The International Multisite ADHD Genetics Project

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IMAGE Sites

- ● Switzerland (CH)
- ● Holland (NL)
- ● Belgium (BE)
- ○ England (EN)
- ●
- ● Ireland (IR)
- ● Spain (ES)
- ●
- ● Israel (IL)
- Germany (DE)

IMAGE Project Investigators

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IMAGE Project Investigators

<u>**Statistical Analysis Team**</u>*:

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Note: Original QTL design based on advice from Prof Sham and from Shaun Purcell

Overview of Attention Deficit Hyperactivity Disorder

- A disorder of inattention, hyperactivity and impulsivity
- Onsets in childhood
- Impairs academic performance, social functioning and occupational performance
- Affects 8 to 12% of youth worldwide

Dr. George Still describes DMC syndrome in Lancet

Methylphenidate indicated for behavioral disorders in children

US Surgeon General: lack of resources a "public crisis in mental health"
CDC: ADHD a serious public health problem

Bradley: benzedrine helps hyperactive children

DSM II Hyperkinetic Reaction

ADHD symptoms described in medical literature as MBD

DSM IV revises criteria to include 3 subtypes of ADHD

FDA approves methylphenidate for depression and nacolepsy

DSM III-R re-emphasizes hyperactivity

DSM III ADD emphasizes attention

DMC **MBD** **HKR** **ADD ADHD**

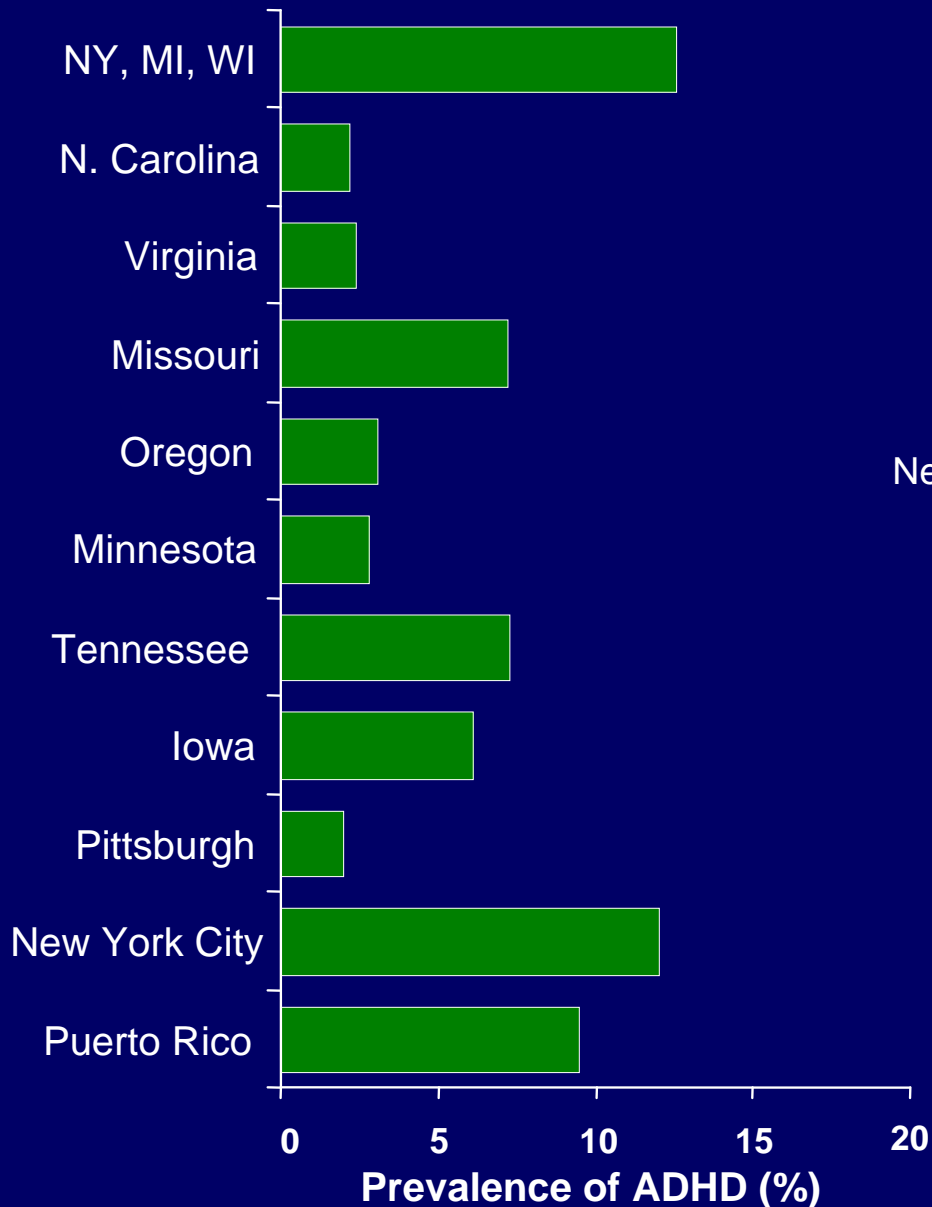**1900s 1910s 1920s 1930s 1940s 1950s 1960s 1970s 1980s 1990s 2000s**

Is ADHD an "American Disorder"?

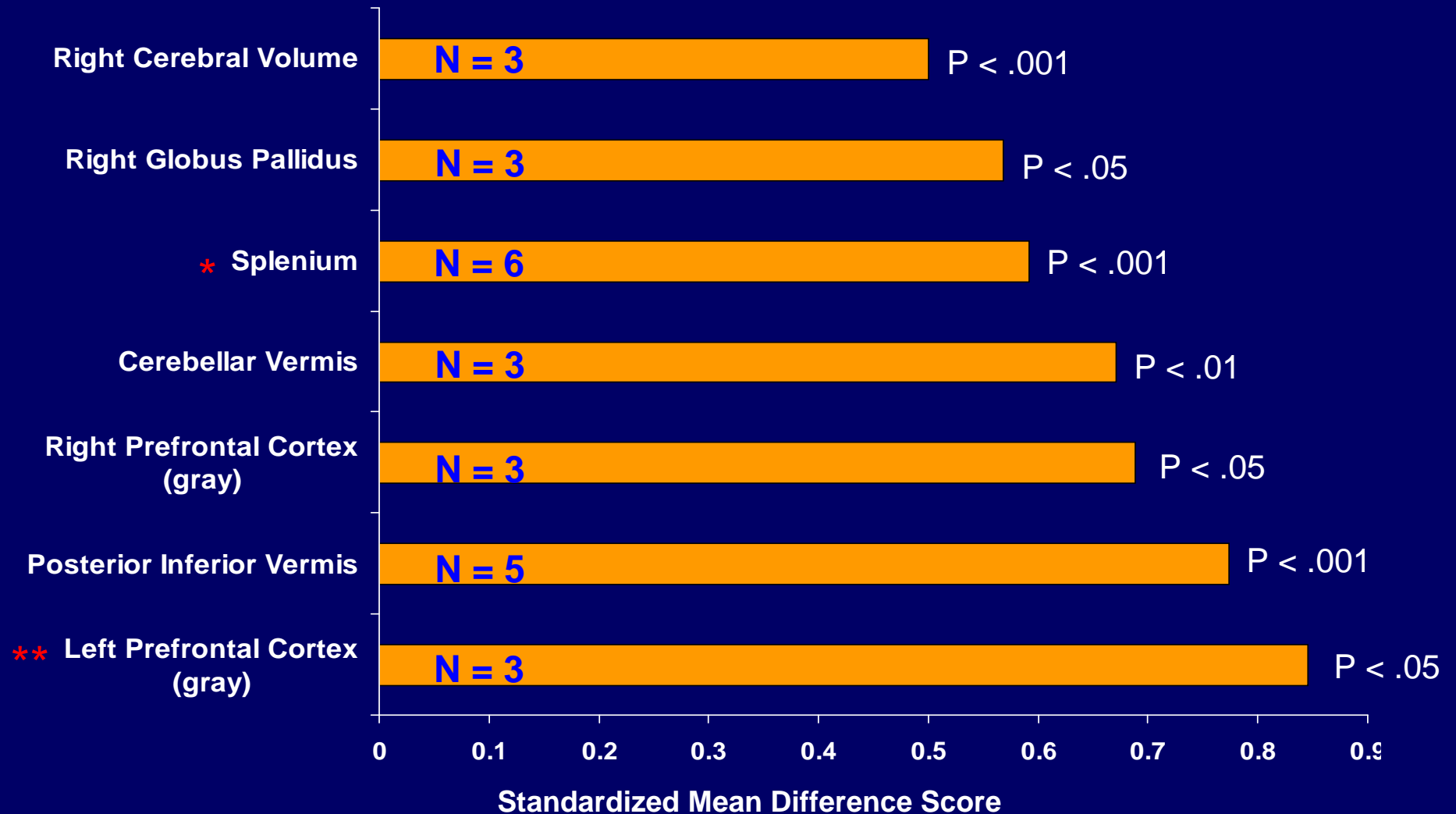**(Faraone et al., World Psychiatry, 2003)**

Concurrent Validity: Structural Neuroimaging
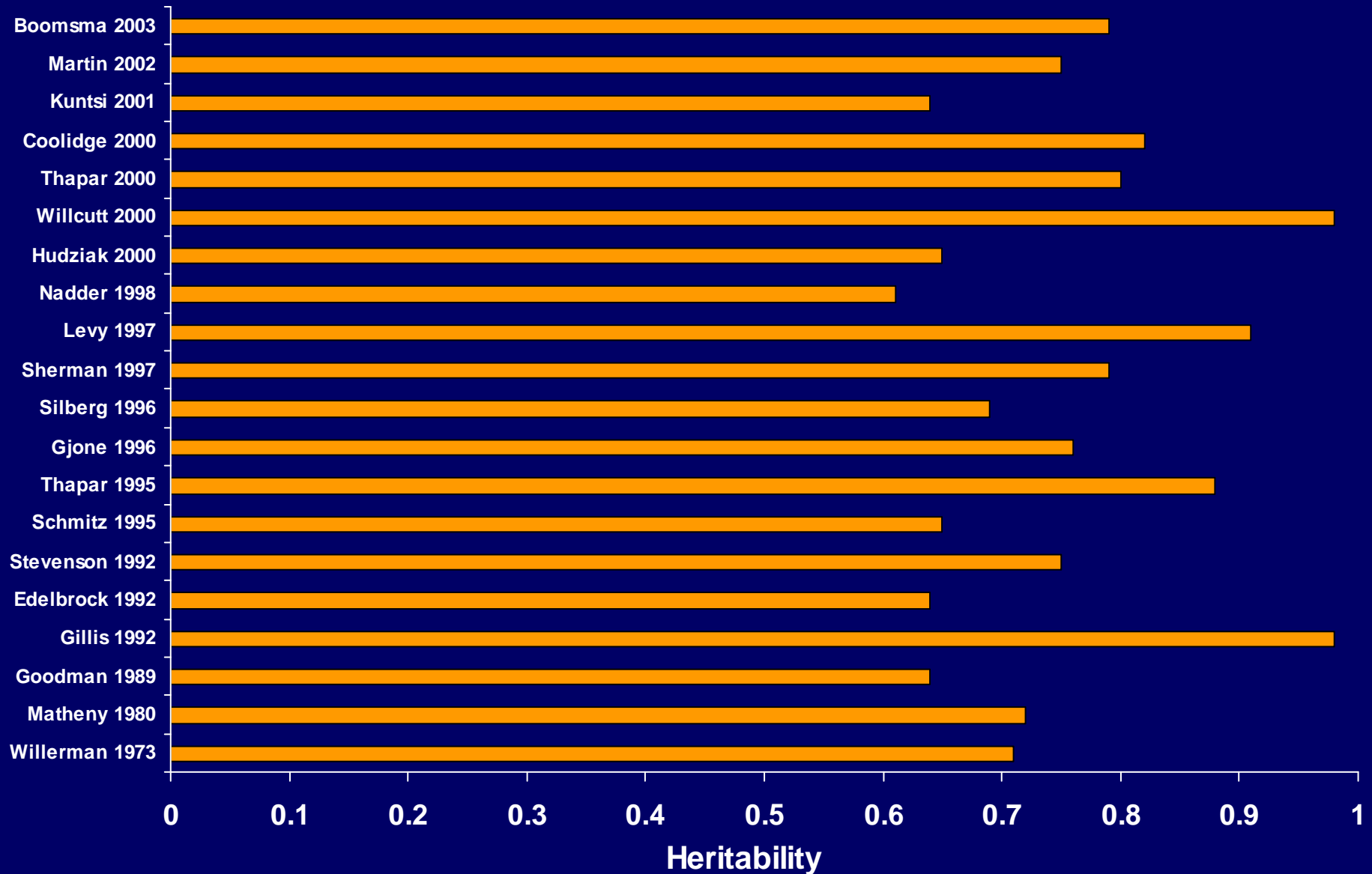**Brain Structures with Largest ADHD Effects**
(Valera, Faraone, et al., Biological Psychiatry, 2006)

Right Cerebral Volume — N = 3 — P < .001

Right Globus Pallidus — N = 3 — P < .05

* Splenium — N = 6 — P < .001

Cerebellar Vermis — N = 3 — P < .01

Right Prefrontal Cortex (gray) — N = 3 — P < .05

Posterior Inferior Vermis — N = 5 — P < .001

** Left Prefrontal Cortex (gray) — N = 3 — P < .05

0   0.1   0.2   0.3   0.4   0.5   0.6   0.7   0.8   0.9

Standardized Mean Difference Score

* Witelson and O'Kusky methods combined. Also significant with Witelson only (N = 4). ** Pub bias.

Adoption Study of ADHD
(Sprich et al.. *JAACAP* 2000)

Legend:
- Biologic
- Adoptive
- Control

Siblings

Parents

% ADHD in Relative

0 5 10 15 20 25 30 35
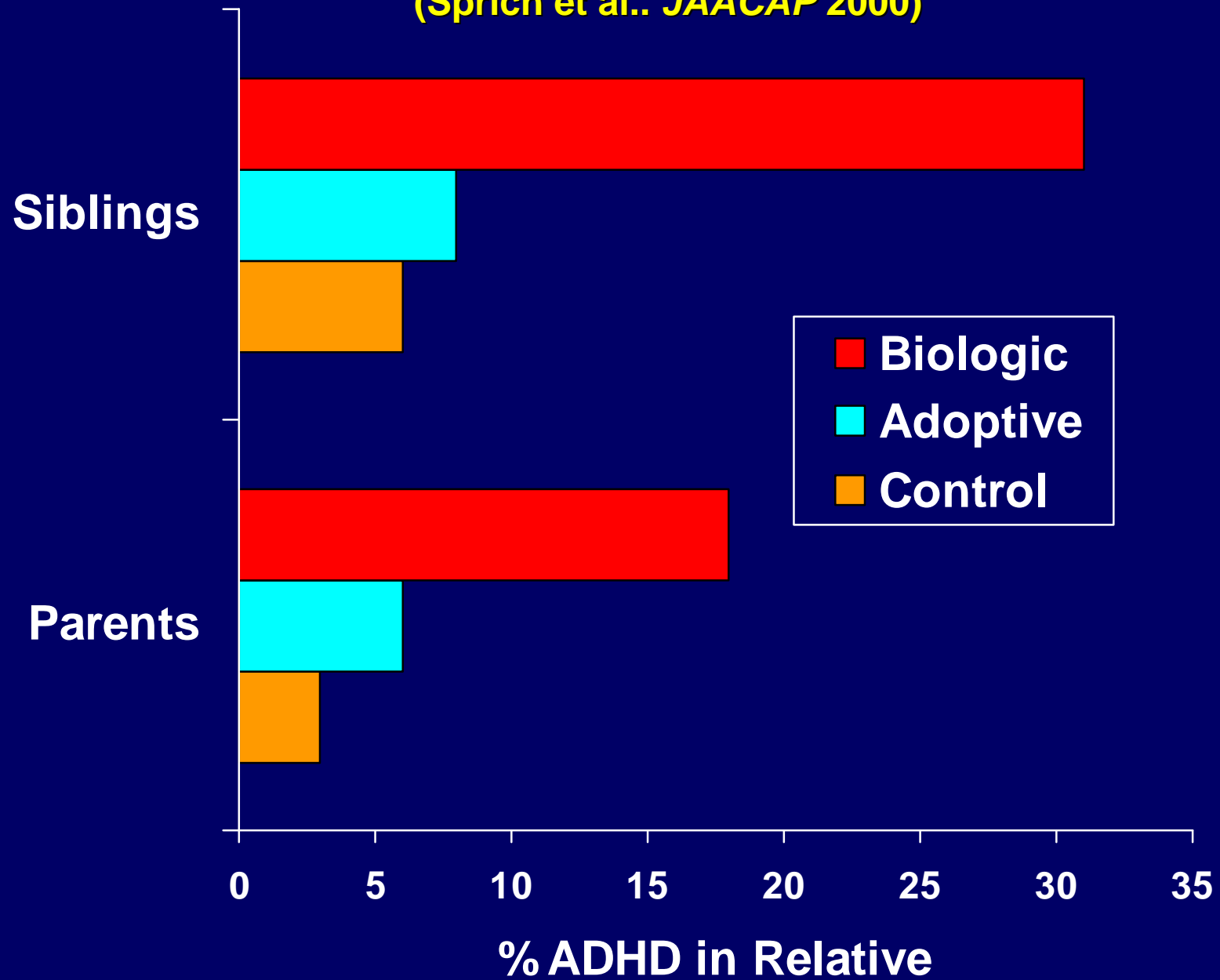
ADHD is a Genetically Complex Disorder
(Faraone et al., Biological Psychiatry, 2005)
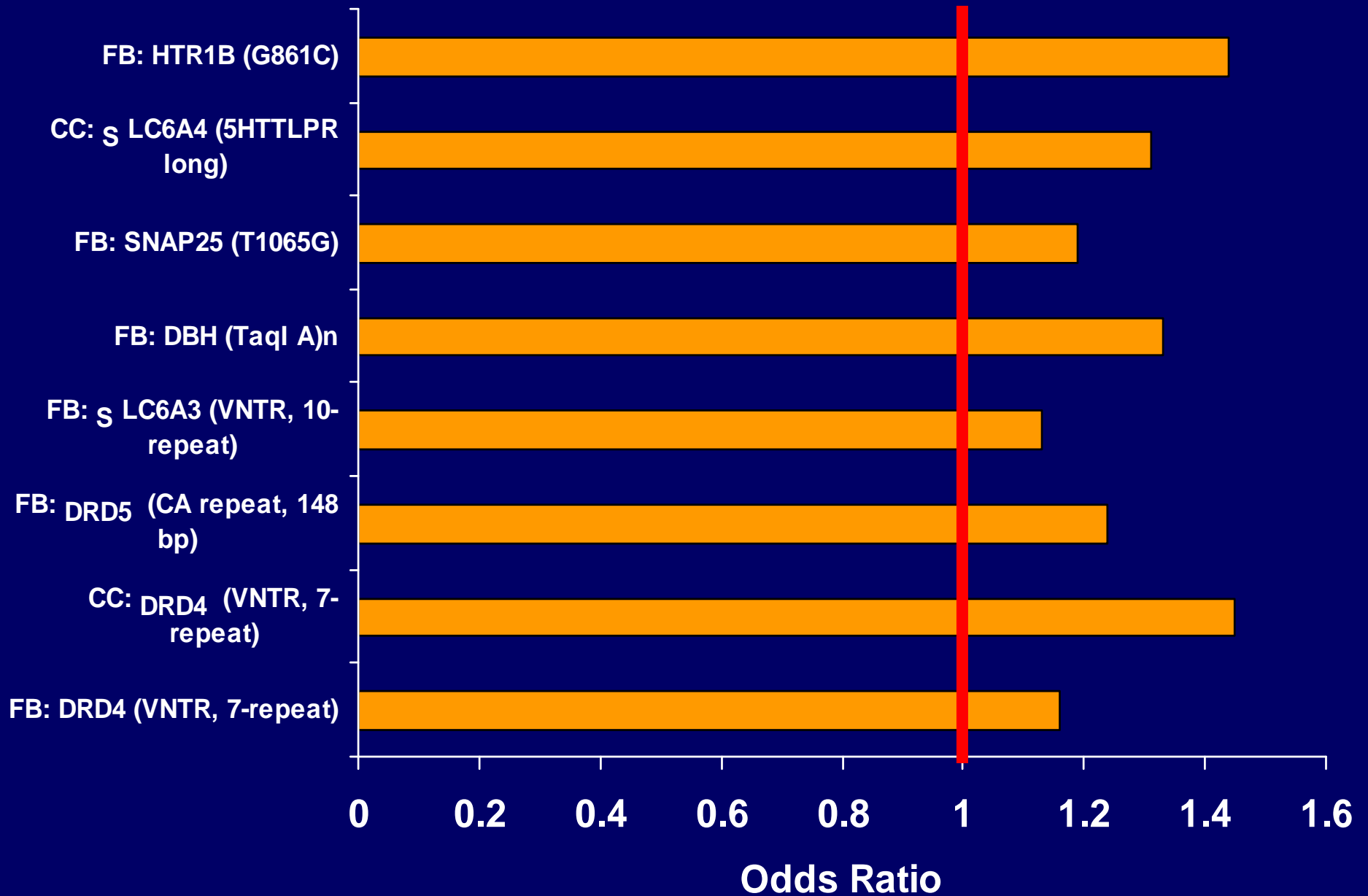
ADHD is an Environmentally Complex Disorder
(Banerjee, Middleton & Faraone, Acta Pediatrica, in press)

- **Pregnancy and Delivery Complications**
- **Exposure to Toxins**
  - **mercury, manganese, lead**
  - **polychlorinated bi-phenyls**
- **Fetal exposure to alcohol**
- **Fetal exposure to maternal smoking**
- **Chaotic family environments**
- **Low social class**

Overview of IMAGE Study
(Kuntsi et al., Beh Brain Functions, 2006)

- **Ascertain a Large Sample of Families Suitable for Quantitative Trait Mapping**
    - Families identified from proband diagnosed with DSM-IV Attention Deficit Hyperactivity Disorder, Combined type
    - Proband assessed clinically
- **Apply Quantitative Trait Linkage and Association Mapping to ADHD**
    - Probands and all siblings assessed with quantitative trait measures of ADHD
- **DNA collected from all family members and sent to Rutgers University Cell and DNA Repository**

ADHD as a Quantitative Trait

- **Quantitative measures of ADHD are highly heritable** (Faraone et al., Bio Psych, 2005)
- **Mathematical modeling of twin data suggest the diagnosis of ADHD is the extreme expression of a trait that varies quantitatively in the population** (Gjone etal. 2006; Levy et al., 1997)

Inclusion Criteria for Probands

- **European-Caucasian ethnicity**
- **Referred to ADHD specialty clinic**
- **Met criteria for DSM-IV combined type ADHD (lower prevalence ~3%)**
  - **6 of 9 symptoms of inattention**
  - **6 of 9 symptoms of hyperactivity-impulsivity**
- **Both parents and one or more sibling available for study**
- **No autism, epilepsy, IQ<70, brain disorder or genetic disorder known to mimic ADHD**

Why Study ADHD in Europe

- Existing network of ADHD investigators
- Prevalence and features of ADHD similar around the world
- Heritability of ADHD similar around the world
- No evidence of heterogeneity of candidate gene effect sizes across America, Europe, Brazil & China
- Assessment instruments had been translated

Assessment Measures

- **Probands diagnosis of ADHD by interview**
    - **Parental Account of Children's Symptoms**
    - **Designed for reliable cross-national studies**
- **Probands and Siblings measured for quantitative ADHD traits**
    - **Conners' Rating Scales-Revised**
    - **Strengths and Difficulties Questionnaire**
    - **Twin data: hierarchical factor model yields composite index with estimated heritability of 79%**
- **Parents not assessed**

Subjects with DNA and Clinical Data

- **Total Sample**
  - **1227 families with 6130 members**
  - **Mean of 5 members per family**
- **Families to be genotyped by GAIN program**
  - **GAIN decided to limit sample to trio families in which the DNA source for all family members was a blood sample. Buccal samples were eliminated**
  - **Final sample: 858 trio families**
- **With 5800 SNP linkage scan we may be able to reconstruct WGA genotypes in siblings (Abecasis, HapMap3 Meeting, 2006)**

Subtypes of ADHD
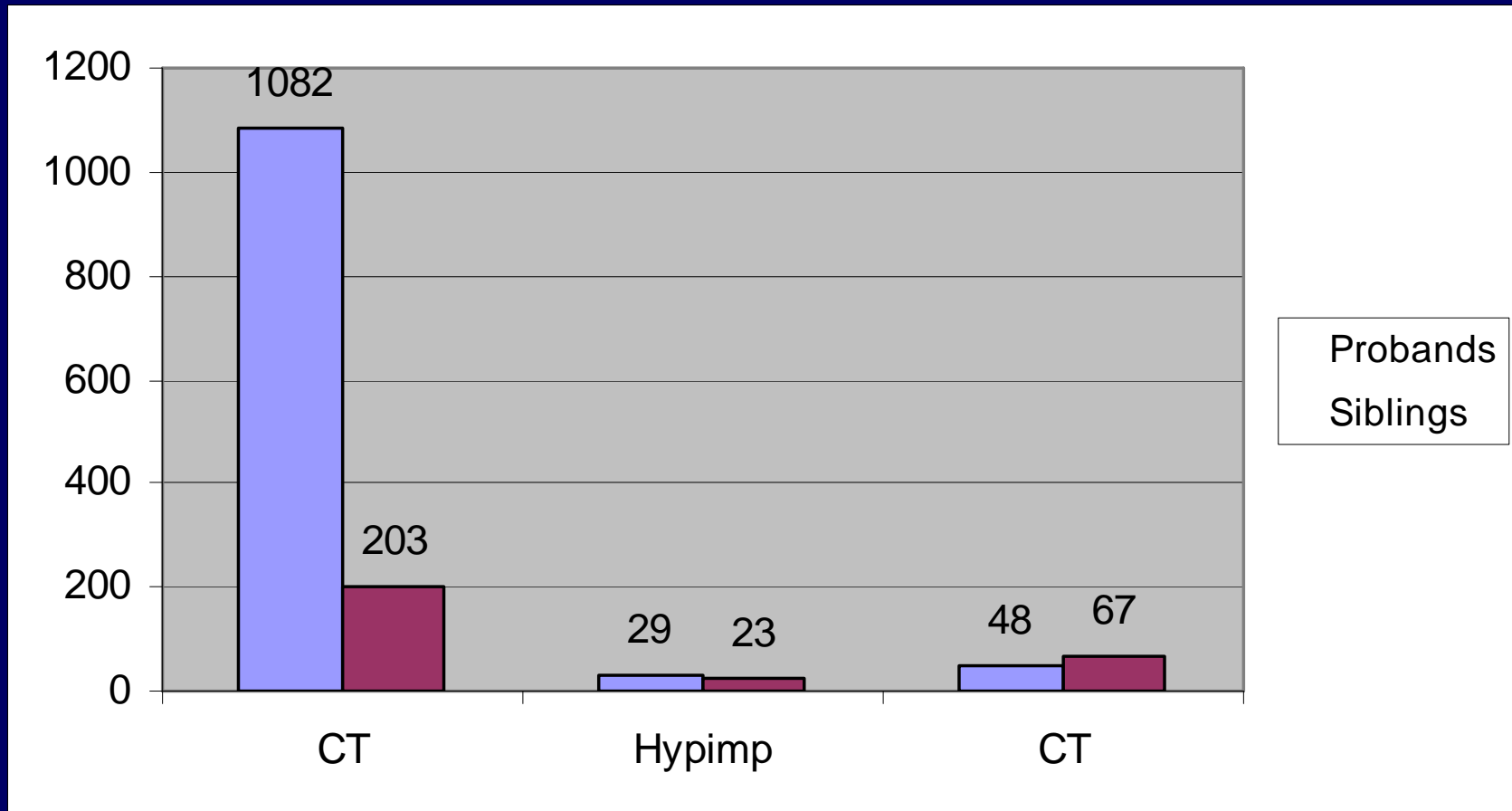
Co-morbidity by subtype for probands
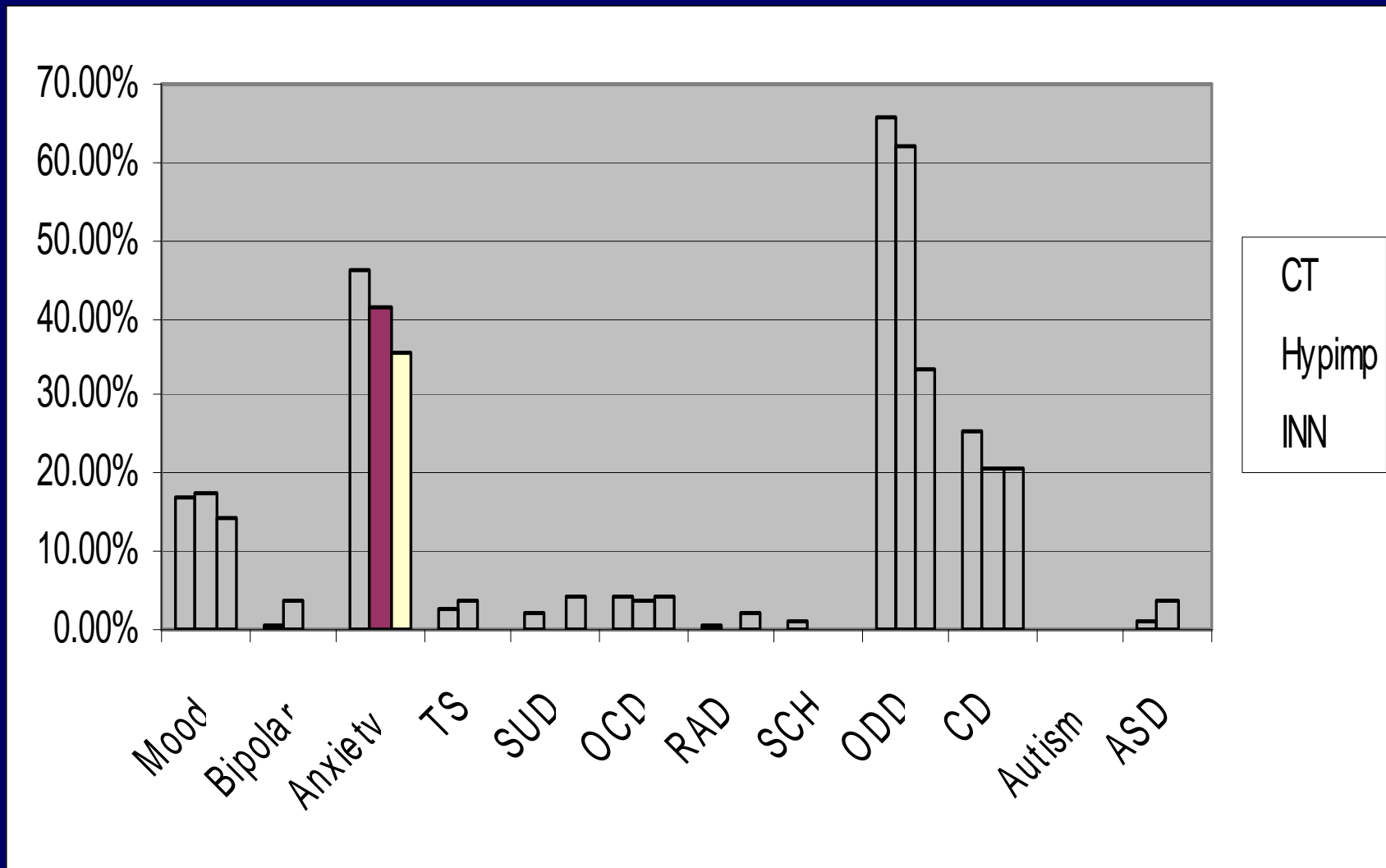
Main milestones for IMAGE sample

Candidate gene scan in stage I sample: April 2006

N=776 combined type probands

Affected sibling pair + QTL linkage analysis: December 2006

N=1,200 families

Whole genome association through GAIN initiative

Nominal and gene-wide significance levels

(Brookes et al, Molec Psychiat, 2006)

Gene	Nominal P-value	T	NT	OR	Global P-value	P_SUM Statistic
TPH2	0.003	207	151	1.37	0.036	0.106
ARRB2	0.004	103	66	1.56	0.022	0.209
DAT1	0.005	349	278	1.26	0.119	0.014
PNMT	0.008	70	42	1.67	0.012	0.024
SLC9A9	0.01	74	46	1.61	0.485	0.114
NET	0.012	133	95	1.4	0.349	0.786
ADRB2	0.013	210	162	1.3	0.088	0.485
HES1	0.016	300	244	1.23	0.076	0.096
ADRA1A	0.017	283	229	1.24	0.443	0.387
PER2	0.017	31	15	2.07	0.124	0.419
MAOA	0.02	175	134	1.31	0.082	—
SNAP25	0.035	155	120	1.29	0.529	0.198
DDC	0.039	161	126	1.28	0.537	0.597
FADS2	0.039	284	237	1.2	0.389	0.727
SYP	0.045	180	114	1.25	0.034	—
CHRNA4	0.05	116	88	1.32	0.503	0.663
HTR1E	0.051	75	53	1.42	0.509	0.214
DRD4	0.055	34	20	1.7	0.199	0.321

Replication dataset

Stage II (n = 383)						
			P value	T	NT	OR
TPH2	rs1843809	Intron 5	0.044	65	90	0.72
SLC9A9	rs9832471	5' to gene	0.03	29	15	1.93
SLC6A3	rs11564750	5' to gene	0.008	54	30	1.80
HTR1E	rs7751022	5'UTR/Intron	0.0004	36	12	3.00

| Stage I + II (n = 1,159)						
			P value	T	NT	OR
TPH2	rs1843809	Intron 5	0.2493	248	223	1.11
SLC9A9	rs9832471	5' to gene	0.001	103	61	1.69
SLC6A3	rs11564750	5' to gene	0.001	181	124	1.46
HTR1E	rs7751022	5'UTR/Intron	0.0005	111	65	1.71

The 10-3 haplotype is associated with ADHD in UK and Taiwanese populations

(Brookes et al., Arch Gen Psych, 2006)
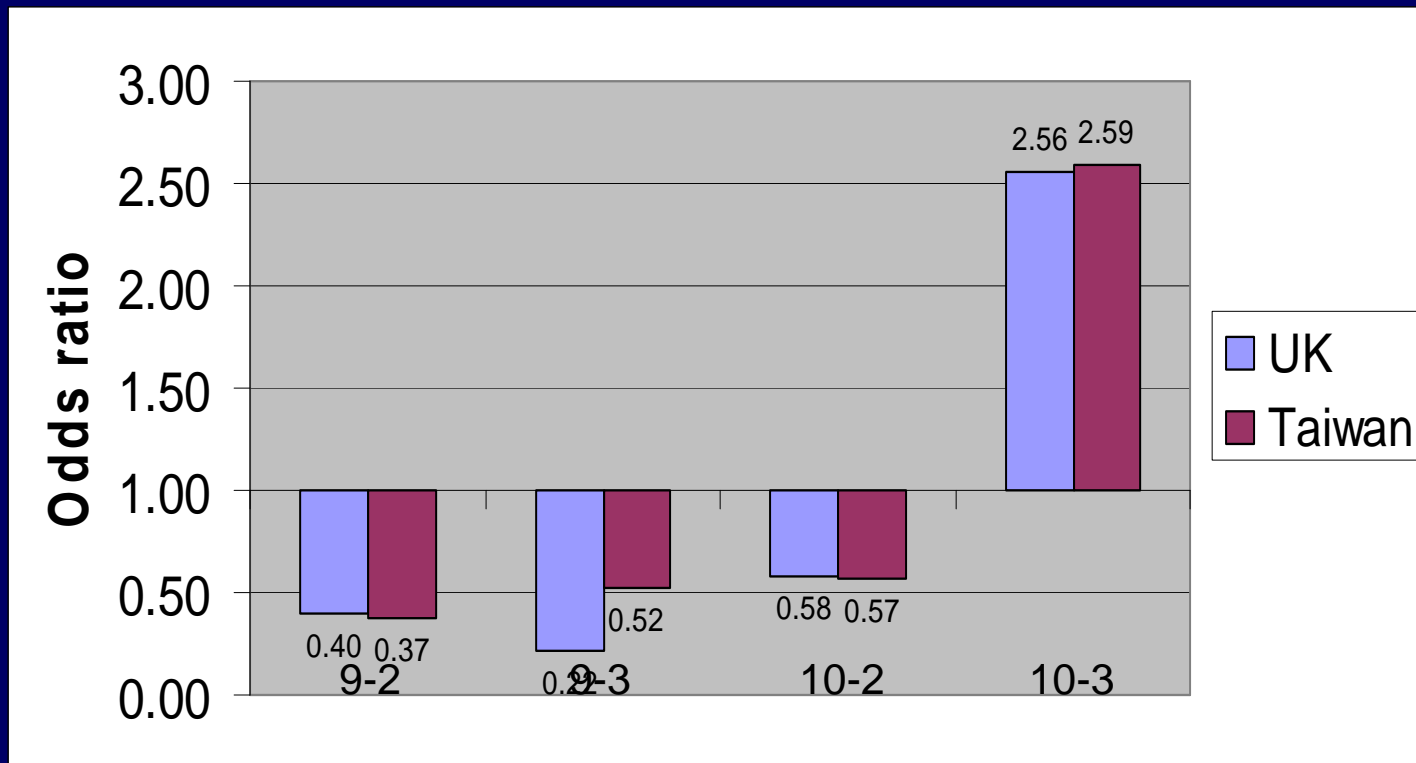
Stage I + II IMAGE sample: Replication of 10-3 haplotype association

(Asherson et al., Molec Psych, in press)
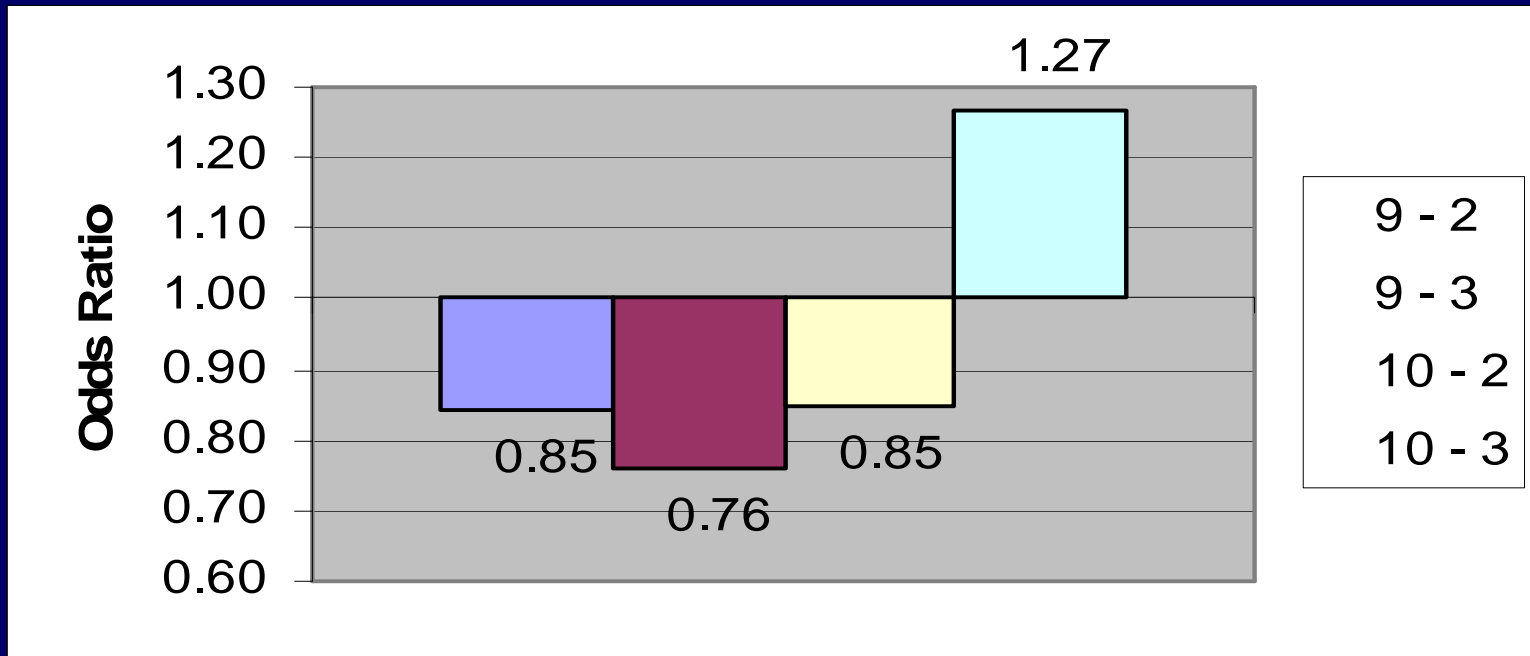
Global p = 0.02, haplotype specific p = 0.002

Restrictions on Data Use

- DNA and clinical data have been sent to NIMH data repositories, which govern their release and use
- Consent forms restrict use
  - for studies of ADHD & associated features
  - for researchers approved by NIMH
- Consents allow same access for academic and industry users

ADHD Samples Available Through the ADHD Molecular Genetics Network

- The ADHD MGN is an international group of researchers that has met yearly for 7 years thanks to an NIMH conference grant
- Among 31 laboratories having DNA and ADHD phenotype data, there are (excluding IMAGE data):
  - 2,300 sibling pair families
  - 4,060 additional nuclear families
  - 3,913 additional ADHD cases
  - 12,209 non-ADHD controls
  - 1,221 ADHD cases with methylphenidate response data