State of The Art

Pieter Hoekstra

Tourette syndrome:
an update on newest findings on treatment and pathophysiology

ESCAP
European Society for Child and Adolescent Psychiatry

17th International ESCAP Congress
TRANSITION Child and adolescent psychiatry in a world of change
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PSY & ASD

Gilles de la Tourette syndrome: an update

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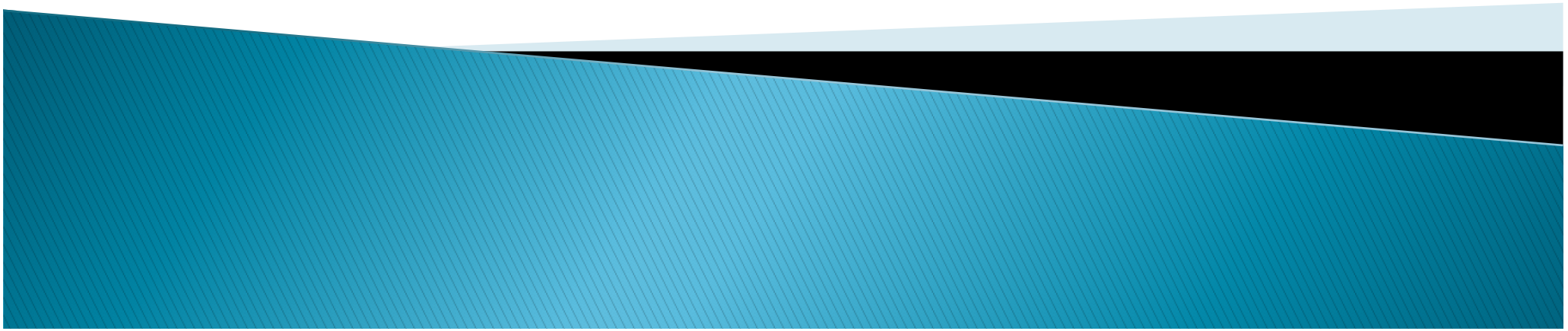


Take Home Messages

- Tourette syndrome is not a rare disorder
- In most cases tics are mild and not very pronounced
- Very often tics are associated with co-occurring problems
- Etiology is a complex interplay between genetics and environmental factors

- Behavioral therapy is treatment of first choice

Definition of tics

- Sudden,
- rapid,
- recurrent,
- nonrhytmic,
- **motor movements** or **vocalizations**

Examples of tics

	Simple	Complex
Motor	•Face, head, torso •Upper and lower extremities	•Touching •Squatting •Deep knee bends •Retracing steps •Twirling when walking
Vocal	•Clicks, grunts •Yelps, barks •Sniffs, snorts, coughs	•Words •Phrases •Only occasionally coprolalia

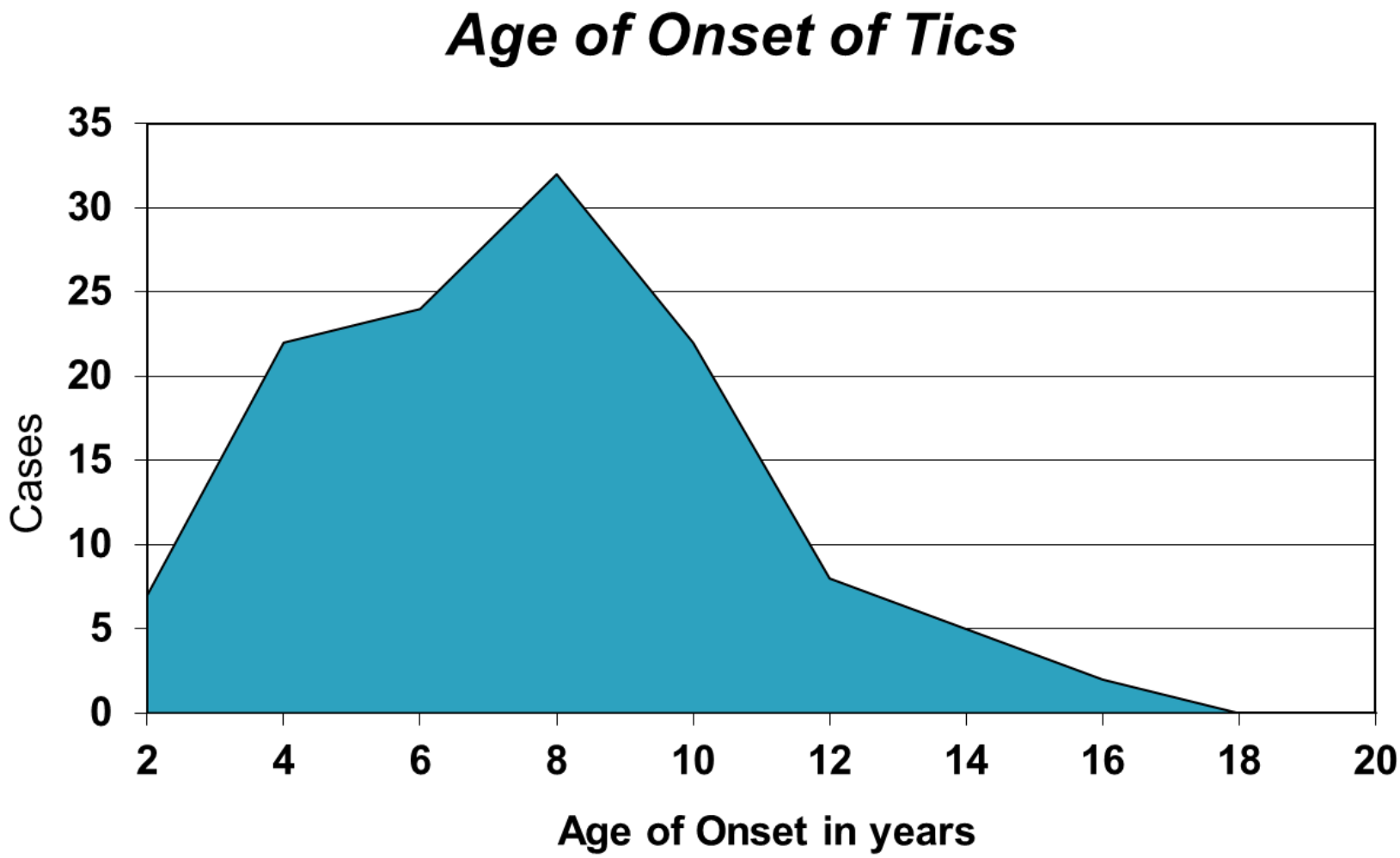
Developmental course of tics

Rostral → Caudal

Simple → Complex

Motor → Vocal

When do Tics Usually Start?



Leckman 2000

Clinical course

- Hyperactivity mostly precedes tics
- Head and neck tic start around age 6-7
- Vocal tics age 8-9
- OC symptoms 11-12
- Peak *tic* severity age 10-11
- Often decrease in adolescence
- Tics life long in 50% tot 60%

Hall marks of tics

- Premonitory urges
- Tics may often be suppressed for a while
- Tics are very context dependent
- Tics come and go

Tourette is not an exotic disorder

- Not rare
- Mostly not very severe
- Most have no coprolalia
- Tics are not necessarily seen in your office

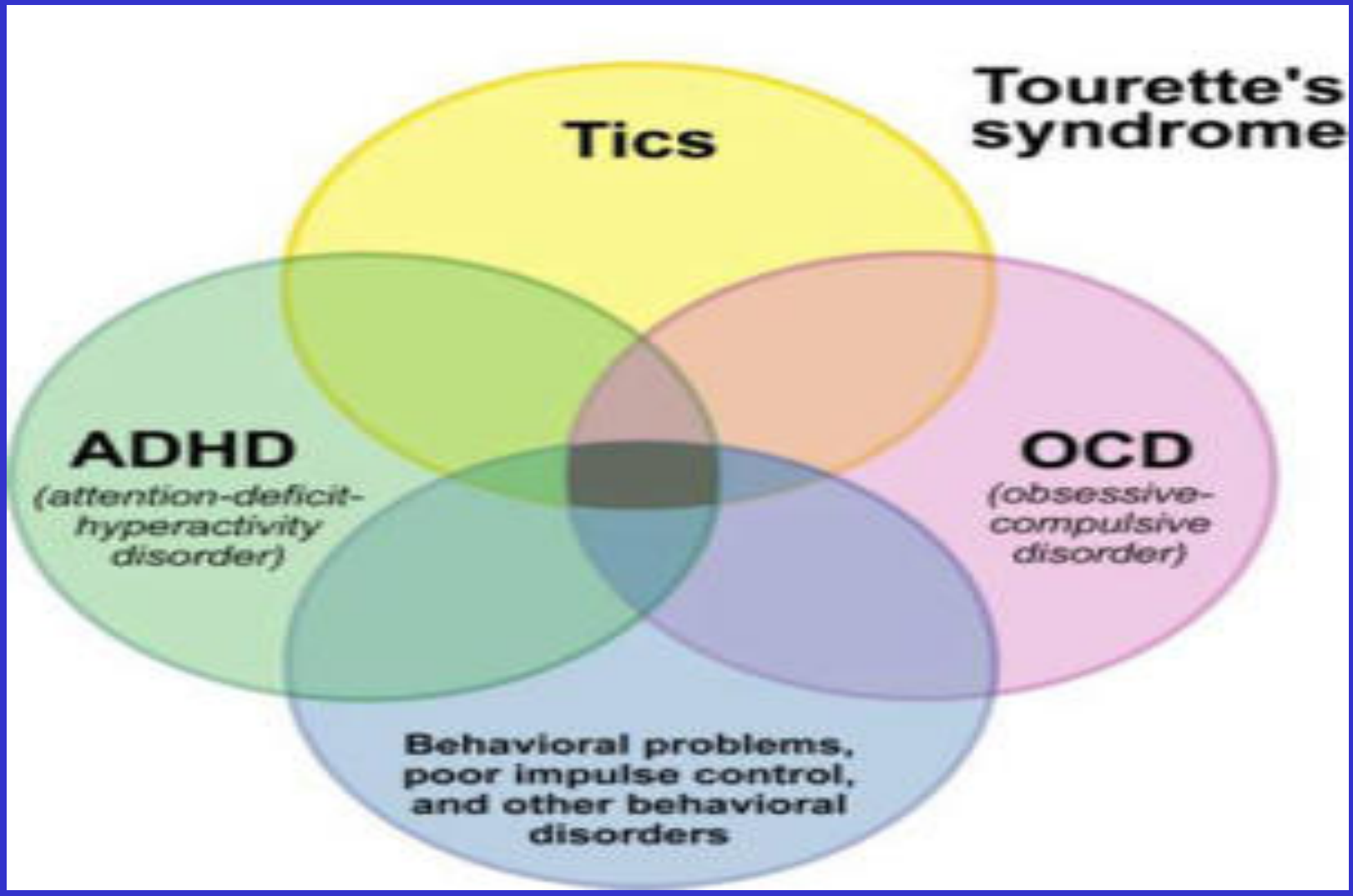
Epidemiology

- 10-20% of children show transient tics
- 1% of all children have Tourette syndrome
- Male > Female (3-to-10 times)
- Prevalence in adults is lower

Frequently associated disorders

- ADHD
- Obsessions / compulsions
- Academic difficulties
- Behavior disorders
- Mood disorders
- Anxiety
- Social problems (incl ASD)

Comorbidity



Nature of compulsions in Tourette Syndrome

- More urge driven than in response to anxious thoughts (checking, cleaning etc less frequent)
- Content: symmetry, aggression, sexual themes, touching, counting
- Earlier onset than in typical OCD
- Male preponderance

Causes

- Genetic factors play major role

- GWAS
- Multiplex pedigrees
- Simplex trio’s: de novo mutations

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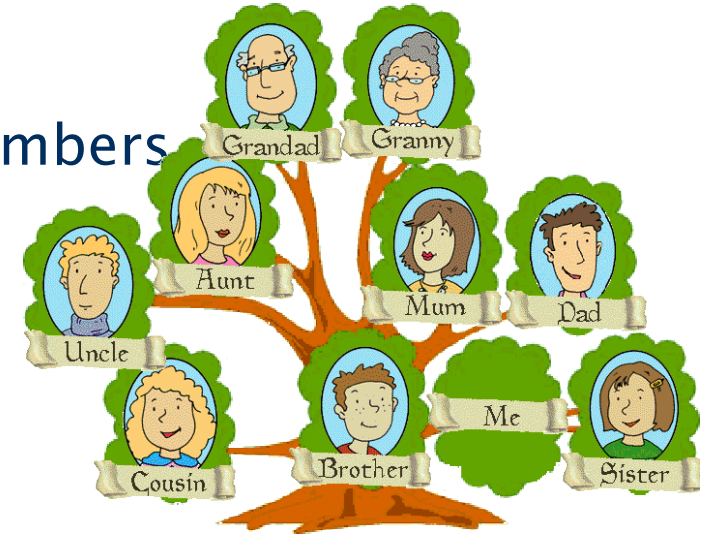
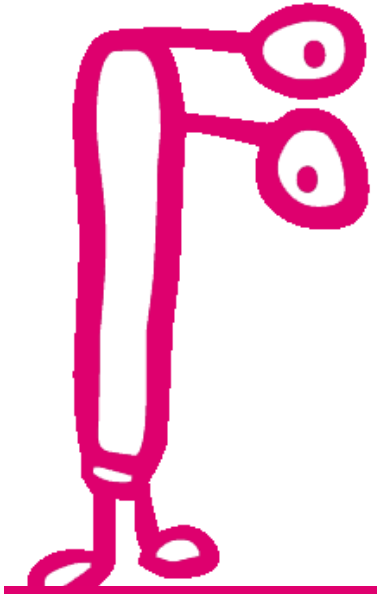
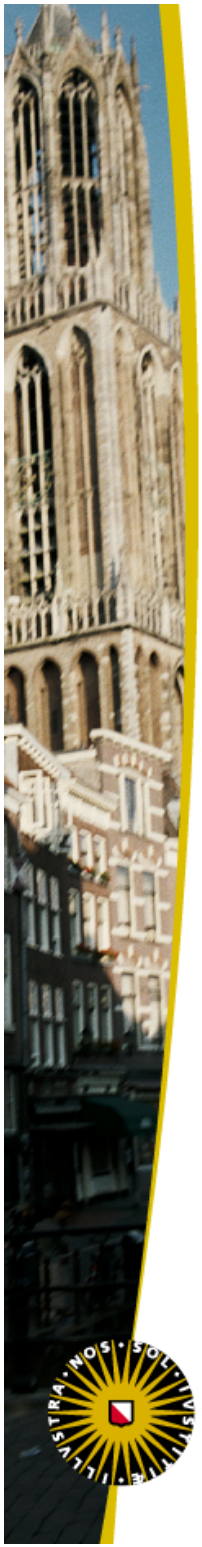
HOW DO WE KNOW THAT TICS ARE GENETICALLY BASED?

- Large scale family studies:
  - Increased risk in family members of affected individuals





- Twin studies:
  - MZ: share 100% van DNA
  - DZ: share 50% DNA
  - Larger concordance in MZ



Tourette twin studies

Price et al. 1985, 45 twin pairs

- MZ: 77% concordant for tics,
  54% concordant
  for Tourette

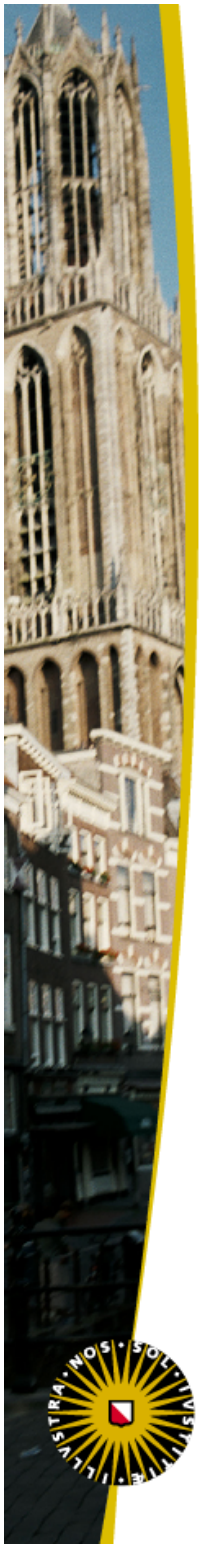
- DZ: 23% concordant for tics
  8% concordant for
  Tourette

GWAS

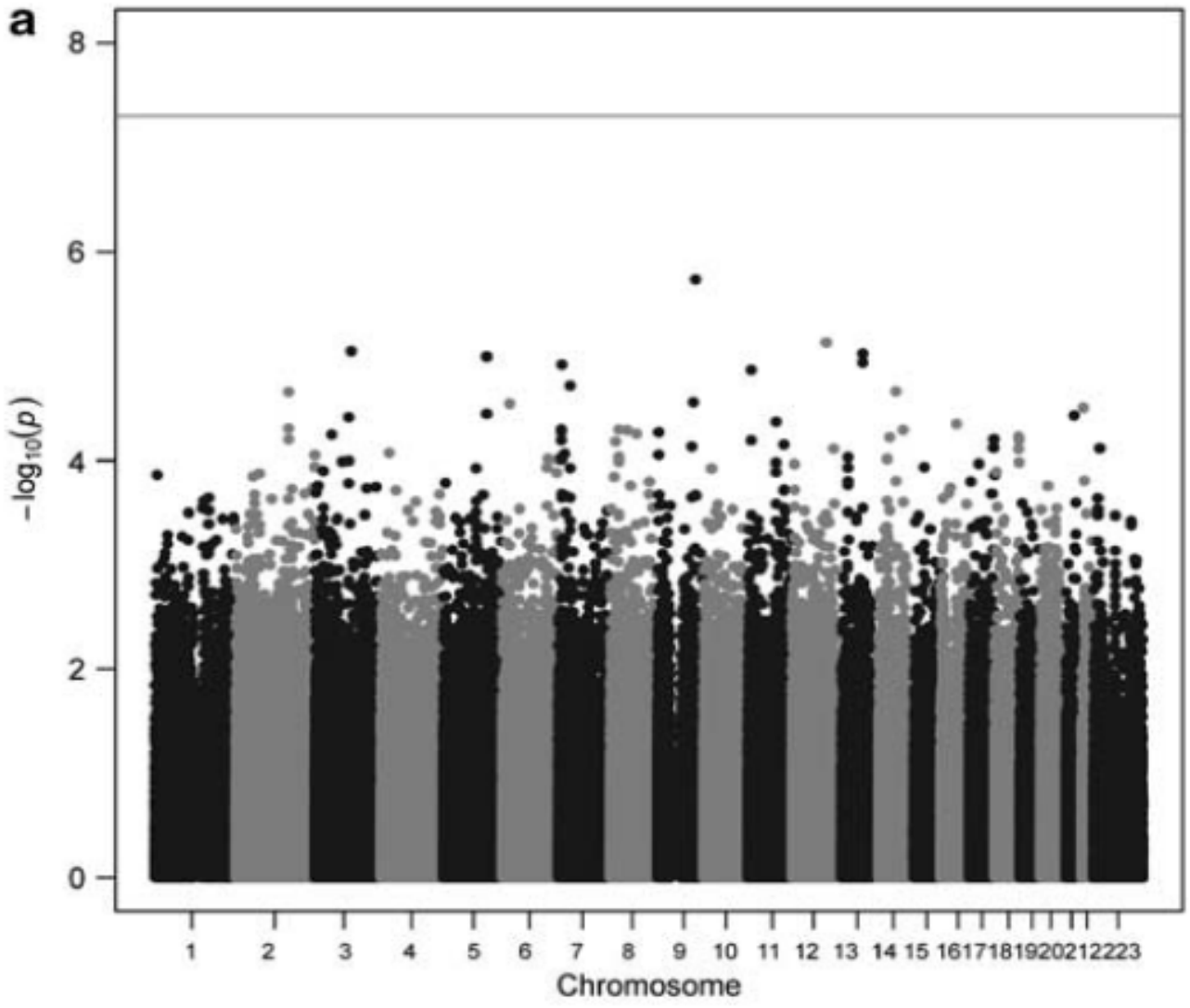
- A test of the association between markers, called single-nucleotide polymorphisms (SNPs), across the genome and disease.

- Hypothesis free approach
  - there is no existing hypothesis about a particular gene or locus

- Common disease common variant (CDCV) assumption
  - common disease are attributable in part to allelic variants present in more than 5% of the population

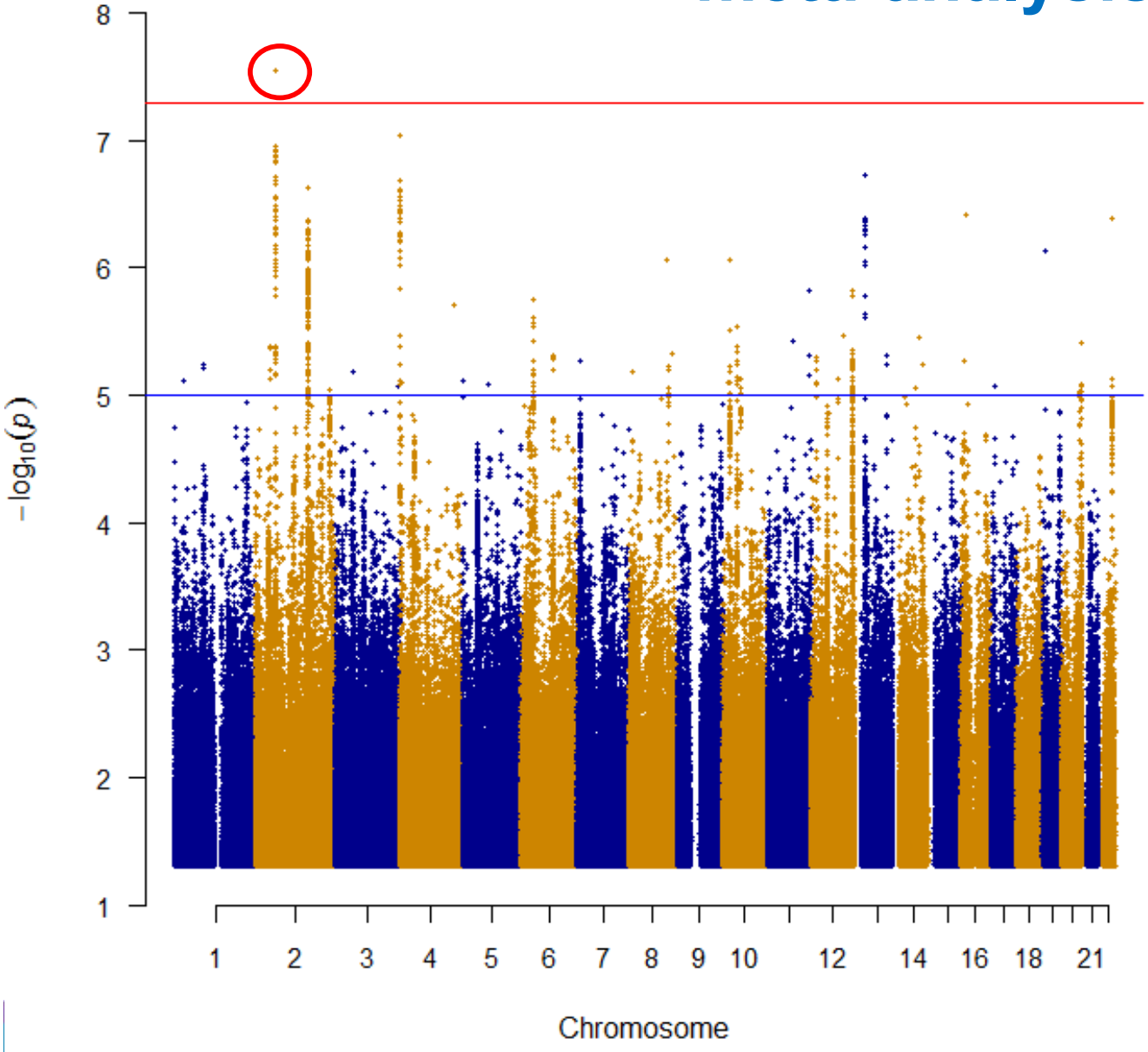


The first GWAS
n=1285 Tourette, n=4964 controls

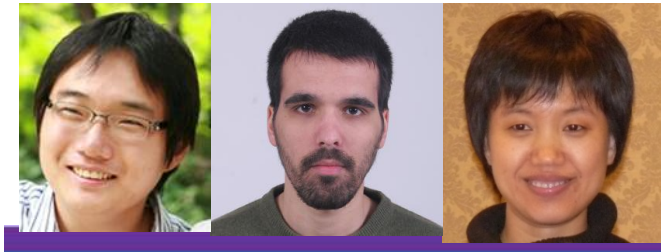


Universite

Manhattan plot for TS GWAS1 & GWAS2 meta-analysis



4231 cases
8282 controls
λ_{1000} **= 1.011**

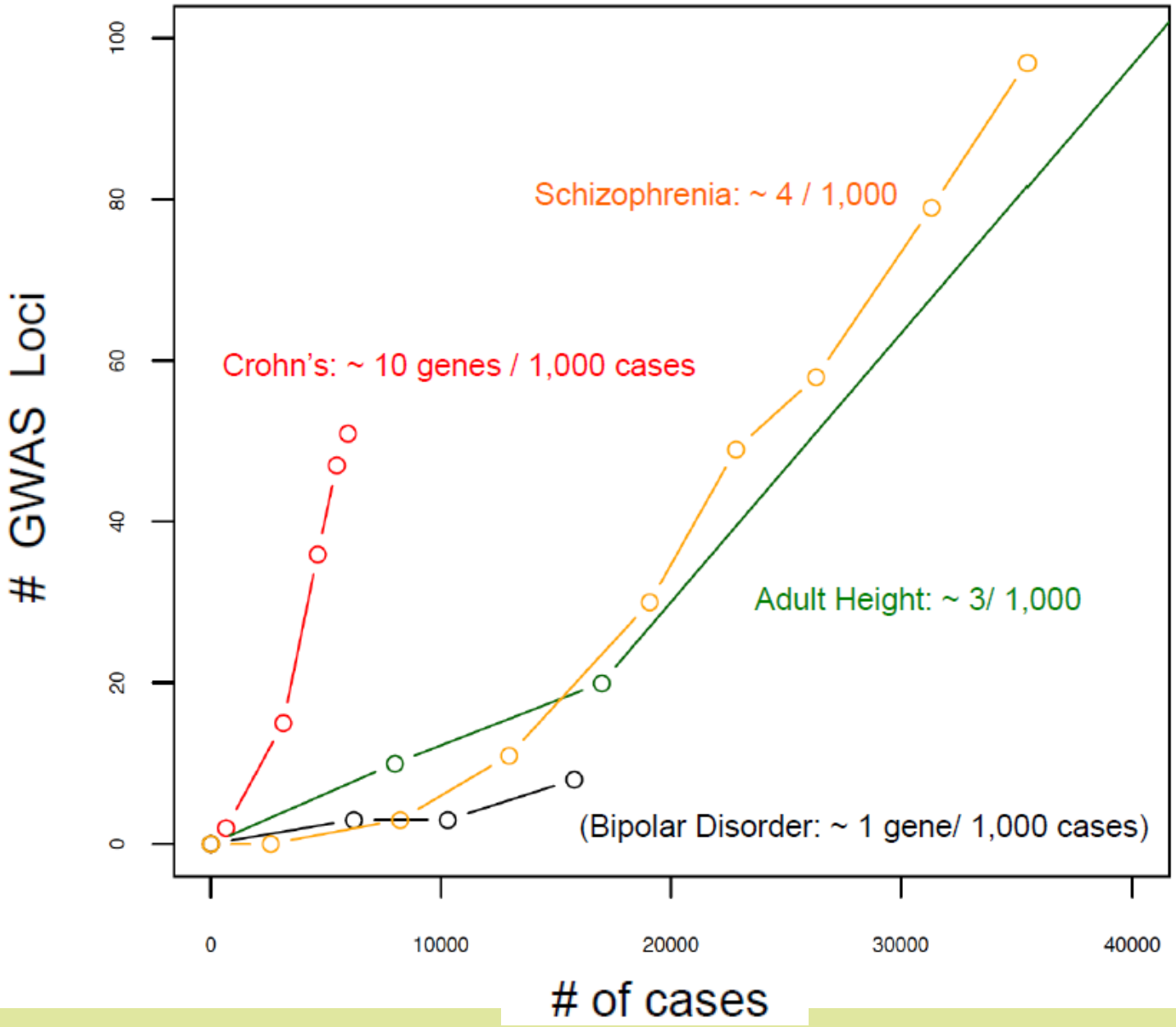


Jae Hoon Sul Fotis Tsetsos Dongmei Yu

Limitations of GWAS

- Needs large effect size
- Explains only small proportion of heritability
- Focus on common variants: common disease common variants

EMTICS
European Multicentre Tics Study



The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278367

Samenvatting GCTA results GTS & OCD Lea Davis 2013

-Common variants explains only ***21%*** of Tourette heritability

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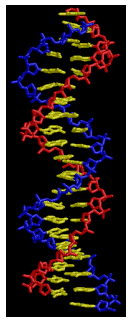
Alternative Assumption

- Common disease rare variants (CDRV)
  - For complex diseases there is extreme genetic heterogeneity and the disease may be caused by multiple rare variants
- Rare variants: allele frequency <1%
- Rare variants contribute to phenotypic expression in conjunction with, or over and above common variants.

Two examples that illustrate rare variants & heterogeneity

- Gene identified in a multiply affected pedigree

- De novo variants (present in child but not in parents)



L-Histidine Decarboxylase and Tourette's Syndrome

A. Gulhan Ercan-Sencicek, Ph.D., Althea A. Stillman, Ph.D., Ananda K. Ghosh, Ph.D., Kaya Bilguvar, M.D., Brian J. O'Roak, Ph.D., Christopher E. Mason, Ph.D., Thomas Abbott, Abha Gupta, M.D., Ph.D., Robert A. King, M.D., David L. Pauls, Ph.D., Jay A. Tischfield, Ph.D., Gary A. Heiman, Ph.D., Harvey S. Singer, M.D., Donald L. Gilbert, M.D., Pieter J. Hoekstra, M.D., Ph.D., Thomas M. Morgan, M.D., Erin Loring, M.S., Katsuhito Yasuno, Ph.D., Thomas Fernandez, M.D., Stephan Sanders, M.D., Angeliki Louvi, Ph.D., Judy H. Cho, M.D., Shrikant Mane, Ph.D., Christopher M. Colangelo, Ph.D., Thomas Biederer, Ph.D., Richard P. Lifton, M.D., Ph.D., Murat Gunel, M.D., and Matthew W. State, M.D., Ph.D.

N Engl J Med 2010;362:1901-8.

SUMMARY

Tourette's syndrome is a common developmental neuropsychiatric disorder characterized by chronic motor and vocal tics. Despite a strong genetic contribution, inheritance is complex, and risk alleles have proven difficult to identify. Here, we describe an analysis of linkage in a two-generation pedigree leading to the identification of a rare functional mutation in the *HDC* gene encoding L-histidine decarboxylase, the rate-limiting enzyme in histamine biosynthesis. Our findings, together with previously published data from model systems, point to a role for histaminergic neurotransmission in the mechanism and modulation of Tourette's syndrome and tics.

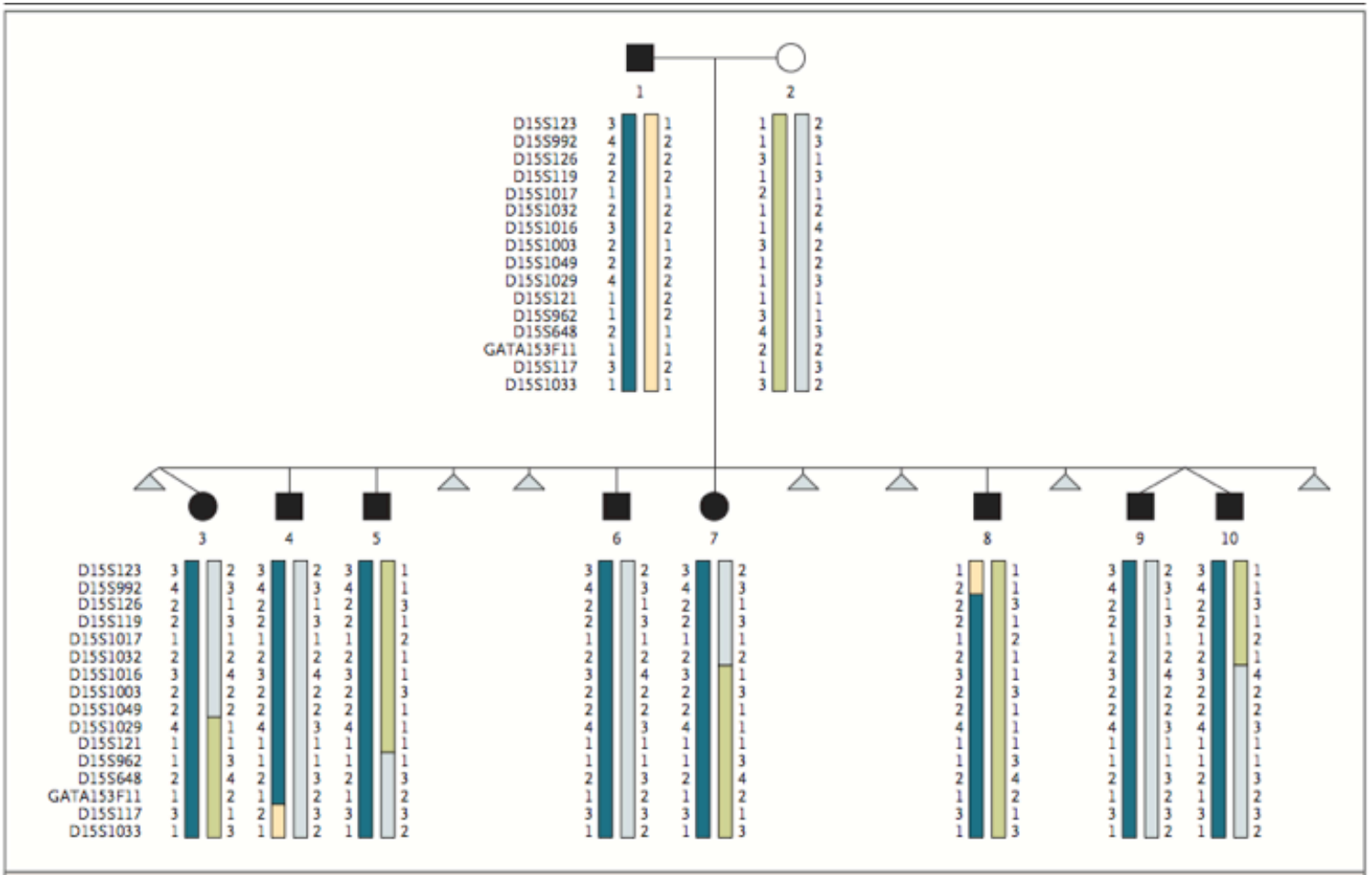
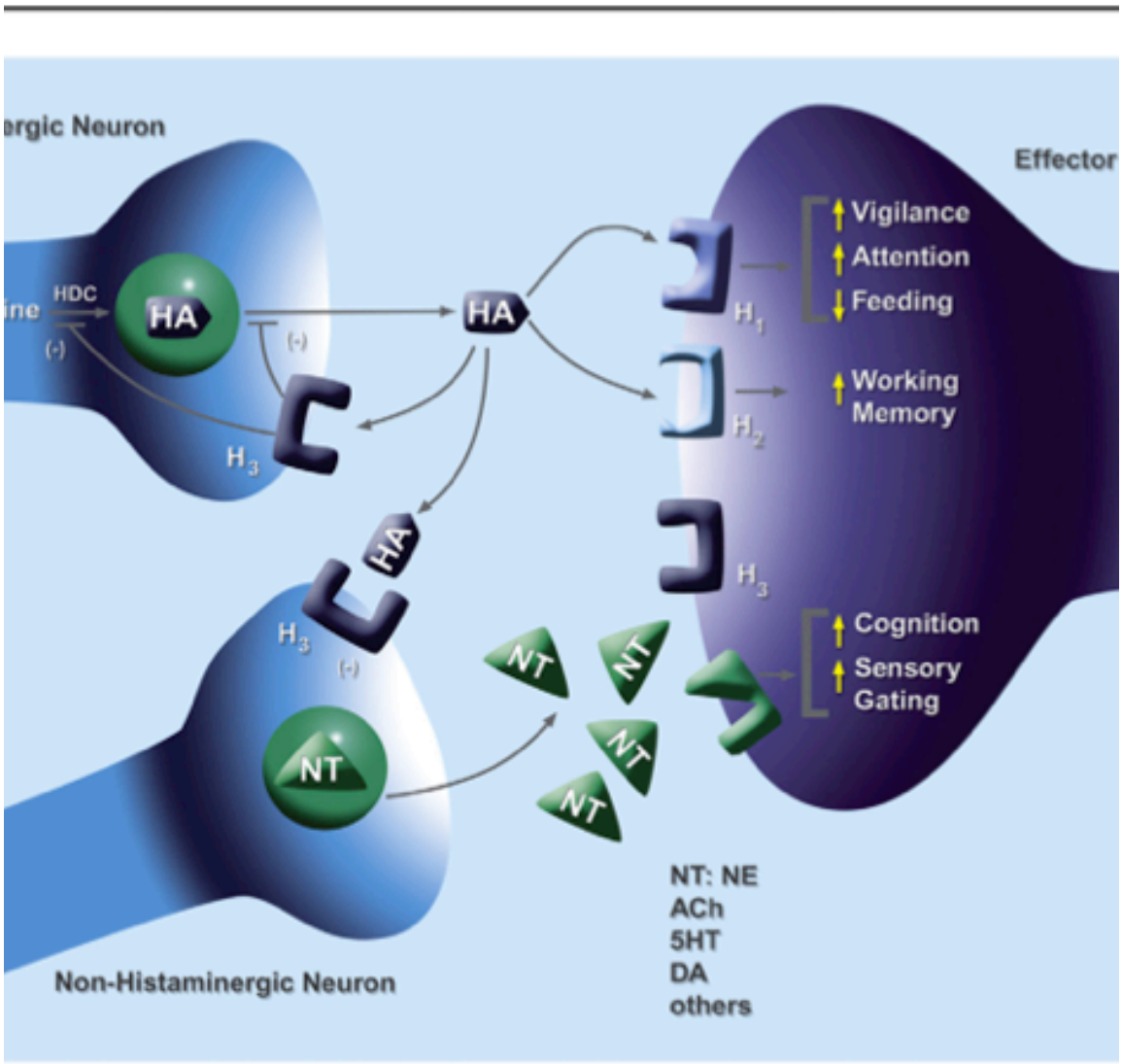


Figure 1. The Two-Generation Pedigree and Results of Haplotype Analysis.

Squares indicate male family members; circles, female family members; solid symbols, persons with Tourette's syndrome; the open circle, the unaffected mother; and gray triangles, miscarriages. The haplotypes illustrated below the pedigree symbols correspond to the 8.13-Mb segment that cosegregates with Tourette's syndrome at 15q21.1–15q21.3. The short-tandem-repeat markers used to confirm linkage are listed to the left, with the corresponding genotypes at these markers represented as numerals 1 through 4 for each chromosome of each proband. The haplotype that segregates with Tourette's syndrome is indicated by the dark blue bar and is bounded by markers D15S126 and GATA153F11. Detailed clinical information is presented in the Supplementary Appendix.

- Histamine receptors are highly expressed in regions implicated in TS
- Neuromodulator that is counter-regulating DA activity
- Mice with decreased histamine (including HDC KO) have increased sensitization and stereotypic behaviors



nsmitter; NE: norepinephrine; HA: histamine; ACh: acetylcholine; 5HT: serotonin; DA: dopamine;

De Novo Coding Variants Are Strongly Associated with Tourette Disorder

A. Jeremy Willsey,[1,2,12] Thomas V. Fernandez,[3,12] Dongmei Yu,[4,5,13] Robert A. King,[3,13] Andrea Dietrich,[6,13] Jinchuan Xing,[7,13] Stephan J. Sanders,[1] Jeffrey D. Mandell,[1,2] Alden Y. Huang,[8,9] Petra Richer,[3,10] Louw Smith,[1] Shan Dong,[1] Kaitlin E. Samocha,[4,5] Tourette International Collaborative Genetics (TIC Genetics), Tourette Syndrome Association International Consortium for Genetics (TSAICG), Benjamin M. Neale,[4,5] Giovanni Coppola,[8,9] Carol A. Mathews,[11,14] Jay A. Tischfield,[7,14] Jeremiah M. Scharf,[4,5,14,*] Matthew W. State,[1,14,15,*] and Gary A. Heiman[7,14,*]

[1]Department of Psychiatry, UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco,

- Study of parent child trios
- In 12% of cases have ***de novo*** mutations been found
- Four new Tourette genes discovered
- In total there must be appr. 400 Tourette genes

Wat does this mean?

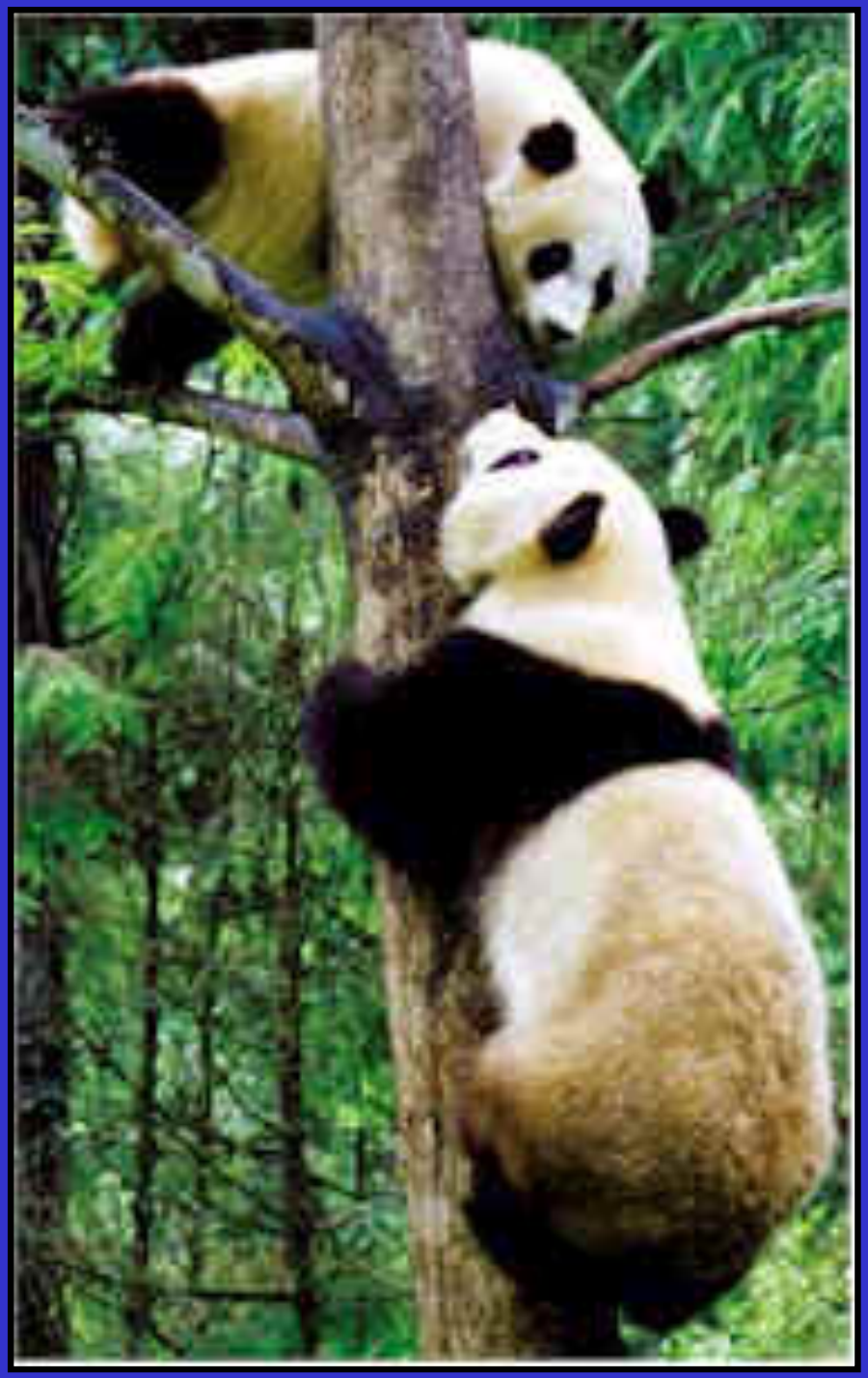
- Once it seemed simple with one major gene
- Tourette is genetically based, but not always hereditary
- There are many different genetic pathways leading to Tourette
- Perhaps Tourette is not one disorder?
- Does genetic heterigeneity reflect clinical heterogeneity?
- Should group studies be discarded?

EUNetGTS
tourette-eu.org

It's not only genes that matter...

- Concordance rates monozygotic twin pairs 53-56% for TS and 77-94% for any tic disorder in co-twins[1,2]
- Several environmental factors implicated in TS:
  - hormonal factors
  - psychosocial stress
  - infections
- Most evidence for prenatal and perinatal adverse events:
  - Pregnancy adversities
  - Labor/delivery complications
  - Neonatal complications.
- Leckman et al (1987): in all seven pairs of discordant monozygotic twins, the co-twins with TS had lower birth weights than the unaffected co-twins

Is PANDAS a valid diagnosis?



Pediatric

Autoimmune

Neuropsychiatric

Disorders

Associated with

Streptococcal infections

PANDAS

5 identifying criteria

*developed for **research by clinical observation***

1. Dramatic emergence or exacerbation of OCD and/or tics
2. Pre-pubertal symptom onset
3. Other neurological signs
4. Association with GABHS
5. Episodic or sawtooth symptom course

Involvement of Autoimunity?

- Model: Sydenham's chorea
- Auto-antibodies due to molecular mimicry between streptococci and brain tissue
- Subsequent infections may lead to symptom exacerbations

Where do we stand?

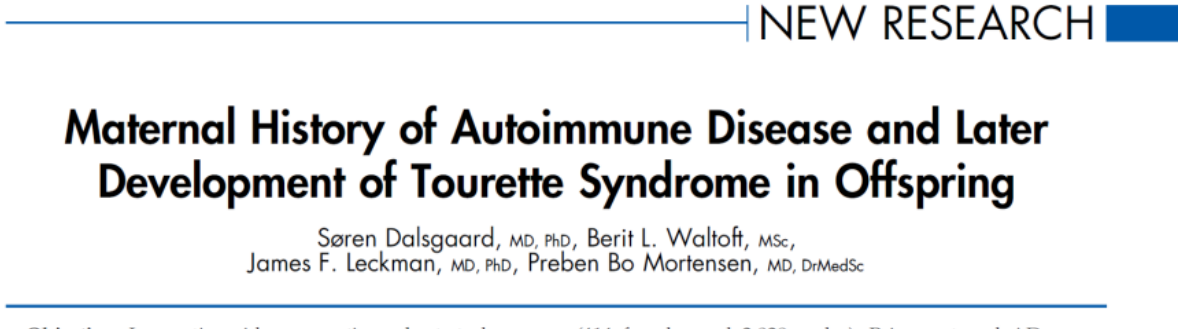
EMTICS
European Multicentre Tics Study

- No direct evidence!
  - But some antibody work
- Indirect evidence from animal models
  - Based on injection of autoantibodies.
  - Based on immunization with microbial immunogen or mimics.
- Circumstantial evidence
  - Association with infections & allergies?
  - Other autoimmune diseases in family?
  - Therapeutic effect of plasma exchange, IVIG, antibiotics?

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 278367

Circumstantial evidence from family history of autoimmunity

EMTICS
European Multicentre Tics Study


NEW RESEARCH

Maternal History of Autoimmune Disease and Later Development of Tourette Syndrome in Offspring

Søren Dalsgaard, MD, PhD, Berit L. Waltoft, MSc,
James F. Leckman, MD, PhD, Preben Bo Mortensen, MD, DrMedSc

Data from national Danish health registers identified a cohort consisting of all children born in Denmark between 1990 and 2007 (n = 1,116,255), followed prospectively from birth until 2011

Maternal AD was associated with a 29% increased incidence rate of TS in male offspring, 110/2442 (4.5%)

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 278367

Cirumstantial evidence from link with infections

EMTICS
European Multicentre Tics Study

- Cross-sectional single time point design: markedly increased serum levels of antistreptococcal antibodies

(Muller et al., 2000; Muller et al. , 2001; Cardona et al., 2001; Church et al. 2003; Creti, 2004; Morer et al., 2005)

- Levels of antistreptococcal antibodies correlate with tic severity

(Cardona et al., 2001)

- Treatment with antibiotics may decrease neuropsychiatric symptoms

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 278367

Negative Studies

EMTICS
European Multicentre Tics Study

Streptococcal Infection and Exacerbations of Childhood Tics and Obsessive-Compulsive Symptoms: A Prospective Blinded Cohort Study

Roger Kurlan, MD[a], Dwight Johnson, BS[b], Edward L. Kaplan, MD[b], and the Tourette Syndrome Study Group

Streptococcal Upper Respiratory Tract Infections and Exacerbations of Tic and Obsessive-Compulsive Symptoms: A Prospective Longitudinal Study

James F. Leckman, M.D., Robert A. King, M.D., Donald L. Gilbert, M.D., Barbara J. Coffey, M.D., M.S., Harvey S. Singer, M.D., Leon S. Dure IV, M.D., Heidi Grantz, M.S.W., Liliya Katsovich, M.B.A., Haiqun Lin, M.D., Ph.D., Paul J. Lombroso, M.D., Ivana Kawikova, M.D., Ph.D., Dwight R. Johnson, B.S., Roger M. Kurlan, M.D., Edward L. Kaplan, M.D.

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Is PANDAS a valid diagnosis?

- No laboratory test!
- Difficult to establish relationship with (strep) infections
- Currently possible PANDAS should have no treatment implications

More questions than answers……

EMTICS
European Multicentre Tics Study

- **How many children** with TS/OCD should have PANDAS?
- Why is **abrupt/acute** symptom onset or exacerbation required?
- **What is the time frame** for a temporal association?
- Do infections or autoimmunity not play a role in **non PANDAS** cases with TS or OCD? How do we know?
- Why not?

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278367

Treatment

Treatment options

- Psychoeducation
- Behavior therapy: habit reversal
- Medication

Key points of treatment

- Is there impairment? What causes impairment? Is it tics? Or rather comorbidity?
- Inform your patient! Take plenty of time for psycho education.
- Monitor the progress of treatment: use rating scales!

Habit Reversal Training

TWO PRIMARY COMPONENTS

Awareness Training

Competing Response

Competing Response

- Competing response: incompatible physical behavior performed in response to:
  - Urge to tic
  - Initial expression of tic itself
- Competing response should be:
  - Opposite to the tic behavior
  - Capable of being maintained for at least one minute
  - Socially inconspicuous - compatible with normal activity

What about medication?

- Long term prognosis often favorable, also without treatment
- Available treatment options do not ‘cure’ tic disorders, only suppress symptoms
- Medications may well have side effects: on the long run, most patients choose to live without medication

Available medications

- Alpha 2 agonist:
  - clonidine
- Antipsychotics:
  - risperidone
  - aripiprazol
  - Pimozide, haloperidol

Clonidine

- Presynaptic alpha 2 agonist that downregulates norepinephrine release form the locus coeruleus
- Takes time to reach effect: weeks to months
- May also improve hyperactivity
- Side effects: sedation, depression, drowsiness, hypotension
- Mostly not as effective as antipsychotics

Risperidone versus placebo (Dion e.a. 2002)

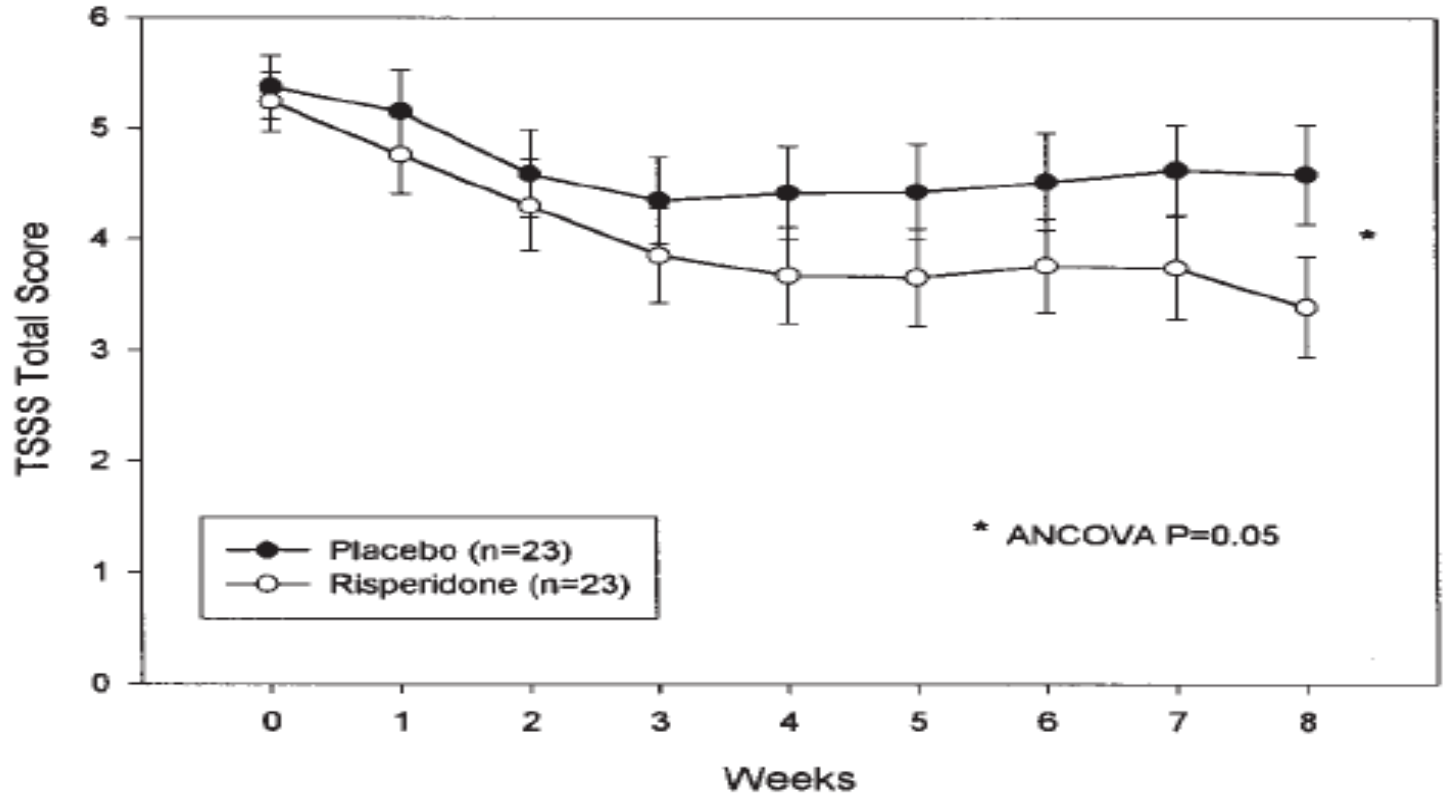

FIG. 1. Total TSSS scores (mean ± SEM) over time by treatment group for the intention-to-treat sample (last observation carried forward).

Finally…what about methylphenidate in children with tics?

TABLE 2

Summary of Study Results: Effect of Medication on Subjects With and Without Preexisting Tics

	Subjects Without Preexisting Tics[a]		
	MPH (n = 51)	Placebo (n = 12)	Total (n = 63)
Tics	10 (19.6)	2 (16.7)	12
No tics	41 (80.4)	10 (83.3)	51
	Subjects With Preexisting Tics[b]		
	MPH (n = 21)	Placebo (n = 6)	Total (n = 27)
Tics	7 (33.3)	2 (33.3)	9
No tics	14 (66.7)	4 (66.7)	18

Note: Values represent no. (%). MPH = methylphenidate.

[a] Fisher exact test (MPH vs. placebo), p = .59, not significant.

[b] Fisher exact test (MPH vs. placebo), p = .70, not significant.

Take Home Messages

- Tourette syndrome is not a rare disorder
- In most cases tics are mild and not very pronounced
- Very often tics are associated with co-occurring problems
- Etiology is a complex interplay between genetics and environmental factors

- Behavioral therapy is treatment of first choice


Thanks for your atten