in support of maternal immune dysregulation as it affects neurodevelopment based on studies on maternal infection, immune activation, and maternal autoantibodies directed toward the developing fetal brain. Pro-inflammatory cytokines such as IL-6 and IL-17 have been implicated in this process, but the mechanisms remain under investigation.
•The postnatal environment echoes those lines of development, with anti-brain antibodies and systemic inflammation providing evidence of anomalies in immune regulation in a subpopulation of children with ASD.
•Groundbreaking work by Louveau, et al., (2015) showing active lymphatic vessels connecting the CNS to the lymphatic system that may possibly act as a conduit for neuroimmunological dysfunction.
•Regulators of the immune system have long featured prominently among the genetic components of autism

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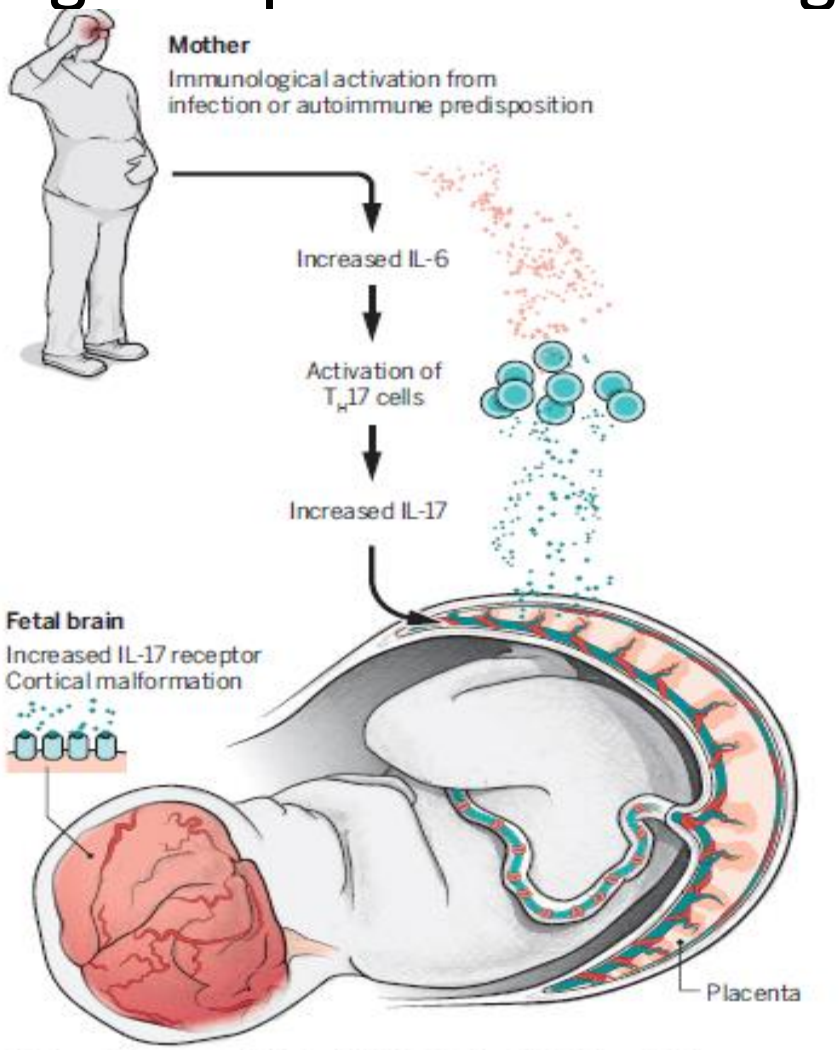
Role of Immune System

Maternal Immune Activation (MIA)

Estes & Mc Allister Science 2016

The study by Choi *et al. suggests* that women with TH17 skewing may have a much higher risk that ultimately warrants intervention. In this regard, alternative approaches to dampening TH17 cell differentiation, such as treatment with vitamin D and/or retinoic acid (a metabolite of vitamin A) *or manipulation* of intestinal microbiota will be exciting avenues of investigation.



Maternal immune activation (MIA). The hypothetical model shown is based on mouse experiments and illustrates that MIA, possibly in combination with a predisposition for autoimmunity, leads to an increase in T_H17 cells in maternal blood. These cells release IL-17, which crosses the placenta and increases expression of the IL-17 receptor in the offspring's brain. This in turn leads to ASD-related cortical and behavioral abnormalities in the offspring.

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Molecular Targets currently in development
(submitted by Linda Brady)

Clinical Development

- Cannabinoid receptor agonist
- Vasopressin 1A antagonist
- Bumetanide
- NMDA receptor antagonist
- Tyrosine hydroxylase inhibitor
- Oxytocin receptor agonist
- GABA A receptor agonist

Preclinical development (also tested for other indications)

- Acetylcholine receptor agonist; Glutamate receptor agonist
- Activity-dependent neuroprotectant; ADP ribose polymerase 1 stimulant
- GABA A receptor agonist; GABA A receptor antagonist
- Apoptosis inhibitor
- 5 Hydroxytryptamine 2A receptor antagonist; Alpha 1 adrenoreceptor antagonist; Dopamine D2 receptor antagonist (Risperidone, Delpor)
- Dopamine receptor agonist; Glial cell derived neurotrophic growth factor agonist
- Muscarinic M2 receptor antagonist; Muscarinic M3 receptor antagonist; Sigma 1 receptor agonist

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Other Molecular Targets in development

- RVT-701 is a reformulation of ketamine, under development by Roivant Sciences for the treatment of autism.
- AgeneBio is developing a novel, positive allosteric modulator GABA A a5 (gamma-aminobutyric acid A receptor, alpha 5) for the treatment of amnestic mild cognitive impairment (aMCI) due to Alzheimer's disease (or prodromal AD), autism and schizophrenia
- Egenix (now Bantam Pharmaceutical) in collaboration with Cloud Pharmaceuticals (formerly TeraDiscoveries) is developing eukaryotic translation initiation factor 4e (eIF4e) inhibitors for the treatment of Autism
- Davunetide (CP-201) is a trans-nasally delivered peptide which is a ADP ribose polymerase 1 stimulant and activity-dependent neuroprotectant, under development by Coronis NeuroSciences for the treatment of ADNP syndrome, an autism spectrum disorder
- CM-AT (Luminenz-AT) is a pancreatic enzyme preparation, under development by CureMark using its proprietary Encaptase technology for the treatment of autism.
- Translational Biosciences is developing allogeneic human umbilical cord tissue-derived stem cells for the treatment of rheumatoid arthritis (RA), multiple sclerosis (MS) and autism
- AEVI-004 is a co-crystal of AEVI-001 with a favorable toxicological profile, under development by Aevi Genomic Medicine for the treatment of autism, attention deficit hyperactivity disorder and other glutamate receptor-linked neuropsychiatric diseases.
- AB-2004 (4-ethylphenylsulfate) is under development by Axial Biotherapeutics, using microbiome discovery platform for the treatment of Autism spectrum disorder (ASD).