The Future of Pediatric Psychopharmacology: Insights from Pediatric Psychosis and the Genome

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Learning Objectives

1. Describe the concepts of heterogeneity, pleiotropy, penetrance, and variable expressivity in regards to the genetics of severe very early onset psychopathology.
2. Identify the extreme bookends of recent genetic debate about genetic causation for schizophrenia and other serious mental disorders starting with the "Common Disease/ Common Variant Hypothesis" as it applies to findings in psychiatric genetics.
3. Discuss the other extreme bookmark of current psychiatric genetics debate the "Common Disease/Rare Variant" hypothesis of genetic causation in psychiatry and how it might lead to new treatments.

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SPOILER ALERT!

Current Psychopharmacology	Future Psychopharmacology
Diagnosis: Disorders based on constellations of symptoms without reference to cause (exception PTSD) and do not track with biology or treatment response.	**Diagnosis:** Diseases defined mechanistically (e.g. gene defect, resulting physiology and environmental interaction)
Treatments: Found by accident and ameliorate only symptoms.	**Mechanisms:** Found by tracing effects of genes to RNA to proteins to cells to brain networks to symptoms
Mechanisms: inferred from accidentally found treatments and so do not lead to any breakthroughs.	**Treatments:** translated from precise knowledge of pathophysiology, halt or reverses disease progression not just decrease symptoms
Outcomes for serious mental illness: poor with 80-90% rates of disability	**Outcomes for serious mental illness:** good by preventing the unfolding of serious mental illnesses

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HOW DO WE GET THERE

- Embrace the opportunities of new technology:
  - Genetic sequencing
  - Induced pluripotent stem cell (iPSC) derived brain cells
  - Genome editing (e.g. CRISPR)
- "Treasure your exceptions"-William Bateson, 1908.
- Enjoy new golden age of clinical description
  - These are newly discovered genetic diseases
  - Genes first approach describes the varied outcomes of a mutation
  - **The indispensable partnership: Clinicians + Basic scientists**

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Phenotype First Approach Leads to Genes First Approach

- Phenotype first approach considers:
  - Heterogeneity?
    - Multiple causal paths to same common disorder
    - Common disorders are actually multiple diseases
  - Very early onset forms lead to gene discovery
- Genes first approach considers:
  - Pleiotropy?: same mutation multiple differing symptom manifestations/disorders
  - Variable expressivity/penetrance (severity)?
-

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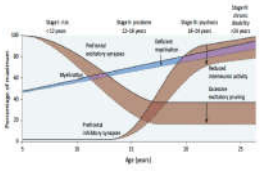
Example: Very Early Onset Psychosis (<14 yrs)

"Typical" Schizophrenia

Symptoms

- **Cognitive impairments:** Deficits include working memory, verbal fluency, social cognition
- **Deficit symptoms:** Loss of motivation, blunted affect, impoverished thought and speech
- **Psychotic symptoms:** Hallucinations, delusions,



Course of Illness

- **Onset:** Cognitive and deficit symptoms in mid-teen years; psychosis follows in late teens, 20's.
- **Trajectory:** Cognitive and deficit symptoms unremitting; superimposed pattern of relapsing and remitting acute psychotic episodes
- **Treatment**: Response to antipsychotic drugs deteriorates over time

Very Early Onset Psychosis:

- Similar symptoms (more visual)
- More baseline neurodevelopmental disorders
- Long-term diagnosis variable, not all schizophrenia

Adapted from slide from Steve Hyman

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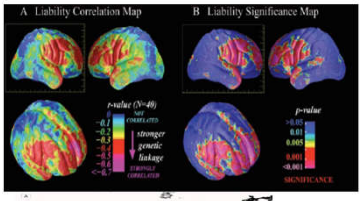
Schizophrenia: anatomic pathology--but no molecular mechanisms



- Excessive cortical thinning during adolescence
- Location, timing consistent with cognitive impairments

Cannon et al. Proc Natl Acad Sci U S A. 99:3228-33, 2002

Control

Schizophrenia

Slide from Steve Hyman

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Gogtay and Lenroot, 2009

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High heritabilities mean that molecular clues to pathogenesis are contained within our genomes

Disorder	λ	Heritability (h^2)
Autism Spectrum	25	0.8
Schizophrenia	9	0.8
Bipolar Disorder	8	0.7-0.8
Major Depression	2-5	0.35

Heritability estimates based on comparing concordance of MZ Vs. DZ twins

Slide from Steve Hyman

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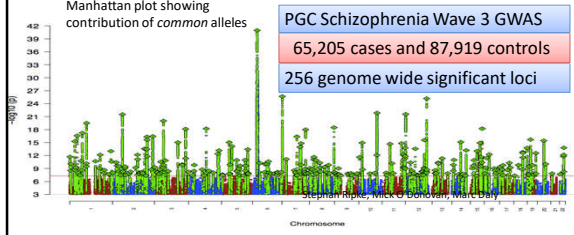
Common Disease Common Variant Hypothesis:

Manhattan plot showing contribution of *common* alleles

PGC Schizophrenia Wave 3 GWAS
65,205 cases and 87,919 controls
256 genome wide significant loci



- Schizophrenia, MDD, bipolar disorder, anxiety disorder, and ADHD correlated and share common variant risk ⇒ "the Genome didn't get the DSM manual in the mail" –Steve Hyman
- Each gene has small effect (<1.4 RR)
- Polygenic risk scores (**PRS:** $\Sigma\beta_i * g_i$) explains ~7% of risk of a schizophrenia ⇒ missing heritability

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SCHEMA Consortium: Rare Variant Association 25,033 cases / 51,507 controls find only two genes with exome-wide levels of significance


TJ Singh

Transmitted rare exome variants associated with typical onset schizophrenia have modest effect sizes.

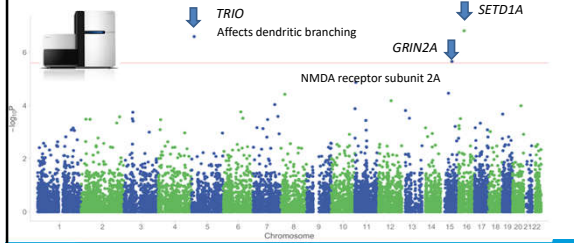
Component of histone methyltransferase

SETD1A

TRIO
Affects dendritic branching

GRIN2A

NMDA receptor subunit 2A



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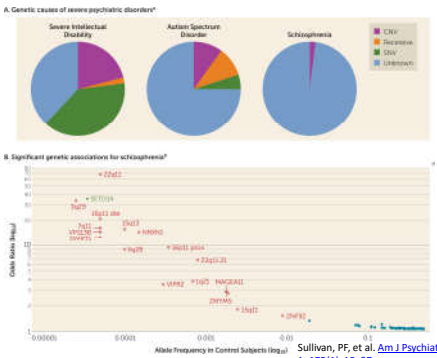


Sullivan, PF, et al. Am J Psychiatry. 2018 Jan 1;175(1):15-27.

DEVELOPMENTAL NEUROPSYCHIATRY RESEARCH CLINIC

Identify New Treatments & Outcome Measures for Children with Early psychosis and Psychosis risk

- **Genetic High Risk for schizophrenia**
  - Copy number variation (CNV) associated with Schizophrenia
- **Clinical High Risk for schizophrenia**
  - Prodrome, ages 7-18 years
  - Hallucinations, paranoia but retain insight
- **Early Psychosis**
  - Especially under age 13 at onset (VEOP)
  - Genetics-CMA & whole exome Sequencing looking for coding region mutations
  - Whole genome sequencing looking for non-coding region mutations
  - Long read sequencing – structural variation missed with above

- **Since 2011**
  - Over 500 children evaluated for early psychosis or high risk
  - 30% are ≤13 years old

Collaborations helping start parallel research clinics:

China: Shenzhen Kangning Hospital

Mexico: Instituto Nacional de Medicina Genómica (INMEGEN)

Very Early Onset Psychosis at BCH

Identify New Genetic Variants, Treatments & Outcome Measures to Support Therapeutic Interventions

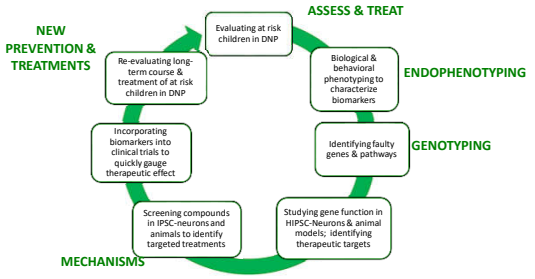
- **Early Psychosis**
  - 170+ patients enrolled (Manton Center for Orphan Disease Protocol)
  - Genetics-CMA & Exome (2013-2018), now whole genome sequencing (2019-)
    - Discoveries include TRRAP, ATP1A3, RCL1
    - Youngest affected children are helping us find highly penetrant genes
  - Early Psychosis Investigation (EPI) Center created in Spring 2019, dedicated to understanding, identifying and treating children and adolescents with psychotic disorders.
    - Satellite EPI Center in Mexico City in development
- **Genetic High Risk for schizophrenia**
  - Copy number variation (CNV) associated with Schizophrenia
    - Created registry of over 200 patients with 16p13.11 del/dup
    - Plan to expand registry to other Schizophrenia associated CNVs

Participant Type	Enrolled	DNA	PBMCs	RNA
Probands	137	130	59	40
Family Members	250	230	84	49
Total	387	360	143	89

*Numbers as of 4/12/2019. There are an additional 11 early onset participants/clinical high risk participants, 3 participants with a genetic risk factor for psychosis, and 9 participants with the 16p13.11 deletion or duplication without psychosis (23 additional participants)

Developmental Neuropsychiatry Program Discovery Cycle

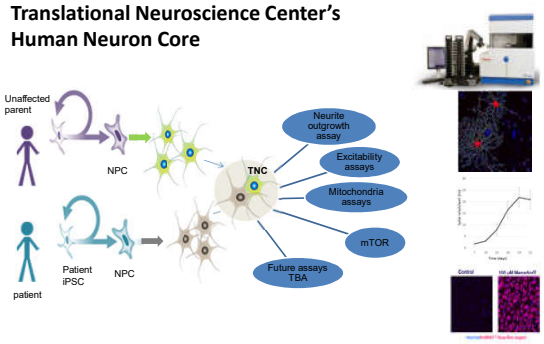
A Road Map for Translational Neuropsychiatric Research



Very Early Onset Psychosis: High Rate of Rare Mutations, Trauma, Suicidality

- Schizophrenia associated CNV rate ~4 x higher than in adult onset schizophrenia ($p<0.001$)
- High rate of Traumatic Events
- High rate of suicidality
- iPSC brain cells as bridge to understanding interaction

Cellular phenotyping via the Translational Neuroscience Center's Human Neuron Core



Schizophrenia & Neurodevelopmentally Implicated CNVs in BCH VEOP Cohort (Schizophrenia CNVs are marked *, genome wide significant Schizophrenia CNV are marked **)		
Schizophrenia & Neurodevelopmental CNVs	**BCH VEOP Cohort Probands**	**Potential System Dysfunction/Conditions to Monitor:**
1q21.1 Duplication*	**1468-01,** 1464-01	Heart disease; Epilepsy; Cataracts; Neuroblastoma
2q13 Duplication	**1110-01**, 1231-01	Liver disorder; Kidney; Heart disease (CHD); Hypotonia; Cranial dysmorphisms
15q11.2 Deletion*	1325-01	Epilepsy
16p11.2 Duplication**	**1384-01**	Kidneys
16p13.11 Duplication*	**0642-01**, 1104-01	Heart disease; Skeletal abnormalities; Vision; Epilepsy
16p13.11 Deletion	**0602-01, 1125-01**	Epilepsy
22q11.2 Deletion**	**1430-01**	Heart disease; Immune; Pulmonary; Kidney; Gastrointestinal

BCH VEOP Cohort Compared to Adult SZ Cohort

	BCH VEOP Cohort	Adult Schizophrenia Cohort (Bergen et al., 2018)	Controls (Bergen et al., 2018)
Schizophrenia CNVs	7 (7.6%)	407 (1.9%)	115
No Schizophrenia CNVs	85	20,681	20,107
Totals	92	21,088	20,222

*The Fisher Exact test value is **p=0.0022** after comparing the BCH VEOP cohort to the Adult Schizophrenia population. The value is **p<0.00001** after comparing the BCH VEOP cohort to controls.

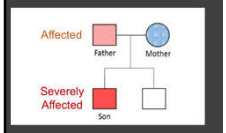
BCH VEOP Cohort Compared To NIMH COS Cohort: Neurodevelopmental CNV Rate

	BCH VEOP	NIMH COS (Ahn et al., 2014)
# of probands	92	126
Neurodevelopmental CNVs from Ahn et al., 2014	11/92 probands (12.0%)	15/126 probands (11.9%)
Neurodevelopmental CNVs also on Psychiatric Genomics Consortium (PGC) significant CNV list (Marshall et al., 2017)	2 out of 7 CNVs (28.6%)	4 out of 10 CNVs (40.0%)

Clinical Take Away Points

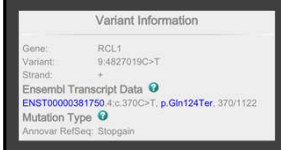
- VEOP have a higher rate of CNV than adult onset schizophrenia (**p=0.0022**).
- The majority (~60%) of CNVs identified in VEOP are not accepted SZ-associated CNVs.
- All of the CNVs in the BCH VEOP cohort indicated the need for medical monitoring.
- **Routine testing for CNV and vigilance for trauma and suicidality is indicated for patients presenting with VEOP.**

Case 1: Investigating RCL1

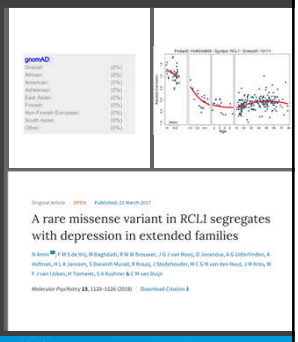


- 18 year old boy
  - Star athlete, good student
  - Over the course of four months, descended into catatonia in with auditory and visual hallucinations, paranoia, aggression, mood dysregulation, and disorganized thoughts.
  - Poor motor coordination
  - CSF found increased protein concentrations, encephalitis test negative
  - Currently responding to Clozapine
  - Child compound het for CAPN1 (Spastic paraplegia 76, autosomal recessive)- doesn't fit phenotype
  - Family history: Paternal aunt has had multiple psychiatric hospitalizations, father has behavioral and anger problems

RCL1 as a candidate EOP gene



Involved in production of ribosomal RNA



A rare missense variant in RCL1 segregates with depression in extended families

Investigating RCL1

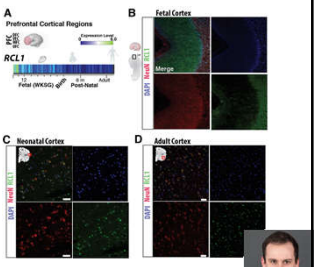
***RCL1* expression is highest during fetal and early post-natal human brain development**

A) Bulk transcriptome analysis of prefrontal cortical regions revealed *RCL1* transcripts are enriched during fetal gestational weeks and decrease postnatally.

B-D) Immunohistochemistry of an anti-body probe against RCL1 and corresponding confocal fluorescence imaging of fetal, 9-month-old, and adult human cortex.

Cell type specific neuronal marker NeuN and nuclei marker (DAPI) show *RCL1* present in both neurons and non-neuronal cell types

Manuscript in preparation



Richard Smith, PhD
Instructor HMS

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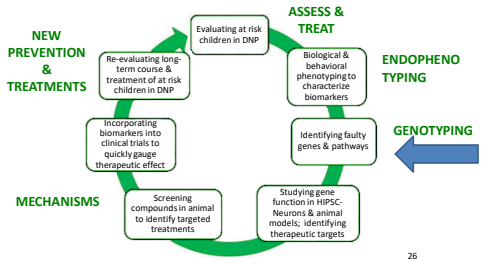
A Road Map for Translational Neuropsychiatric Research



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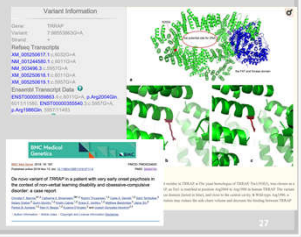
Case 2: TRRAP Variant in Childhood Onset Psychosis

- The proband is a 12-year old Caucasian boy who first presented to neurology at age 5 for concerns about school performance
  - Evaluation showed delays in gross motor skills and some behavioral concerns but above average intelligence
- At age 7, concern for ADHD and compulsive behaviors (severity decreased over time) and mild social delays.
- At age 9, proband referred for psychotherapy evaluation for paranoia and hallucinations. Reports that he started hearing voices at age 7.
- Diagnosed with major depression with psychotic features in the context of NVLD (non-verbal learning disability) and OCD
  - Fear of being hunted, voices listening to him, mortality
  - Treated with Fluoxetine and responded

TRRAP: involved in histone acetyltransferase activity (HAT), epigenetic transcription activation, DNA repair



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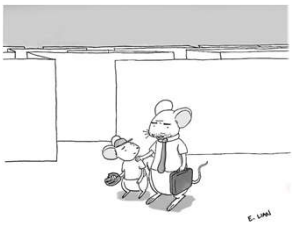
Mouse model

- Using CRISPR/Cas9 to create a mouse model with the exact amino acid change as the patient

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants



"Sorry, kiddo. Your old man has to work so you can go to the best drug trials in the country."

screening

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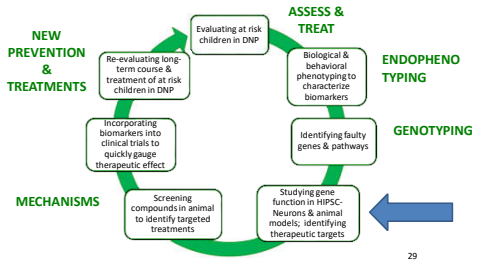

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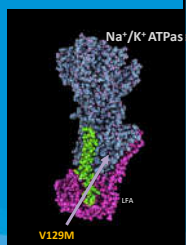
Role for the Na^+/K^+ ATPase subunit (*ATP1A3*) in Childhood Onset Schizophrenia and Beyond

Proband

-Diagnosed at age 3 with selective mutism and depression
-Described as having mood swings, lack of emotional control, and severe anxiety
-Severe self-injurious behaviors
-Presented with command hallucinations and behavioral worsening meeting full DSM 5 criteria for COS at 6 years of age (now 9 y.o.)



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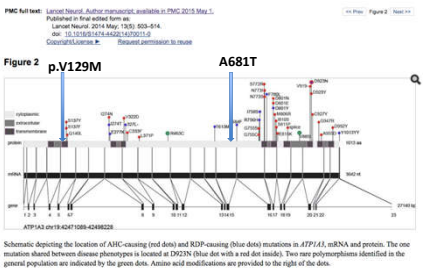
Patient #1: Genetic Finding

- **WES identified a *de novo* missense change in ATP1A3**: NM_152296.4:c.385G>A and **p.V129M** (hg19).
  - This variant has not been previously described.
  - The gene is highly conserved and the variant is predicted to damage the protein's function.
- The *ATP1A3* gene codes for neuron specific isoform 3 of the alpha subunit of the Na+/K+-ATPase (NKA) complex which is expressed in GABA projection neurons of basal ganglia.
- ATP1a3 mutations are linked to Alternating Hemiplegia of Childhood, Rapid Dystonia Parkinsonism, and CAPOS syndrome (Brashear et al., 2008; Ozelius, 2012; H Rosewich et al., 2014; Sweney, Newcomb, & Swoboda, 2015).
- **3 additional unrelated cases with rare ATP1a3 mutations and COS identified subsequently** (Chaudette et al., 2018)

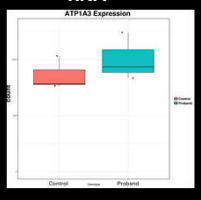
ATP1A3 in neuropsychiatric disorders



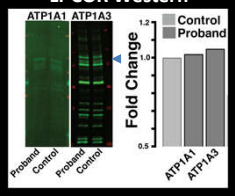
Schematic depicting the location of AHC-causing (red dots) and RDP-causing (blue dots) mutations in *ATP1A3*, mRNA and protein. The one mutation shared between disease phenotypes is located at D923N (blue dot with a red dot inside). Two rare polymorphisms identified in the general population are indicated by the green dots. Amino acid modifications are provided to the right of the dots.

ATP1A3 level is comparable between proband and control neurons

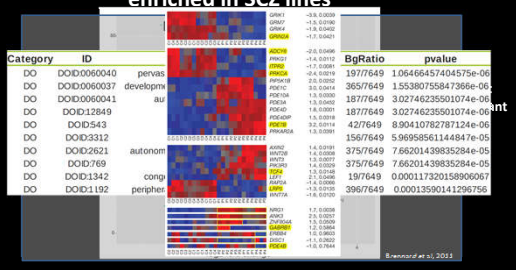
RNA



LI-COR Western



Proband is enriched for pathways differentially enriched in SCZ lines



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DO	DOID:1192	peripher	396/7649	0.00013590141296756

ant

Brennand et al, 2011

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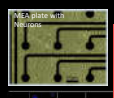
Spontanous and evoked spiking activity unchanged between patient & Control

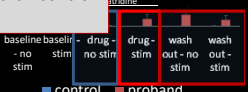
Action Potential bursts: proband recovers from Veratridine treatment better than proband



PATCH CLAMP VALIDATION

COS neurons were more resistant to veratridine challenge than controls cells, showing smaller veratridine induced depolarization than control neurons.

Veratridine- Blocks sodium channel inactivation (more excitability)



-Mean firing NOT changed between proband and control
-Bursts per well NOT changed between proband and control

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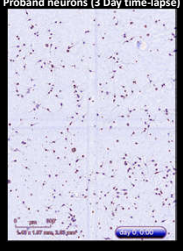
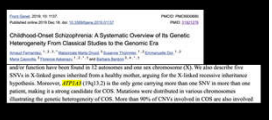
Live cell tracking of differentiated COS neurons

Proband neurons (3 Day time-lapse)



Phenotype Testing	Effect (N=2 clones, 2 differentiations)
Cell Viability / Short-term survival	Increased 60% in Proband
Neurite Length	Mild Decrease (large variability)
Neurite Branching	No Change (large variability)
Cell Body Size	No Change

Proband neurons has increased rates of survival post plating



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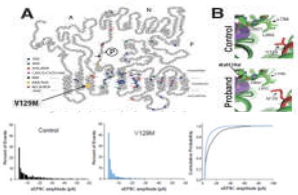
BCH ATP1a3 Mutation in COS: Probable Gain of Function leads to Psychosis



Additional side-chain bulk from the V129M mutation may alter pump function

EPSP amplitude decreased in Cortical neurons from ATP1a3 patient-derived iPSCs

CRISPR correction of mutations reverses observed electrophysiologic cell phenotype

Hypothesis: Under stress abnormal pump function impacts neuronal function more

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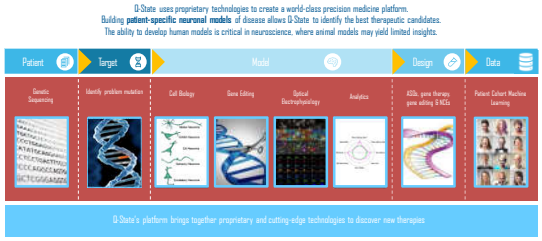
Q-State precision medicine platform



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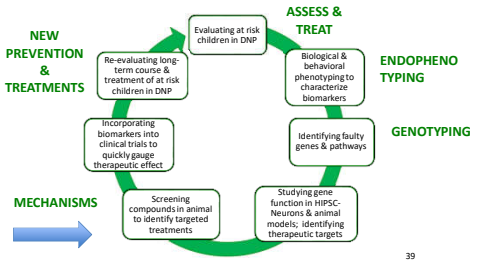
Developmental Neuropsychiatry Program Discovery Cycle

A Road Map for Translational Neuropsychiatric Research



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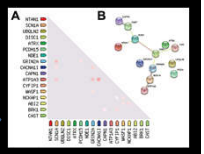
Future Directions

Total VEOP Manton Recruitment

Participant Type	Enrolled	DNA	PBMCs	RNA
Probands	138	130	66	52
Family Members	265	239	92	73
Total	403	369	158	125

As of 9/12/2019. *There are an additional 21 probands with early onset psychosis/clinical high risk, 3 probands with a genetic risk factor for psychosis, and 27 probands with the 16p13.11 deletion or duplication without psychosis (51 additional probands).



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Clinical Take Way Points

- Very Early Onset Psychosis (VEOP) broadly defined, not just very onset schizophrenia has a high rate of discoverable rare likely causative genetic variation.
- The rate of de novo rare predicted damaging variants in highly conserved genes is considerable, ~6% in our sample.
- Many of the genes implicated are implicated in other central nervous system diseases.
- Whole Exome Sequencing of VEOP patients and parents is justifiable so as to
  - highlight additional medical risks
  - Eventually give families answers about causality and risk to other family members
  - Inform field

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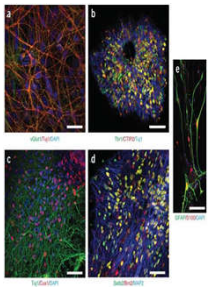
NEXT STEPS

Unprecedented Opportunity to Develop Therapeutics to Prevent Schizophrenia

- **Genes**
  - Youngest affected children are helping us find highly penetrant genes
- **Neurons**
  - Neuronal cell cultures to identify cell autonomous effects
- **Networks in Living Brain**
  - From rodent knock out models to human clinical trials



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