

**UIC Autism Center of
Excellence: Interdisciplinary
Studies of Insistence on
Sameness (IS) in ASD**

Ed Cook, MD
on behalf of the
UIC/Vanderbilt/U Chicago
ACE Team

Theme – insistence on sameness & serotonin

- Insistence on Sameness (IS) – one of two emphases of Kanner in 1943 and an interest in our lab for over 20 years
- Serotonin and autism – goes back to finding of elevated blood 5HT in autism from Schain and Freedman in 1961 – i.e. this has been a circumscribed interest/line of research for 46 years in the laboratory currently at UIC

Translational Studies on Insistence on Sameness – P50 (co-PI John Sweeney, Ph.D.)

- 3 cores
 - Administrative
 - Assessment
 - Data
- 4 projects submitted
 - Neurochemistry and genetics
 - Neurocognitive and neuroimaging (human and rodent)
 - Pharmacogenetic
 - Mice with serotonin transporter variants found in humans with autism and/or OCD

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- 3 cores
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Administrative Core

- Arranging for within center communication including with on-site and off-site collaborators
- Communication outside the ACE
- Midwest Autism Consortium
 - Series of seminars ranging from presentations by clinical programs throughout the region to clinical research to molecular genetic research
 - Goal – improve communication among researchers and clinicians & recruitment

Assessment Core – Leventhal

- All subjects with full assessment have had blood drawn for karyotype, blood sent to NIMH Genetics Repository for transformation of cell lines and sharing with other approved researchers, blood for platelet and genetic studies

Assessment Core (Leventhal)

- Core Measures
 - ADI-R, ADOS, Vineland, cognitive testing, CHARGE physical examination, medical and family history, karyotype
 - Additional Clinical Measures
 - RBS-R (repetitive behavior)
 - Childhood Routines Inventory
 - Aberrant Behavior Checklist-Community Version (ABC-CV)
 - Parental BAPQs

Data Core – Gibbons/Cox

- Robert Gibbons (UIC) – analysis of imaging and neurocognitive data and longitudinal data in pharmacogenetic trial
- Nancy Cox (U Chicago) – analysis of genetic data (with Emily Kistner Griffin)
- Opportunity – connecting strengths of Gibbons and Cox from 2 fields that don't communicate directly that often
- Data entry and sharing through NDAR

Project I – Cook/Sutcliffe(Vanderbilt) /G. Pandey(UIC)

- Previous studies have indicated increased blood 5HT in 1/3 of subjects with autism
- Hypothesis: higher in high IS group compared to low IS group
- Identify a group with high blood 5HT and study mechanism
- Hypothesis: increased serotonin transporter function, decreased 5-HT_{2A} binding, or altered integrin beta 3 (ITGB3) function

Project I - Rationale

- Many studies of the serotonin transporter gene in autism, original finding from our lab of short allele transmitted has been replicated in the largest sample and meta-analysis including the largest sample (Devlin et al, 2008)
 - Heterogeneity test positive
- Heterogeneity may be related to phenotype (Brune et al, 2006) and and/or to neurochemical subtypes (i.e. normal 5HT vs. high 5HT)
- High blood (platelet 5HT) likely heterogeneous (previous studies suggested ½ were high outliers for 5HT uptake and a different ½ were low outliers for 5HT_{2A} receptor binding)

Project I – relation to other projects

- Genotyping of common variants and identification of rare variants (e.g. in serotonin transporter) that inform projects II and III

Project II – Sweeney/Ragozzino

- Mike Ragozzino who has been studying set-shifting in rodents and not realizing its relationship to autism
- Set of neurocognitive and neuroimaging studies of set-shifting in which the human paradigms have correspondence to the rodent studies
- Adding a component related to emotional processing that may be key (see RSMB vs. IS later)
- Rodent pharmacology studies related to the neurochemistry of project I and pharmacology of project III

Project III – Owley to Najjar

- Pharmacogenetics of Autistic Disorder
 - Variability in response to escitalopram
 - Variation
 - Serotonin transporter gene
 - Serotonin 5-HT_{2A} receptor gene
 - Integrin beta 3
 - ITGB3 (interacts with serotonin transporter)

Escitalopram for Treatment of IS

- Citalopram trial of repetitive behavior in ASD negative
 - Previous trials of potent 5HT transporter inhibitors positive (CMI, fluvoxamine, fluoxetine)
 - Difference may be in nature of repetitive behavior
 - RSMB vs. IS
 - Recent distinction consistent across factor analyses – IS is more “OCD-like”

“Project IV” – Blakely

- Blakely lab (& Jeremy Veenstra-VanderWeele) at Vanderbilt
- Making mice that have rare protein variants (e.g. G56A) found in patients with ASD and OCD and studying behavior and brain development – plan to understand effects on brain development in ways that can't be studied in humans
- Note: we continue to stay in active contact with Blakely and Veenstra-VanderWeele

Project IV

- Cut from the center grant
- Some funding through K award to Veenstra-VanderWeele at Vanderbilt (mentored by Blakely)
- Pending ARRA grant

Developing Junior Colleagues

- Suma Jacob, M.D., Ph.D.
 - K awardee studying oxytocin, vasopressin, related receptors and their genes
 - Allows study of this important system and interaction with 5-HT
 - One example

NDAR Update

- Two big days for ACE Centers and Networks
 - Jan 15 and July 15 – data upload deadlines for core measures by Dec 1 and June 1
 - Up-to-date with ADI-R, ADOS, Vineland, CHARGE histories and physical forms, some cognitive instruments, Fragile X and karyotype*
 - Waiting for NDAR to be ready for Vineland-II and DAS-II

Approaches to Heterogeneity

- Two approaches to genetics (prob both correct)
- Common variants
- Rare variants
- Approach to heterogeneity should take this into account
- Should we be looking for correlations across neurochemistry, clinical and genetic measures or convergent outliers

Copy Number Variation (CNV) Prediction – for NDAR Karyotype

Samples genotyped on Illumina 1M Duo v3 chip at TCAG core

↳ Genotypes and SNP intensity data analyzed with Illumina BeadStudio

↳ Genotypes reclustered and SNP intensities normalized within BeadStudio

↳ Genotypes and SNP intensity data exported from BeadStudio

↳ Samples with poor quality intensity data identified and discarded

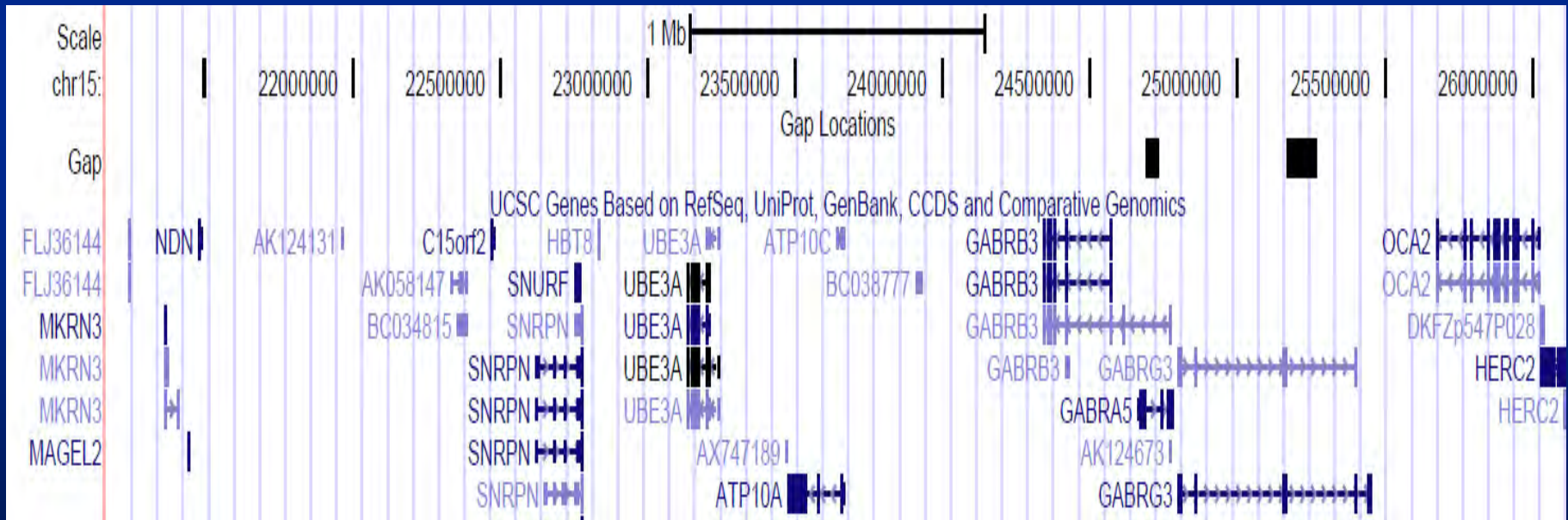
↳ CNVs predicted with 3 different algorithms, only 1 positive required (for sensitivity)

↳ CNV > 500 kb and < 5% control rate in DGV prioritized for more detailed manual curation

Molecular Karyotype (1M Illumina)

- 1 Mb threshold (well below G banding) or known syndrome (e.g. 16p11.2) and not in controls (Database of Genomic Variants)

15q11-q13 Interstitial Duplication



15q11-q13 Interstitial Duplication

- 15q11-q13 Duplication(BP2-BP3)
 - Uploaded to NDAR
 - Did not stand out in sample re: clinical phenotype, aside from the predicted high IS (high RBS-R) and entered into project III
 - RBS-R reduced from 45 to 19
 - ABC-Irr reduced from 17 to 8
 - Not remarkable for 5HT lab measures

Progress

- 1st Year – successful initiation
- 2nd Year – keeping momentum of data collection and entry
- Years 3 – 5 – sufficient data to begin to look at preliminary data and consider next steps
- Goal beyond specific aims – work more to connect with those involved in novel medication development, esp. re: 5-HT and IS

Possible Connection to Novel Rx

- Escitalopram improves switching in rat task
- 5-HT₆ antagonist has same effect
- Risperidone has 5-HT₆ antagonist effect in vitro (Roth)
- Possible effects of risperidone without toxicity of D2 antagonist effects
- MUCH WORK TO BE DONE

NDAR and NIMH Genetic Repository

- Question arising July 13
- Parent asked about her six year-old
 - Will this be useful to him if he has children some day?
 - Very good question from typically astute parent
- Should parents/subjects have access to their data at NDAR at some point?
 - e.g. – what about questions that arise and I'm no longer there to help answer them?

Thanks !

- People with ASD and their families
- NIH
- Collaborators
- Many, many others