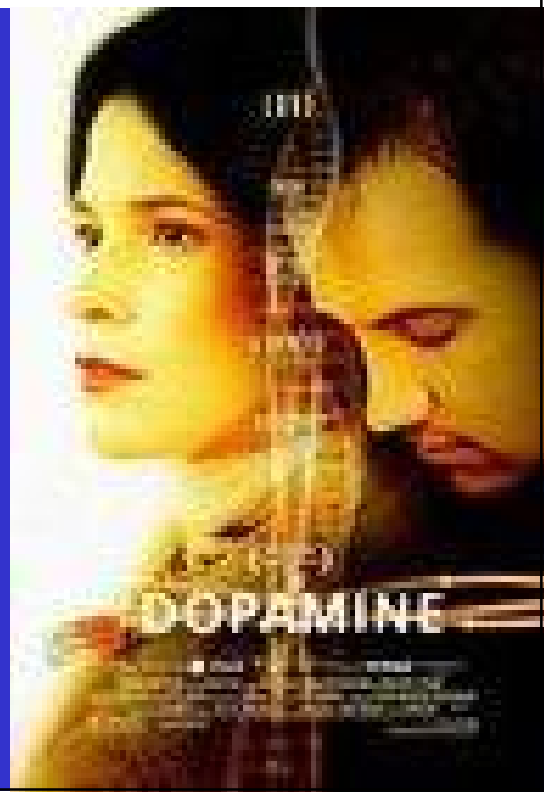
Genetics of Childhood Psychiatric Disorders

Dr. Cathy Barr

The Toronto Western Hospital

The Hospital for Sick Children

Associate Professor
Department of Psychiatry,
University of Toronto



PDF created with pdfFactory Pro trial version www.pdffactory.com

Current Projects

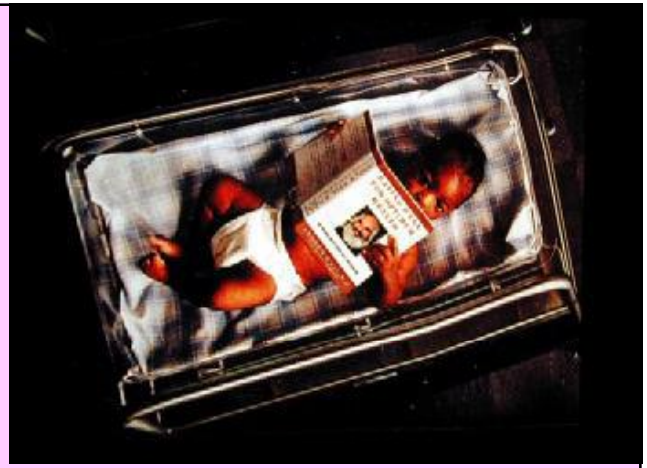
- Attention Deficit Hyperactivity Disorder (ADHD)
- Childhood-onset depression
- Reading disabilities (developmental dyslexia)
- Cognitive deficits in ADHD
- Rapid automatized naming
- Tourette Syndrome
- ADHD and related behaviors and cognitive risk factors in normal twins (QNTS)
- Developmental Trajectories
- Population studies of learning and memory
- Cytokine levels in depression

PDF created with pdfFactory Pro trial version www.pdffactory.com

ADHD is characterized by extremes in the domains of inattention, hyperactivity and impulsivity

PDF created with pdfFactory Pro trial version www.pdffactory.com

Complications in the Genetic Study of ADHD



Diagnosis is based on description of the behaviour
Informant Bias

Clinically heterogeneous Disorder

DSM-IV subtypes -- Hyperactive/impulsive, inattentive, combined

Genetic relationship of co-morbid disorders unclear

Developmental changes and gender effects

PDF created with pdfFactory Pro trial version www.pdffactory.com

Genome Scan

D19S229
D19S247
D19S204
D19S221
D19S179
D19S248
D19S178
D19S246
D19S180
D19S254

Systematically screen all of the chromosomes for linkage using DNA markers spaced at regular intervals

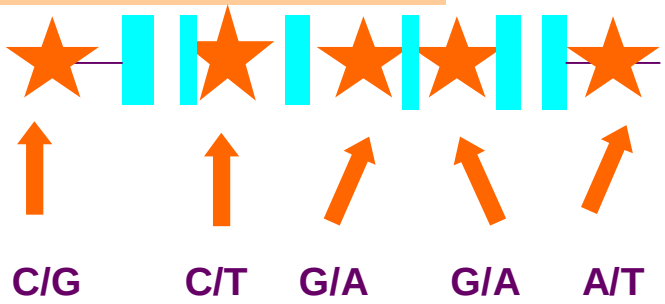
Advantage

PDF created with pdfFactory Pro trial version www.pdffactory.com

Candidate Gene Studies

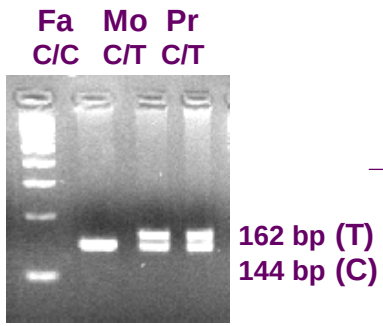
select candidate gene

- animal models
- pharmacological interventions
- biology
- related disorders



identify polymorphisms (common DNA changes)

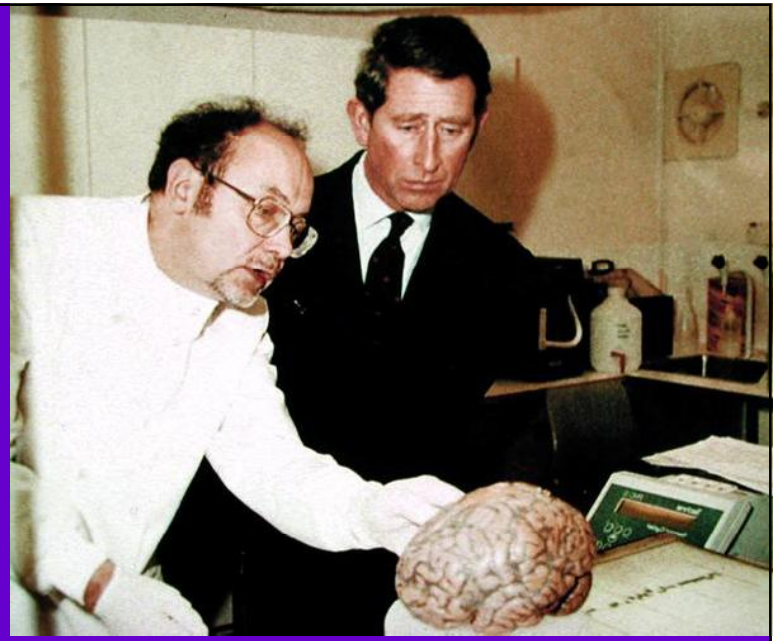
genotype multiple polymorphisms across the gene



statistical analysis

PDF created with pdfFactory Pro trial version www.pdffactory.com

Hypothesis



The genetic susceptibility to ADHD is related to an inherent dysregulation of the neurotransmitter systems

Primary Systems involved:

Dopamine
Adrenergic
Serotonin

PDF created with pdfFactory Pro trial version www.pdffactory.com

Molecular Genetic Studies of ADHD

Published Studies by year

1995	**n=3**
1996	**n=2**
1997	**n=2**
1998	**n=7**
1999	**n=8**
2000	**n=19**
2001	**n=19**
2002	**n=19**
2003	**n=12**

PDF created with pdfFactory Pro trial version www.pdffactory.com

Genetic Studies of ADHD

Published Studies since 1995	**n=91**
Number of Genes Studied	**n=28**
Number of Genes Reported to be Linked or Associated	**n=13**

PDF created with pdfFactory Pro trial version www.pdffactory.com

Genes Reported to be Linked or Associated with ADHD

Gene	Positive reports/Number of studies
Dopamine Receptor D4 (DRD4)	11/19
Dopamine Transporter (DAT1)	7/13
Dopamine Receptor D5 (DRD5)	3/5
Dopamine Receptor D1 (DRD1)	1/2
Synaptosomal associated protein of 25 kd	3/3
serotonin receptor 2A	1/2
serotonin receptor B	2/2
Dopamine Beta Hydroxylase (DBH)	3/5
Dopamine Receptor D2 (DRD2)	1/3
Cathecol-O-Methyl Transferase (COMT)	1/6
serotonin transporter	3/4
DRB1 (HLA class II gene)	1/1

PDF created with pdfFactory Pro trial version www.pdffactory.com

Issues for Genetic Studies -- Power

All studies thus far have used relatively small sample sizes

- *** false positive
- *** false negatives

Genes of small effect may not be identified in these samples

PDF created with pdfFactory Pro trial version www.pdffactory.com

Issues for Genetic Studies -- Heterogeneity

population studied ethnic differences

- **linkage disequilibrium between marker and functional variant**

population studied clinical differences

- **ascertainment**
- **inclusion/exclusion criteria**
- **comorbidity**

PDF created with pdfFactory Pro trial version www.pdffactory.com

Toronto ADHD Project

Canadian Institutes of Health Research funded project to collect nuclear families with an ADHD proband

Progress Year 7:
Assessed over 590 children
463 met criteria for ADHD
80 affected siblings

Cathy Barr (P.I.)	**SickKids, TWH**
Russell Schachar	**SickKids**
Wendy Roberts	**SickKids**
Molly Malone	**SickKids**
Rosemary Tannock	**SickKids**
Abel Ickowicz	**SickKids**
James Kennedy	**CAMH (Clarke)**

PDF created with pdfFactory Pro trial version www.pdffactory.com

Diagnostic Assessment

Measures of ADHD and Comorbid Conditions:

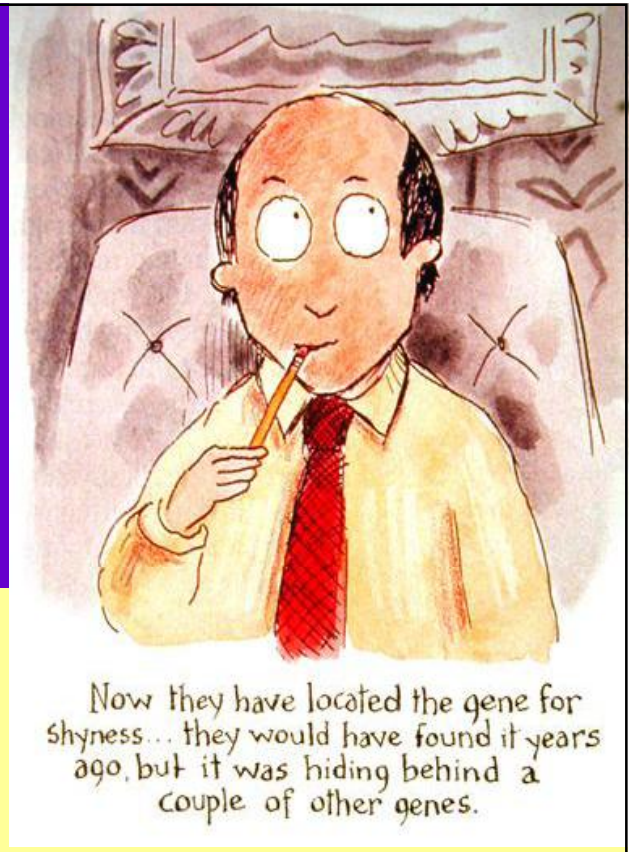
- Semistructured Interview for Parents (PICS)
- Semistructured Interview for Teachers (TTI)
- Ontario Child Health Survey Scales-R
- Conner's Parent and Teacher Scales-R
- Children's Manifest Anxiety Scale
- Child Depression Inventory

Measures of Academic Achievement:

- Wechsler Intelligence Scale for Children
- Wide Range Achievement Test (reading, spelling, math)
- Clinical Evaluation of Language Fundamentals

PDF created with pdfFactory Pro trial version www.pdffactory.com

Genes with evidence for linkage in our sample



Dopamine Receptor D4 (DRD4)

Dopamine Transporter (DAT1)

Dopamine Receptor D5 (DRD5)

Dopamine Receptor D1 (DRD1)

Serotonin receptor 2A (HTR2A)

Serotonin receptor 1B (HTR1B)

Calcyon

Synaptosomal associated protein of 25 kd (SNAP-25)

PDF created with pdfFactory Pro trial version www.pdffactory.com

Synaptosomal-Associated Protein of 25 kDa (SNAP-25)

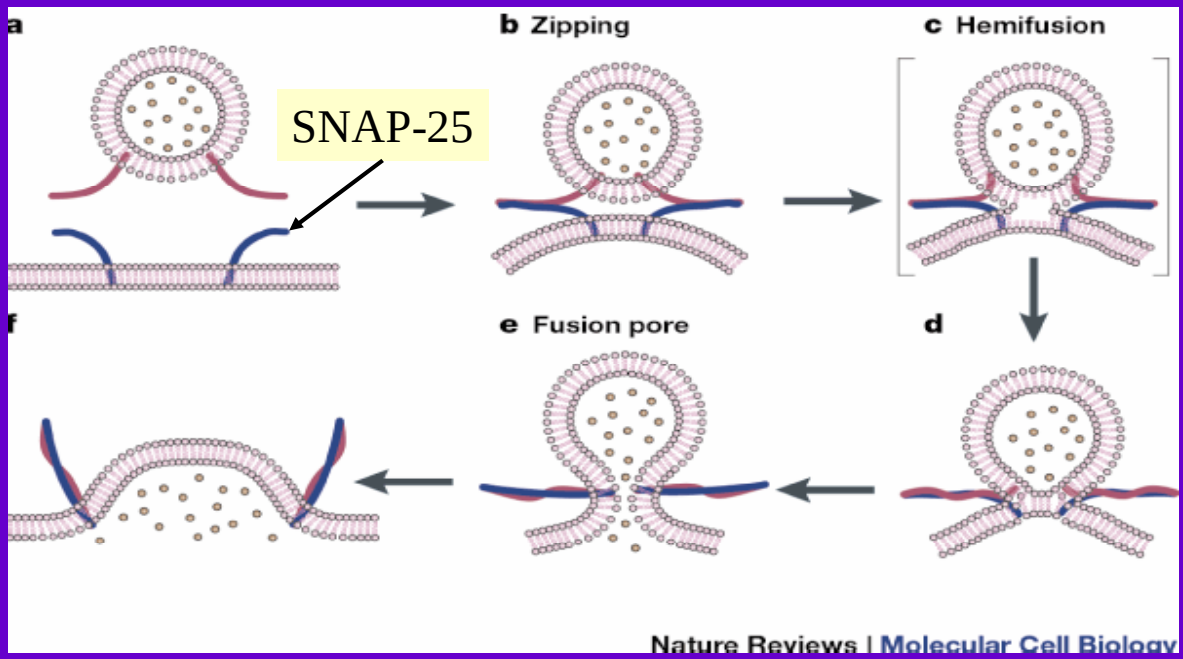
Rationale: **mouse irradiation mutant strain *Coloboma* is hemizygous for a 2 cM region that includes the SNAP-25 gene.**

1) displays spontaneous hyperactivity
2) responsive to dextroamphetamine
3) not responsive to methylphenidate
4) delayed in some developmental milestones
- **righting reflex**
- **bar holding**

PDF created with pdfFactory Pro trial version www.pdffactory.com

SNAP-25

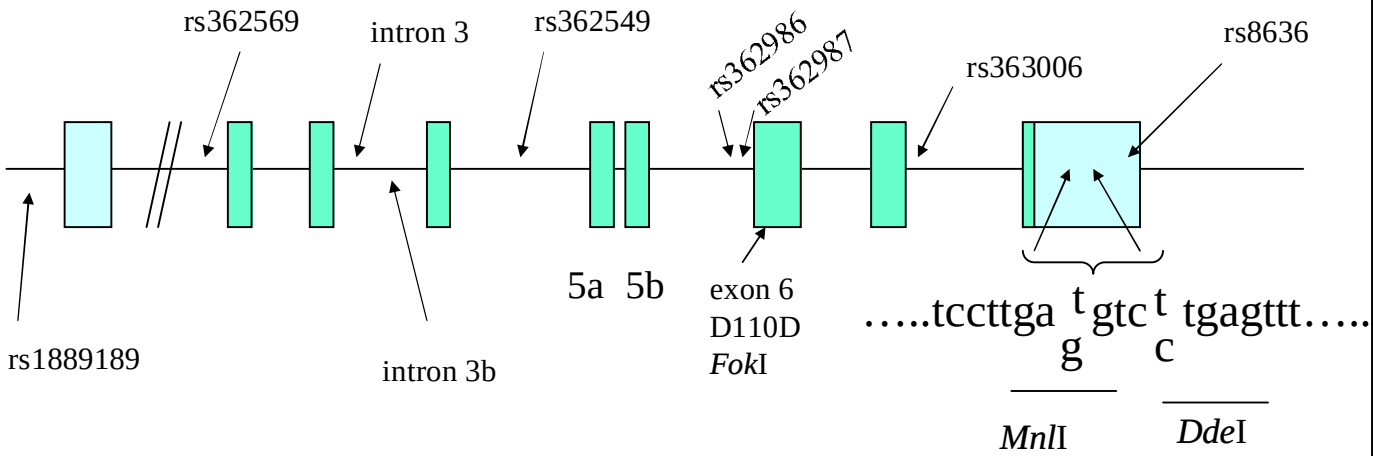
- Critical for controlled release of neurotransmitters into the synaptic cleft
- Loss of expression of a single copy of the gene results in dysregulation in the controlled release of glutamate, dopamine, and serotonin in select brain regions



PDF created with pdfFactory Pro trial version www.pdffactory.com

Association Studies of SNAP-25

polymorphisms identified by screening all coding regions by SSCP

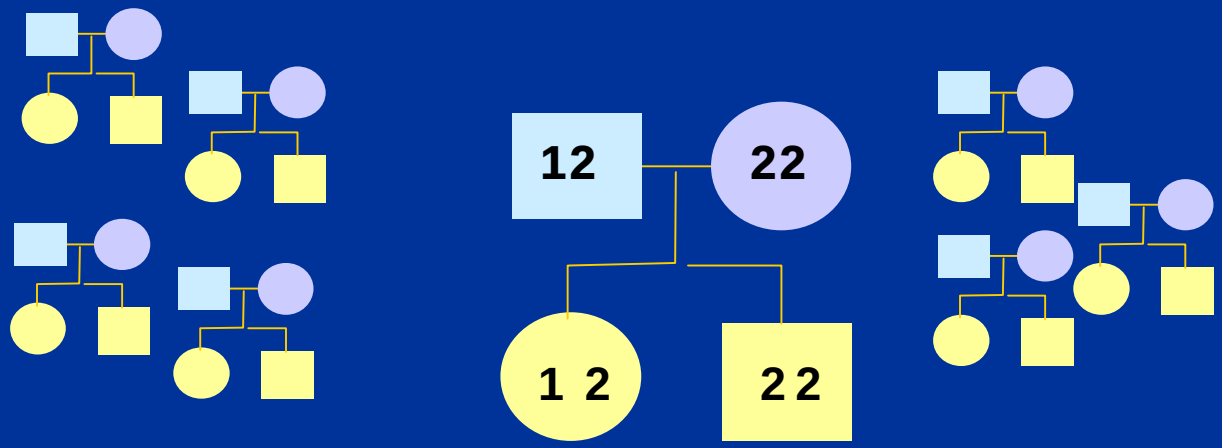


We found evidence for association of this gene in our sample for two markers in the 3' UTR (Barr et al., 2000).
Evidence for association has also been reported in 3 independent samples (Irish, UK, UCLA) however not in a 4th sample (Irvine CA).

PDF created with pdfFactory Pro trial version www.pdffactory.com

Transmission Disequilibrium Test (TDT)

Biased transmission of alleles from heterozygous parents to affected offspring



$$\text{TDT } \chi 2 = \frac{(\text{1 allele transmitted - 1 allele not transmitted})^2}{\text{1 allele transmitted + 1 allele not transmitted}}$$

PDF created with pdfFactory Pro trial version www.pdffactory.com

Transmission Disequilibrium Test (TDT) of the SNAP-25 polymorphisms

Toronto Sample		**n = 182 nuclear families with 48 affected siblings**				
intron 3	C	0.504	111	73	7.848	0.005
intron 4	A	0.503	108	74	6.352	0.012
intron 5	A	0.506	113	84	4.269	0.039
exon 6	C	0.94	28	13	5.488	0.019
Irvine Sample		**n = 99 nuclear families with 3 affected siblings**				
intron 3	C	0.518	26	34	1.067	0.302
intron 4	A	0.509	23	32	1.473	0.225
intron 5	A	0.535	26	35	1.328	0.249
exon 6	C	0.943	6	9	0.6	0.439

Feng et al., 2005

PDF created with pdfFactory Pro trial version www.pdffactory.com

Possible reasons for the different findings between the two samples

Differences in selection of the samples

1) DSM-IV subtypes

2) Ethnic differences

3) Methylphenidate response

PDF created with pdfFactory Pro trial version www.pdffactory.com

Transmission Disequilibrium Test of the SNAP-25 polymorphisms in the Toronto sample by DSM-IV subtype

subtype	polymorphism	Trans	Not trans	$\chi 2$	p value (1 d.f.)
inattentive	intron 3	19	15	0.471	0.493
	intron 4	19	16	0.257	0.612
hyper/impul	intron 3	11	7	0.889	0.346
	intron 4	11	8	0.474	0.491
combined	intron 3	64	37	7.218	0.007
	intron 4	61	35	7.042	0.008

PDF created with pdfFactory Pro trial version www.pdffactory.com

SNAP25 -- next steps

- Subtype -- we can conclude that the differential results are not due to DSM-IV subtype
- Ethnicity -- Could be to differences in ethnicity. We will investigate the frequencies of the markers in world populations in collaboration with Ken Kidd
- Medication Response – We cannot rule this out as a factor. Collect a sample of subjects that have been assessed in a controlled medication trial

PDF created with pdfFactory Pro trial version www.pdffactory.com

Steps after a Linkage or Association Finding

- **Confirm linkage in a larger sample**
- **Gene identification**
- **Determine the molecular basis for the linkage findings** *Is there a functional change in the protein? Is there a change in the amount of the mRNA or protein?*
- **Functional studies**
- **Correlate the genotype with the phenotype**
- **Model gene-gene interactions**

PDF created with pdfFactory Pro trial version www.pdffactory.com

Dopamine Receptor D1 (DRD1)

D1 receptors are prevalent in the prefrontal cortex (PFC), a brain region strongly implicated in ADHD

- PFC lesions produce deficits that resemble symptoms of ADHD
  - deficits in sustained attention and inhibition of responses to distracting stimuli
  - lack of restraint and increased motor activity
- D1 receptors in the PFC modulate working memory function
  - Individuals with ADHD are impaired on tests of frontal lobe function, including working memory
  - Correlations between working memory capacity and attentional ability in the general population

PDF created with pdfFactory Pro trial version www.pdffactory.com

DRD1-knockout mice are hyperactive.

- Locomotor hyperactivity
- Hyperactive and disorganized grooming behaviour
- Poor motor coordination

Aberrant D1 function in two animal models of ADHD

1. Spontaneously Hypertensive Rat (SHR):
   - v Genetic defect in D1 signalling

2. Naples High Excitability (NHE) rat:
   - v Abnormally low level of DRD1 expression in the PFC

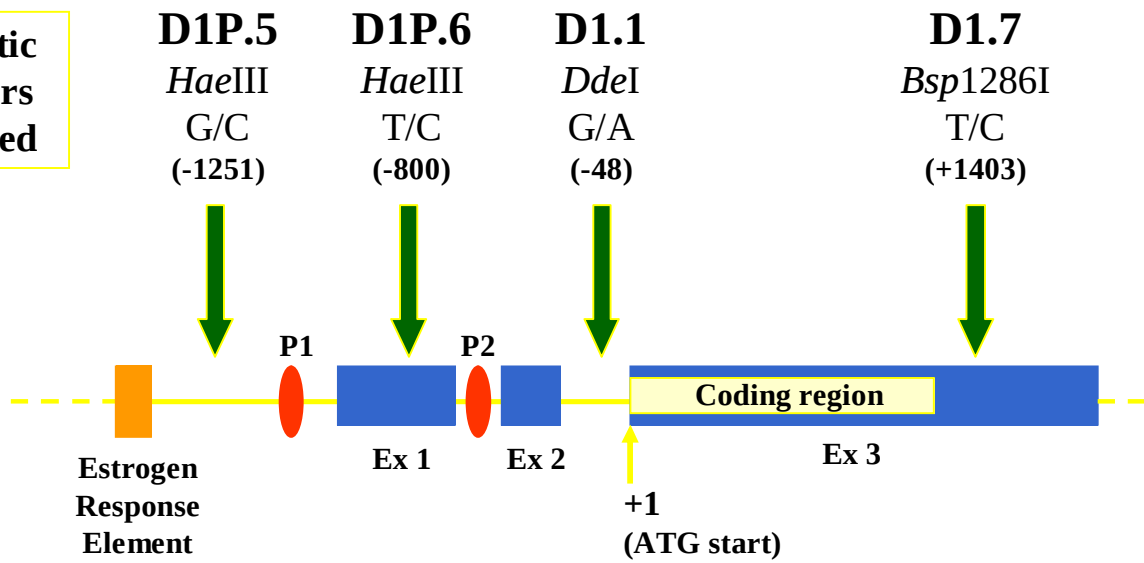
PDF created with pdfFactory Pro trial version www.pdffactory.com

TDT Evidence for Association of the DRD1 gene with ADHD

Biased transmission of Haplotype 3 (p = 0.008)

Haplotype 3	Allele 1 (G)	Allele 1 (T)	Allele 1 (G)	Allele 2 (C)

4 genetic markers analyzed



PDF created with pdfFactory Pro trial version www.pdffactory.com

Quantitative TDT:

Association of Haplotype 3 with the Inattentive (IN) symptoms, but not the Hyperactive/Impulsive (HI) symptoms, of ADHD

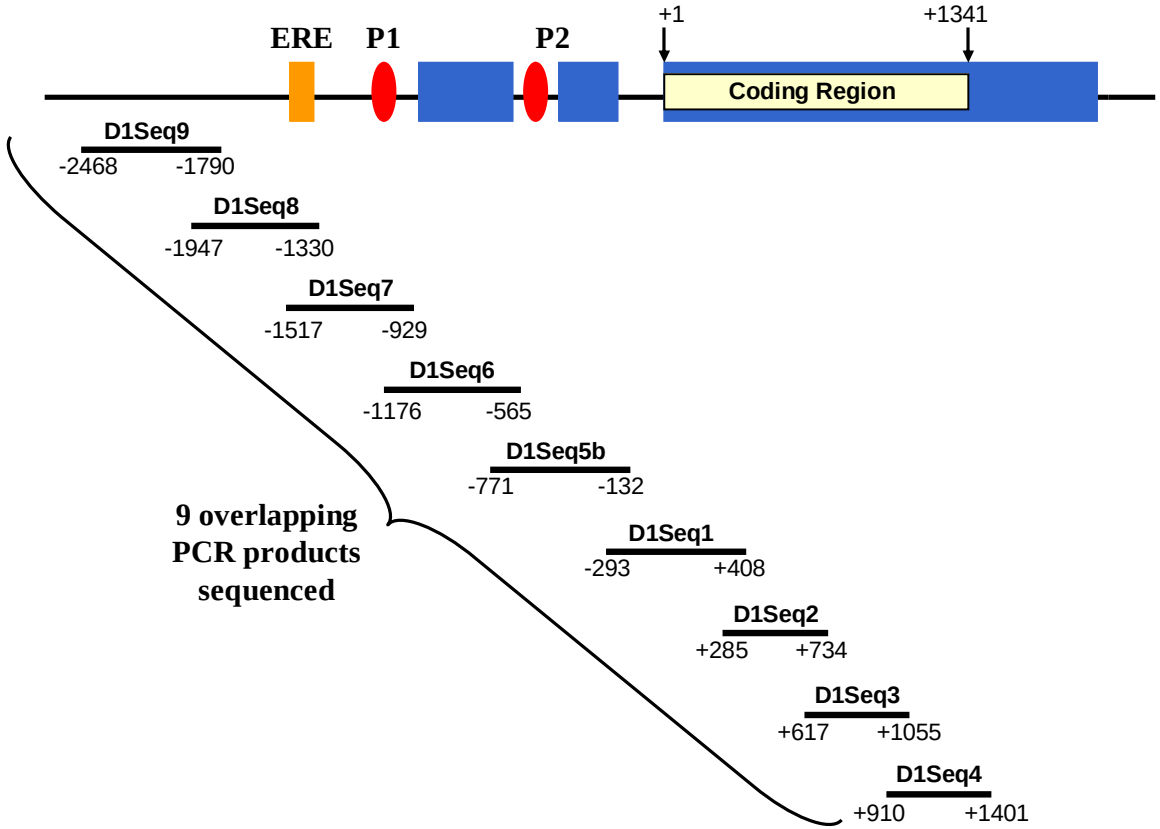
Phenotype		S[a]	E[b]	Z	*p*-value[c]
Symptom Score:					
Parent-reported	IN	487.8	415.8	1.973	**0.024***
Teacher-reported	IN	431.7	365.2	1.877	**0.030***
Parent-reported	HI	461.0	412.9	1.316	0.094
Teacher-reported	HI	377.7	346.8	0.958	0.169

[a]Test statistic [b]Expected value of S under the null hypothesis of no association [c]1 d.f.

Recently replicated the relationship between inattention symptoms in an independent sample

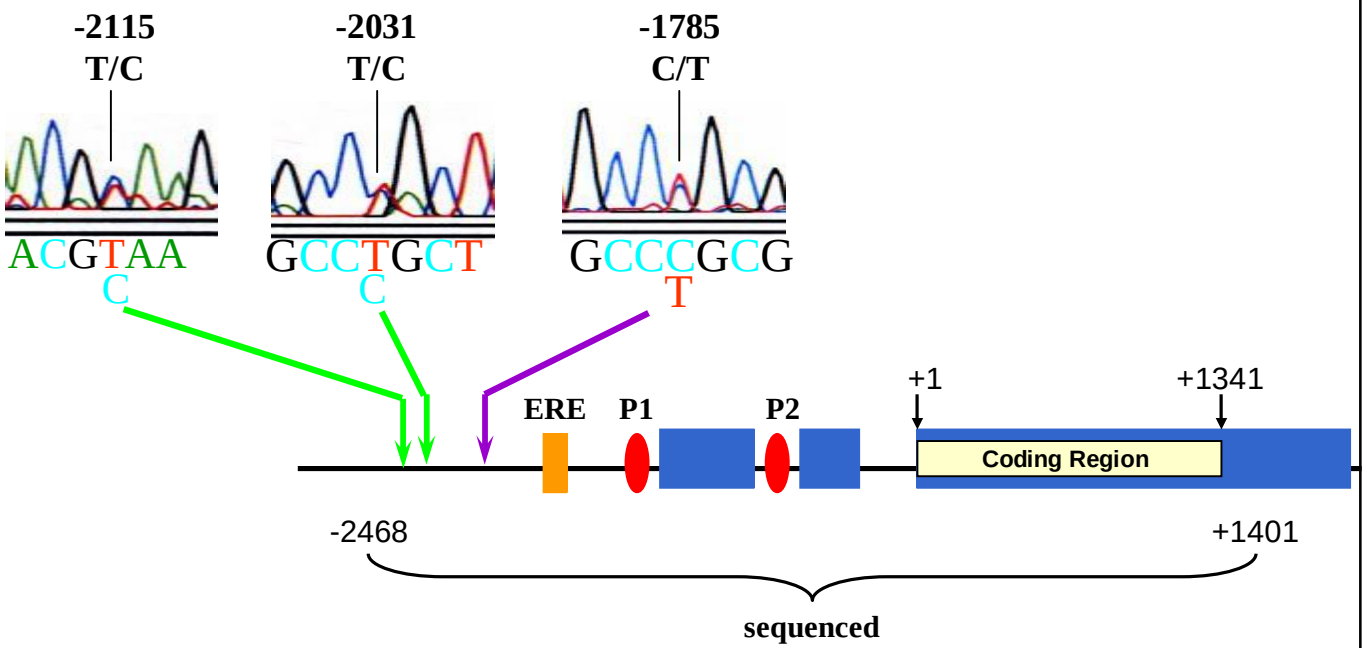
PDF created with pdfFactory Pro trial version www.pdffactory.com

Misener et al., (2004) Dopamine Receptor D1 (DRD1) Sequencing Strategy:



PDF created with pdfFactory Pro trial version www.pdffactory.com

***Result*: Three DNA variants were identified in the 5' regulatory region of the gene in 2 of the 60 children analyzed**



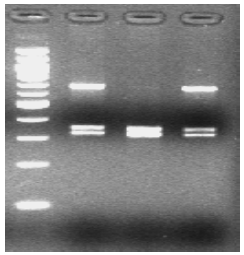
PDF created with pdfFactory Pro trial version www.pdffactory.com

DRD1 promoter variants

Capano, Misener et al., in prep

Variant 1
-2115 T/C

Fa Mo Pr
T/C T/T T/C

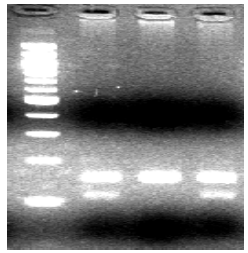


679 bp (C)
350 bp (T)
329 bp

PCR/*Hpy*CH4IV digest

Variant 2
-2031 T/C

Fa Mo Pr
T/C T/T T/C

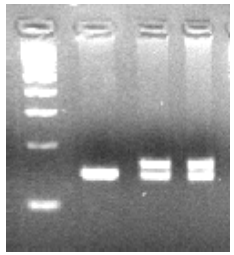


152 bp (T)
114 bp (C)

PCR/*Aci*I digest

Variant 3
-1785 T/C

Fa Mo Pr
C/C C/T C/T



162 bp (T)
144 bp (C)

PCR/*Bgl*I digest

*Allele frequencies**

-2115	-2031	-1785
T: 0.992 C: 0.008	T: 0.970 C: 0.030	T: 0.997 C: 0.003

*Allele frequencies calculated from the parental chromosomes

PDF created with pdfFactory Pro trial version www.pdffactory.com

Ø **Variant 2:** -2031 T>C:possible loss of a Pax-6 site

Possible relationship between PAX6 activity and ADHD?

- Pax6 is involved in eye and forebrain development
- haploinsufficiency results in aniridia, absence or defect of the iris
- In the embryonic mouse, Pax6 expression is found in areas that develop into dopaminergic neurons.
- In the adult mouse, Pax6 is the only member of the Pax family expressed in the Prefrontal cortex.
- In humans, there is a Pax6 mutation that has been found to co-segregate with aniridia and a behavioural phenotype of poor inhibitory control.
- In humans, Pax6 mutation is also associated with reduced white matter in the PFC and with reduced PFC activity during tests of frontal lobe function.

PDF created with pdfFactory Pro trial version www.pdffactory.com

Next steps for *DRD1*

- Replicate association finding in an independent sample
- Determine if this site does in fact bind Pax-6 and if the DNA change results in a change of binding
- Identify other regulatory DNA changes that may be involved

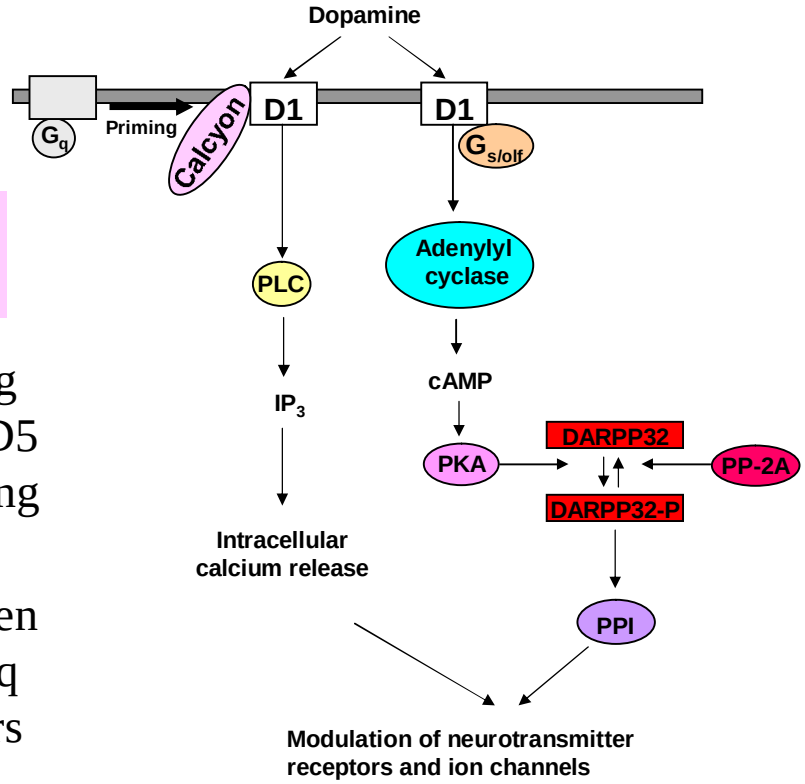
PDF created with pdfFactory Pro trial version www.pdffactory.com

D1 signalling pathways:

Laurin et al. 2005

Calcyon (DRD1IP)
DRD1 interacting protein

- Brain specific interacting protein involved in D1/D5 receptor calcium signaling
- may serve as cross-talk accessory protein between D1-like receptors and Gq protein-coupled receptors



PDF created with pdfFactory Pro trial version www.pdffactory.com

Genetic Evidence supporting Calcyon in ADHD

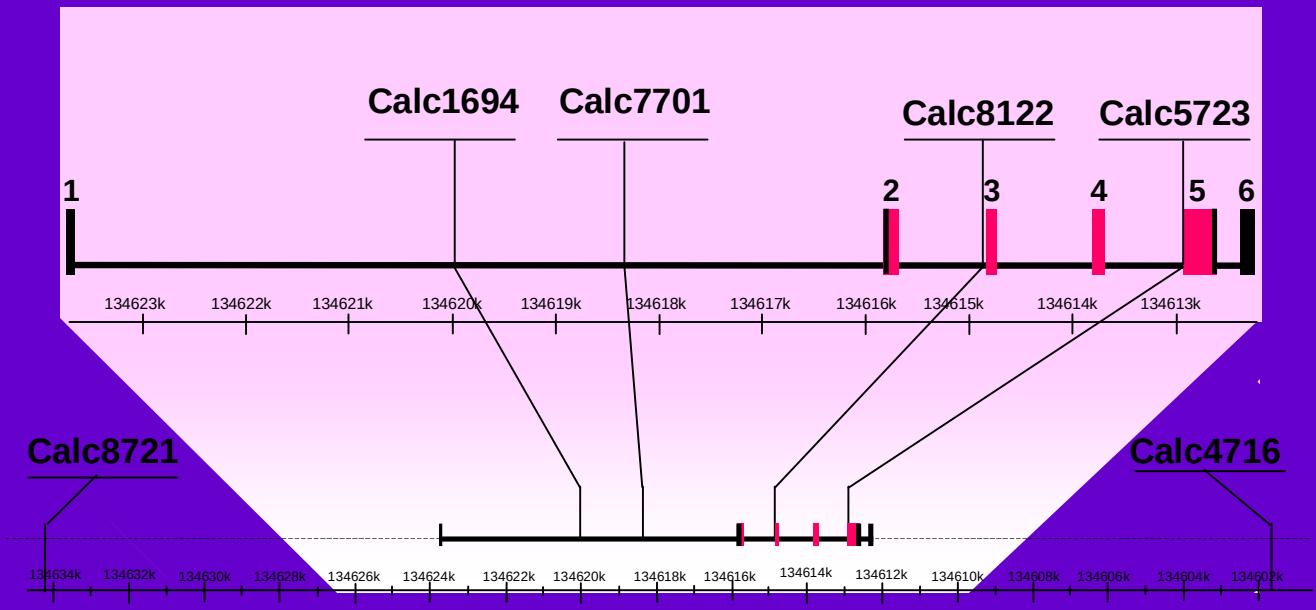
1. Resides at 10q26 – region with weak support for linkage (LOD 1.66) from the first genome scan of ADHD (Fisher, 2002).
2. deletion syndrome of 10q25.2-26

   learning difficulties

   behavioural problems including hyperactivity

PDF created with pdfFactory Pro trial version www.pdffactory.com

Calcyon Gene



TDT Results for the Calcyon gene:

Biased transmission of one haplotype, designated Haplotype 1 (p =0.029)

PDF created with pdfFactory Pro trial version www.pdffactory.com

Quantitative TDT:

Association of Calcyon Haplotype 1 with both the Inattentive (IN) and Hyperactive/Impulsive (HI) symptoms of ADHD

Phenotype		*p*-value
Symptom Score:		
Parent-reported	IN	**0.008**
Teacher-reported	IN	**0.003**
Parent-reported	HI	**0.012**
Teacher-reported	HI	0.096

Coding regions screened – no functional changes
Results await replication

PDF created with pdfFactory Pro trial version www.pdffactory.com

The real reason we invaded Iraq

To defeat terrorism we have no choice but to invade ~~Afriganist~~ Afgan ~~Aphghanis~~ ~~Afgah~~ Iraq.

PDF created with pdfFactory Pro trial version www.pdffactory.com

Toronto Genetics of Reading Disabilities Project

Year 5 of a CIHR funded project to collect nuclear families identified through a proband with reading problems.

Investigators	
Cathy Barr (P.I.)	**TWH, Sickkids**
Rosemary Tannock	**SickKids**
Maureen Lovett	**SickKids**
Tom Humphries	**SickKids**
Coordinator	
Barbara Anderson	**SickKids**

PDF created with pdfFactory Pro trial version www.pdffactory.com

Evidence for a Genetic Relationship of ADHD & Reading Disabilities

Comorbidity

25 to 40% of individuals with RD have symptoms of ADHD
15 to 26% of individuals with ADHD have RD

Twin Studies

Gilger et al., 1992 Twin study using RD twins suggested ADHD with RD is a genetic subtype

Wilcutt et al., 2001. twin studies suggests genetic overlap differs for dimensions of ADHD.
95% of the overlap between inattention and RD &
21% of the overlap for hyperactive/impulsive symptoms and RD due to common genetic influences.

Linkage Studies

Evidence for linkage of the ADHD phenotype in families with RD
J. Williams -- linkage of the ADHD phenotype to the 15q region in families with RD
E. Willcut -- linkage of the ADHD phenotype to the 6p region
Bakker et al., (2003) -- genome scan for ADHD in a Dutch sample identifies 15q region

PDF created with pdfFactory Pro trial version www.pdffactory.com

Reading Disabilities (Developmental Dyslexia)

Developmental dyslexia or specific reading disability (RD) is a heritable phenotype defined as severe difficulty in reading despite average intelligence and adequate opportunity.

6p21.3
15q15-21
2p15-p16
1p34.3-36.3
6q13
18p11
11p15.5

PDF created with pdfFactory Pro trial version www.pdffactory.com

Reading Genes?

Despite replicated findings for linkage (sharing of chromosomal regions in affected family members), until recently there have been no genes identified as contributing to RD

Is *EKN1* the first gene for RD?

PDF created with pdfFactory Pro trial version www.pdffactory.com

EKN1 (or ENK1 to the Dyslexic)

Taipale et al., 2003 PNAS 100(20):11553-8

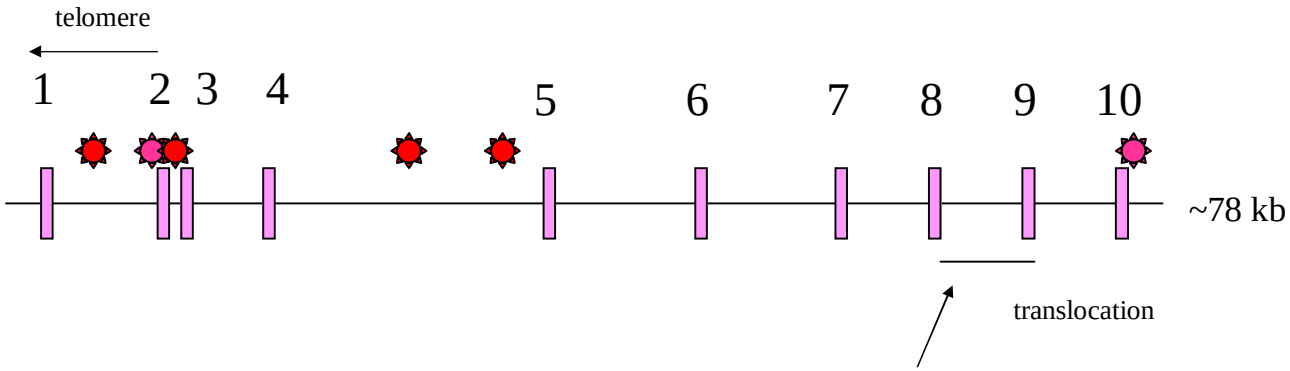
What is EKN1?

"En Keksi Nimeä 1", translated into English approximately "Can't Name It 1"

Gene of unknown function

PDF created with pdfFactory Pro trial version www.pdffactory.com

What is the evidence that EKN1 is a gene for RD?



- translocation t(2;15)(q11;q21) cosegregates with dyslexia in one Finnish family (father and 3 kids)
- identified breakpoint in gene of unknown function, EKN1, between exons 8 & 9
- Conclude that -3A and/or 1249T are contributing to RD

PDF created with pdfFactory Pro trial version www.pdffactory.com

EKN1 Expression -- everywhere

Taipale et al., 2003
heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, spleen, thymus, prostate, testis, ovary, small intestine, colon, leukocytes

NCB1 UniGene

cDNA sources: pooled ; Pituitary ; Testis ; head_neck ; pooled germ cell tumors ; carcinoma, cell line ; testis ; glioblastoma (pooled) ; glioblastoma ; hypernephroma ; Trabecular meshwork ; lung ; kidney ; pooled colon, kidney, stomach ; Stomach ; Primary Lung Epithelial Cells ; adenocarcinoma ; Liver ; melanotic melanoma ; Purified pancreatic islet ; Human Lung Epithelial cells

PDF created with pdfFactory Pro trial version www.pdffactory.com

Homology

Listed below are the nucleotide sequence comparisons used in determining homology.The pairs below represent reciprocal best hits; each alignment is the best one for both organisms. The percent ID below represents identity over an aligned region.

Organism-Gene	Organism-Gene	PercentID
H.sapiens -EKN1	M.musculus - 1700010I24Rik	82.8
H.sapiens -EKN1	C.intestinalis - Cin.5317 (sea squirts)	74.1
H.sapiens -EKN1	Danio rerio - Dr.15037 (zebrafish)	70.7

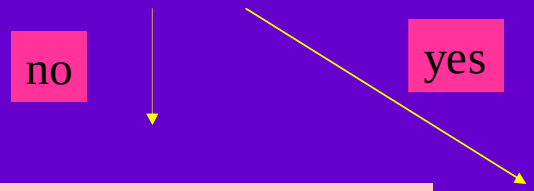
	differs from humans by ## AA
chimps	3
pygmy chimps	2
gorilla	5
orangutan	6

PDF created with pdfFactory Pro trial version www.pdffactory.com

Recruitment of Subjects

Probands identified with reading problems (age 6-16) are recruited from local schools

prescreened for Attention Deficit Hyperactivity Disorder (ADHD)



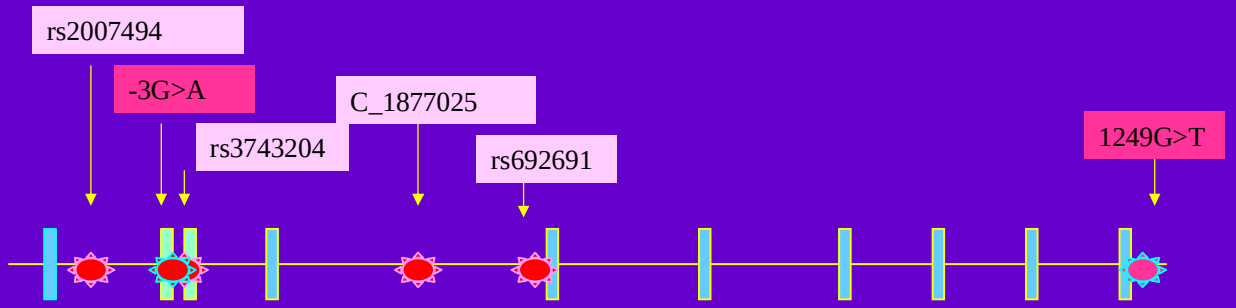
proband and siblings in the age range recruited to study

ADHD genetics study

n=273 families, with 107 siblings

PDF created with pdfFactory Pro trial version www.pdffactory.com

EKN1 DNA Markers



- 6 markers genotyped in EKN1
- the 2 markers positive in Taipale et al., study
- 4 others identified from public databases
- -2G/A and 4C/T also genotyped but not polymorphic

Wigg et al., 2004

PDF created with pdfFactory Pro trial version www.pdffactory.com

TDT Categorical Analysis

	Allele	Allele Frequency	Transmissions	Non-Transmissions	$\chi 2$	p-value
rs2007494	A	0.745	29	23	0.692	0.405
	C	0.255	23	29	0.692	0.405
-3G>A	**G**	**0.922**	**15**	**8**	**2.130**	**0.145**
	A	0.078	8	15	2.130	0.145
rs3743204	C	0.745	29	23	0.692	0.405
	A	0.255	23	29	0.692	0.405
C_1877025	**T**	**0.664**	**20**	**38**	**5.586**	**0.018**
	G	**0.336**	**38**	**20**	**5.586**	**0.018**
rs692691	C	0.594	31	35	0.242	0.623
	T	0.406	35	31	0.242	0.623
1249G>T	G	0.901	15	10	1.000	0.317
	T	0.099	10	15	1.000	0.317

For the categorical analysis, subjects must score below 1.5 Standard Deviations (S.D.) on 2 out of 3 core reading measures: Word Attack, Word ID and WRAT reading, or 1 S.D. below the mean on the average of the three.

83 probands and 18 siblings made this criteria.

PDF created with pdfFactory Pro trial version www.pdffactory.com

EKN1 in other studies

- Scerri et al., 2004 (Oxford) found association with the common alleles (-3G/1249G)
- Cope et al. 2005 (Wales) no association of these specific alleles
- Marino et al., 2005 (Italy) no association of these specific alleles
- Smith some indication for association of 1249G/T

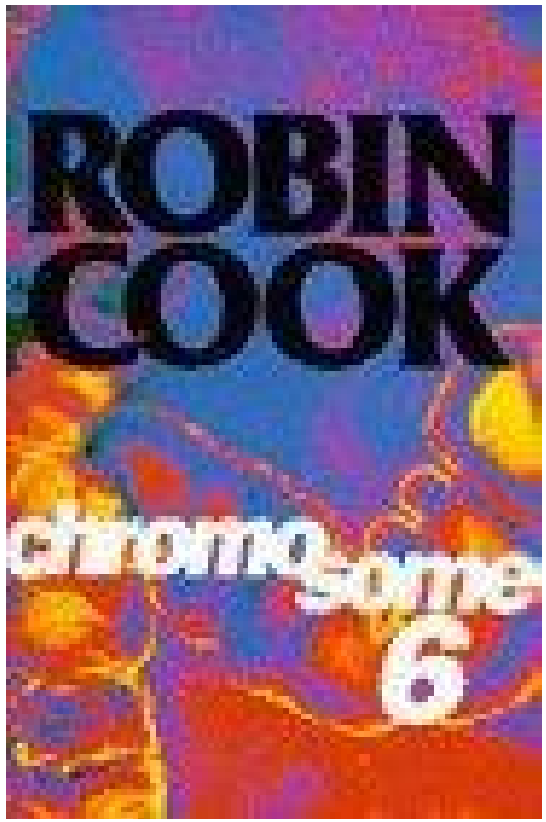
PDF created with pdfFactory Pro trial version www.pdffactory.com

Is EKN1 the first gene for reading disabilities?

- some support for this gene as a susceptibility locus
- does not confirm the two previously reported variants as contributing to RD – can rule these out as the DNA change contributing to RD
- Is this the gene or could it be a gene nearby? a positional effect?

PDF created with pdfFactory Pro trial version www.pdffactory.com

Chromosome 6p



"A typical Robin Cook medical thriller - ***another real page turner.***"

PDF created with pdfFactory Pro trial version www.pdffactory.com

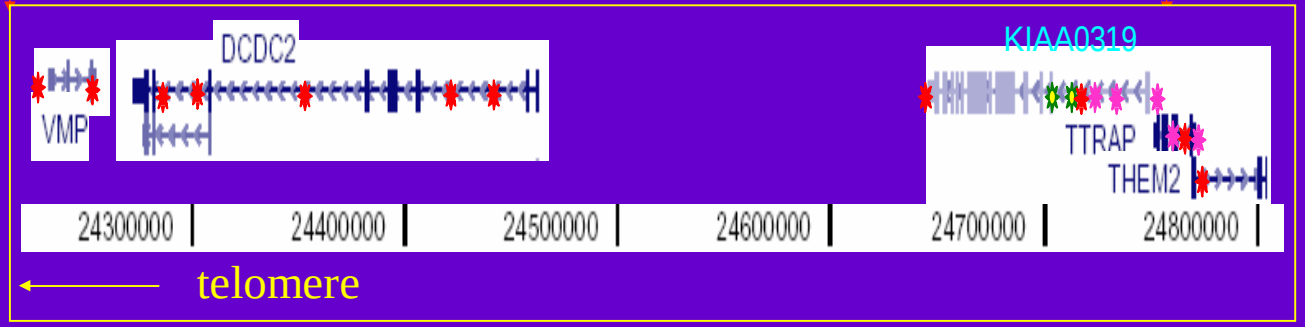
The 589 Kb Region on Chromosome 6p

Three independent studies have found evidence for association of DD to a region containing brain-expressed genes

USA

Oxford (UK)

Cardiff (UK)



PDF created with pdfFactory Pro trial version www.pdffactory.com

International Consortium for Childhood-Onset Mood Disorders

Toronto Cathy L. Barr, James L. Kennedy

Pittsburgh Maria Kovacs

Hungary **Agnes Vetro, ** Eniko Kiss, ** Kristina Kapornai, *** Julia Gádoros **I. Benák, ***M. Besnyő, **E. Dombovári, ****M. Gácser, **E. Kaczvinszky, **V. Kothenc-Osváth *****L. Mayer, **J. Székely,

**Szeged University Medical Faculty Department of Child and Adolescent Psychiatry Szeged Hungary
*** Vadaskert Hospital Budapest Hungary
****Pándy Kálmán Hospital Department for Child and Adolescent Psychiatry Gyula Hungary
***** Margit Hospital Csorna Hungary

PDF created with pdfFactory Pro trial version www.pdffactory.com

Hungarian COMD Genetics Study Design

International Consortium for Childhood-Onset Mood Disorders

Subjects: children (ages 7-14) with DSM-IV mood disorder that are referred to all major inpatient and outpatient psychiatric clinics across Hungary. Interview Schedule for Children and Adolescents - Diagnostic Version (ISCA-D) [Sherrill and Kovacs 2000]. Probands were interviewed twice, approximately one month apart. Consensus diagnosis of two independent child psychiatrists was used as final diagnosis.

Goal -- Recruit to the study 275 families with a proband and an affected sibling for genome scan
Recruit 550 families with a proband for association studies with family based controls

PDF created with pdfFactory Pro trial version www.pdffactory.com

Hypothalamus-Pituitary-Adrenal axis

- **well-characterized role of the HPA axis in the response to stress**
- **the relationship of hyper-arousal to affect regulation**
- **the findings of alterations in HPA peptides in depression**
- **increased corticotrophin-releasing hormone (CRH) in cerebral spinal fluid of untreated depressed individuals**

PDF created with pdfFactory Pro trial version www.pdffactory.com

HPA axis

- **CRHR2-- Corticotropin Releasing Hormone Receptor 2**
- **CRHR1-- Corticotropin Releasing Hormone Receptor 1**
- **GRL - Glucocorticoid Receptor**
- **POMC (ACTH) – propiomelanocortin (adrenocorticotropin)**
- **CRH -- Corticotropin Releasing Hormone**
- **ACTH-R/MC2R**
- **CRHBP --Corticotropin Releasing Hormone Binding Protein**

No positive findings at this time for any of these genes based on the first 195 families

PDF created with pdfFactory Pro trial version www.pdffactory.com

The Adrenergic System

- **The adrenergic system is implicated in the action of antidepressants**
- **involves a number of behavioural and cognitive functions that further implicate this system in the development of depression**

attention
memory
response to stress
behavioral impulsivity
anxiety

The recent genome scan of early-onset depression (Zubenko et al., 2003) identified the chromosomal locations of three of the adrenergic receptors

PDF created with pdfFactory Pro trial version www.pdffactory.com

The Adrenergic System

Gene	Receptor	Chromosomal Location
ADRA1A	α1A	8p21-p11.2
ADRA1B	α1B	5q23-q33.3
ADRA1D	α1D	20p13
ADRA2A	α2A	10q24-q26
ADRB1	β1	10q24-q26
ADRA2B	α2B	2p13-q13
ADRA2C	α2C	4q16
ADRB2	β2	5q32
ADRB3	β3	8p12-p11.2

Genes in red are located in regions identified by the genome scan of early-onset depression

No positive findings for these genes based on the first 189 families

24 markers in total, 14,442 genotypes (in press)

PDF created with pdfFactory Pro trial version www.pdffactory.com

Inflammatory Response System (IRS) genes and depression

- administration of IL-2 or IFN-α, which induce production of IL-1, IL-6 and TNF-α by inflammatory cells has depressogenic effects in non-psychiatric patients
- behavioural changes collectively known as sickness behaviour
- characteristics: fatigue, somnolence, psychomotor retardation, anhedonia and impaired cognitive functioning

PDF created with pdfFactory Pro trial version www.pdffactory.com

Depression and IRS

- administration of pro-inflammatory cytokines has been found to induce neuroendocrine and neurotransmitter changes (*eg*. HPA activation, decreased 5-HT) that are reminiscent of those implicated in depression.
- Some studies have also detected cross-sensitization between the activities of psychological stressors and cytokines, leading to the further suggestion that such cross-sensitization may promote the evolution of depressive states
- IL-1β is known to decrease BDNF levels

PDF created with pdfFactory Pro trial version www.pdffactory.com

IRS Genes tested thus far

Misener et al., in preparation

Proinflamatory

- IL-1α and IL-1β two isoforms of the inflammatory cytokine IL-1
- IL-6
- TNFα

Anti inflamatory

- IL1RNa a critical regulator of IL-1 activity
- Il-10

All negative at this time

PDF created with pdfFactory Pro trial version www.pdffactory.com

Neural Plasticity and Depression

R.S. Duman 1997, The inability of neural systems to exhibit appropriate adaptive plasticity could contribute to the pathogenesis of depression

• chronic antidepressant treatment up-regulates the cAMP signal transduction cascade

• increased expression of CREB (cAMP response element binding protein) with different classes of antidepressant treatment

• time-course consistent with the therapeutic actions of treatment

• phosphorylation and transcriptional activity of CREB is increased

• leads to increased transcription of target genes including BDNF

PDF created with pdfFactory Pro trial version www.pdffactory.com

Genes involved in Synaptic Plasticity

CREB1 (Burcescu et al., 2005)

TRKB (BDNF receptor) (Adams et al., 2005)

NMDA receptors (Dorval in prep)

- GRIN2A
- GRIN2B
- GRIN2C
- GRIN2D
- GRIN1

All negative

PDF created with pdfFactory Pro trial version www.pdffactory.com

Recent support for BDNF in mood disorders

BDNF polymorphisms have been found to be associated with bipolar disorder in two samples with adult probands (Neves-Pereira et al., 2002, Sklar et al., 2002)

BDNF associated with COMD in the our COMD case-control sample (Strauss et al., 2004 Neuropsychiatric Genetics)

Alleles at $(GT)_n$ were highly associated with COMD in this sample (χ^2= 17.8; d.f.=5; p= 0.0032).

The odds of carrying the 168 bp allele were 3.94 times greater for cases than controls.

Alleles of Val66Met were not significantly associated with COMD.

PDF created with pdfFactory Pro trial version www.pdffactory.com

BDNF TDT Results

BDNF-- Brain-Derived Neurotrophic Factor [11p14.1]

Marker	Allele	Freq.	Trans.	Not	Chi-square	P value
val66met	C(val)	0.80	44	27	4.07	0.04
BDNF_1	A	0.78	52	25	9.46	0.003
BDNF_2	A	0.77	38	17	8.02	0.005
BDNF_3	G	0.84	39	20	6.12	0.014
BDNF_4	T	0.76	41	21	6.45	0.012
(GT)n	174bp	0.19	10	25	6.43	0.012
	170bp	0.71	26	14	3.6	0.06

Strauss J,et al. Brain-derived neurotrophic factor variants are associated with childhood-onset mood disorder: confirmation in a Hungarian sample. *Mole Psych*, 10(9): 861-867, 2005.

PDF created with pdfFactory Pro trial version www.pdffactory.com

Chromosome Region 15q25.3-26.2

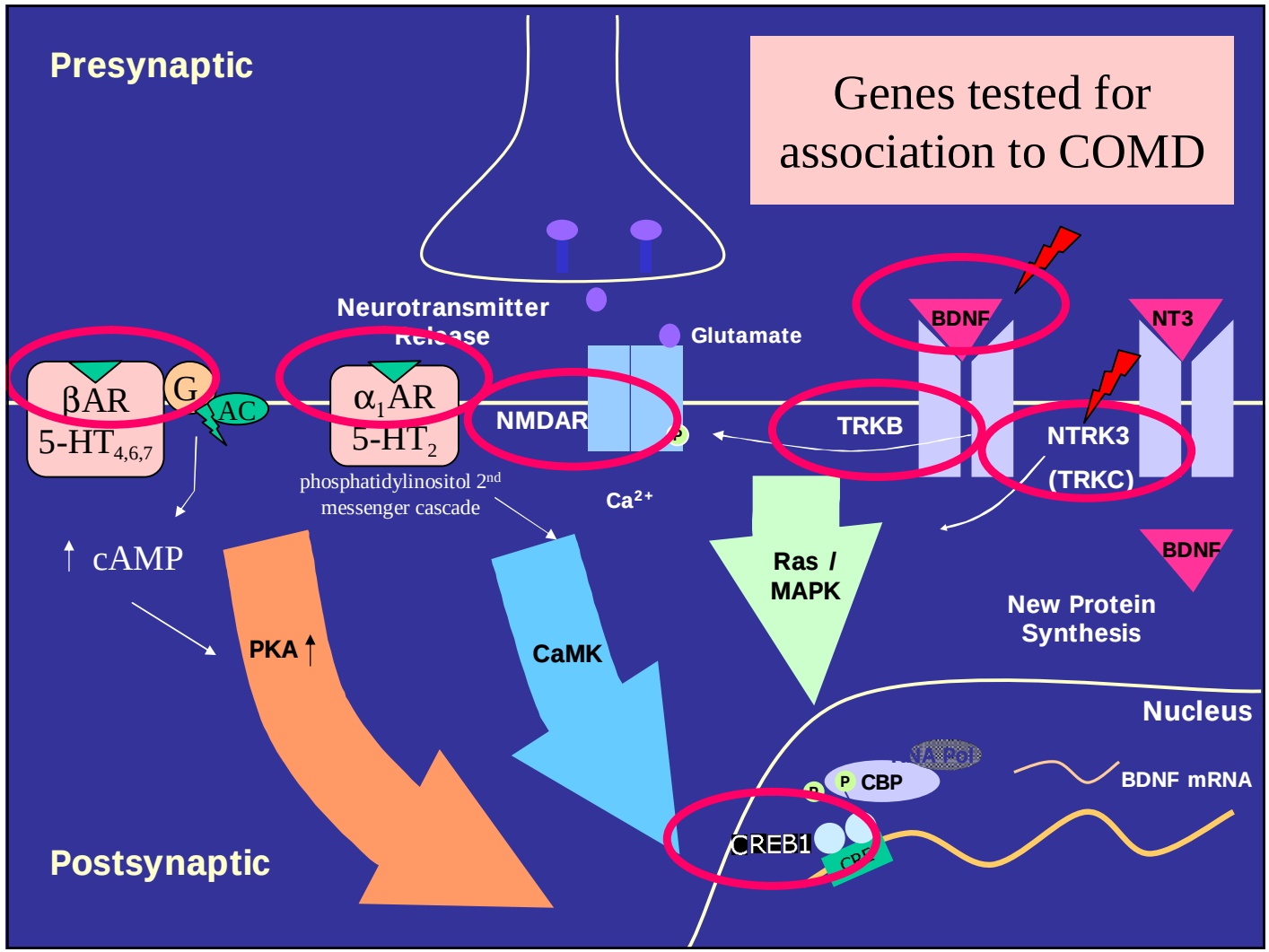
rationale: identified in genome scan for COD (Holmes et al., 2004)

top candidates in this region

- NTRK3 (neurotrophic tyrosine kinase, receptor, type 3)

- RGMA (Repulsive guidance molecule)
- GABRAPL3 (GABA(A) receptor associated protein like 3)
- NEUGRIN (mesenchymal stem cell protein DSC92, important for neuronal differentiation)
- TORC3 (transducer of regulated cAMP response element binding protein, CREB)
- SV2B (synaptic vesicle glycoprotein, brain specific, expressed at highest levels in the cortex and hippocampus)

PDF created with pdfFactory Pro trial version www.pdffactory.com



PDF created with pdfFactory Pro trial version www.pdffactory.com

Summary and Next Steps

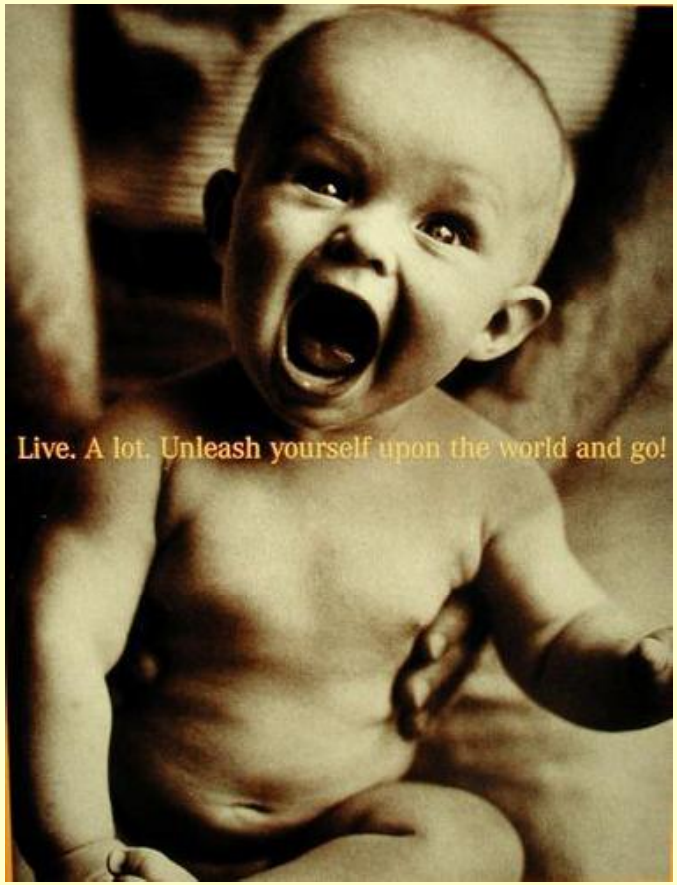
- Thus far BDNF is the strongest finding for COMD
- Some indication for NTRK3
- Molecular analysis of the BDNF and NTRK3 genes
- Suggests that other genes in this pathway are strong candidates for genetic susceptibility

PDF created with pdfFactory Pro trial version www.pdffactory.com

Genetics of Childhood-Onset Psychiatric Disorders Implications for Families

- Runs in families (familial)
- Heritable (twin studies)
- but inheritance not in a clear or predictably Mendelian manner
- Severity in parents does not predict severity in child

PDF created with pdfFactory Pro trial version www.pdffactory.com



Implications for Families

- Genetic risk for the genes identified thus far very low
- cannot be used for diagnosis or prediction

PDF created with pdfFactory Pro trial version www.pdffactory.com

Why are molecular genetic studies important?

- we need to know how it works
- knowledge of biological underpinnings reduces stigma and can improve self esteem
- understanding of the biology may allow for intervention by reduction of environmental risks
- may influence our thinking on interventions or help with the development of new treatments

PDF created with pdfFactory Pro trial version www.pdffactory.com

Barr Lab

Current Lab Members

Jill Couto
Karen Wigg
Yu Feng
Ginger Misener
Nancy Laurin
Kim Dorval
Irina Burcescu
Lissette Gomez
Stephanie Almeida
Jong-Hun Lee
Jon Mill
Emma Dempster

PDF created with pdfFactory Pro trial version www.pdffactory.com