# DISEASE DEFINITION

- Disease is a fluid concept influenced by societal and cultural

attitudes that change with time and in response to new scientific and medical discoveries.

# SYYMPTOM BASED DEFINITION

- Historically, doctors defined a disease

according to a cluster of symptoms. As their clinical descriptions became more sophisticated, they started to classify diseases into separate groups, and from this medical taxonomy came new insights into disease etiology

# DIAGNOSIS

- Diagnosis is the act of labeling someone as diseased through clinical, laboratory, and pathological findings, combined with clinical knowledge and judgment.
- Disease is generally considered to

be an attribute of a patient, whereas diagnosis is the belief that the patient has a disease, a belief that may or may not be true.

# DIAGNOSES

- Diagnoses are intended to inform patients and to tell clinicians who and how to treat.
- Labeling someone as "diseased," however, has enormous individual, social, financial, and physical implications. Irrespective of disease symptoms, the label itself may lead to significant distress

- Boorse defines disease as "a type of

  internal state which is either an impairment of normal functional ability--that is, a reduction of one or more functional abilities below typical efficiency--or a limitation on functional ability caused by environmental agents."

  This type of philosophical definition is impractical clinically

- Nominalists label symptoms with a disease name, such schizophrenia, and do not offer an explanation of the underlying etiology.
- Essentialists argue that for every disease there is an underlying pathological etiology and that the disease state should  be defined by the essential lesion

# DIAGNOSES

- Scadding suggests that diseases defined according to the essentialist tradition may be "precisely wrong," whereas those  defined in the nominalist traditional may be "roughly accurate", labeling the disease state according to only the phenotype (symptoms) or the CAUSE(genetic abnormality) is unsatisfactory

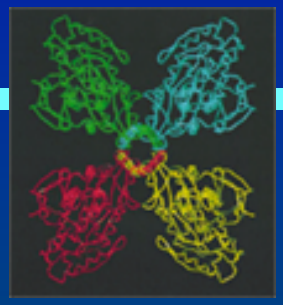
# DISEASE

- disease is a state that places individuals at increased risk of adverse consequences clinical criteria and genetic abnormalities can be used to define a disease state, and the choice of definition will vary according to what one wishes to achieve .

- When determining states

that are associated with disease, the challenge is to describe potential adverse outcomes comprehensively and explicitly. Criteria defining which individuals are diseased are important because abnormalities, EG:elevated blood pressure, may occur in otherwise asymptomatic patients

# Tryptophan hydroxylase (TPH) belongs to a superfamily of aromatic amino acid hydroxylases



Tryptophan —(TPH; BH4 & $Fe^{2+}$)→ 5-HTP —(AADC)→ Serotonin ⇢ Melatonin

Tyrosine —(TH; BH4 & $Fe^{2+}$)→ L-DOPA —(AADC)→ Dopamine ⇢ Norepinephrine / Epinephrine

Phenylanaline —(PAH; BH4 & $Fe^{2+}$)→ Tyrosine

# Regulation of Serotonin Neurotransmission

1. Synthesis (TPH)
2. Storage (VMAT)
3. Release
4. Re-uptake (SERT)
5. Action (serotonin receptors)
6. Degradation (monoamine oxidases)

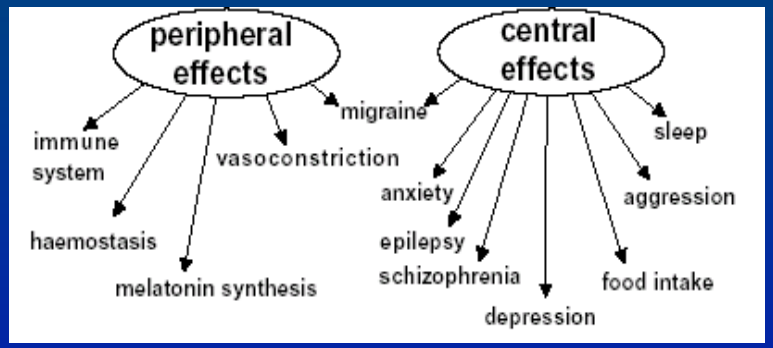
# TPH is the rate-limiting enzyme in serotonin synthesis

**Tryptophan**

↓ **TPH**

↓ **AADC**

**Serotonin**



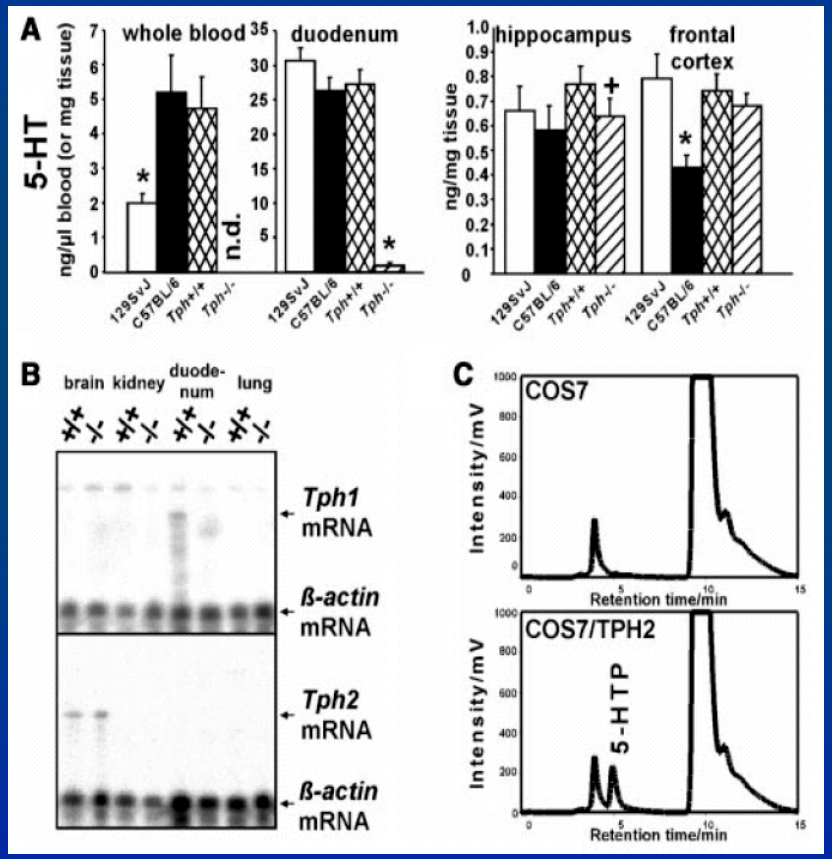
# Previous Project in Marc Caron Lab:

## Tissue-specific Expression in Brain Serotonergic Neurons Using TPH Promoter

# Synthesis of Serotonin by a Second Tryptophan Hydroxylase Isoform

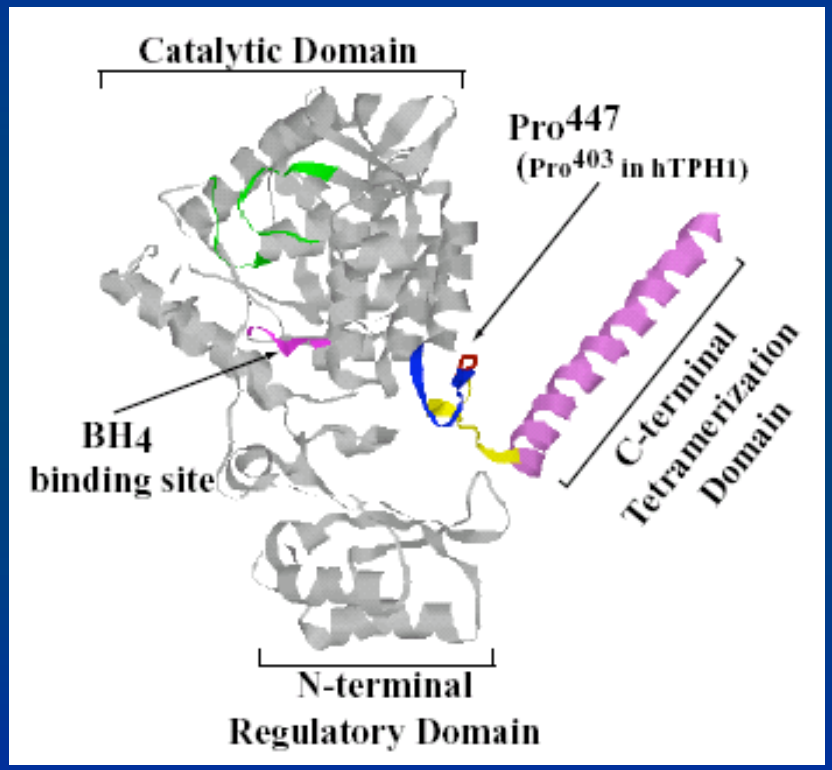
Diego J. Walther,[1]* Jens-Uwe Peter,[1] Saleh Bashammakh,[1]
Heide Hörtnagl,[2] Mechthild Voits,[2] Heidrun Fink,[3] Michael Bader[1]*

*Science* **299**, 76 (2003)




- Human TPH1 and TPH2 share 72% amino acid identity
- TPH2 (Chromosome 12q21.1) *vs.* TPH1 (Chromosome 11p14-15.3 )

# Potential Role of Pro$^{447}$ (Pro$^{403}$ in hTPH1) in TPH2 Enzyme Activity



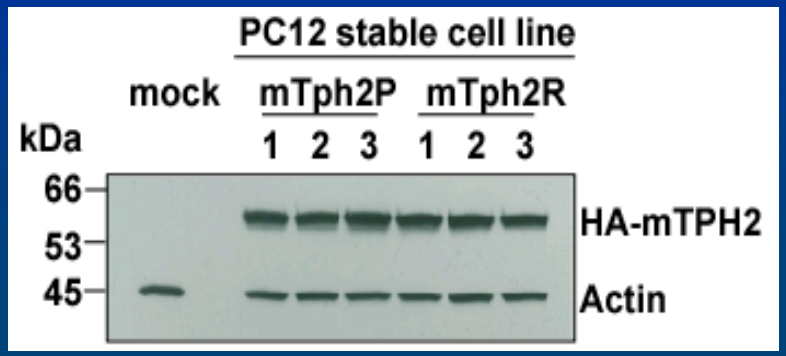

Adapted from predicted TPH1 structure

*J. Mol. Biol.* **302**, 1005-1017 (2000)

| Plasmid | Enzyme | | kDa | Relative activity (%) |
|---|---|---|---|---|
| phTPH2 | wt (1-444) | 1–104–325–411–444 | 91 | 100 |
| phTPH7 | 165-444 | 165– | 73 | n.d. |
| phTPH10 | 92-444 | 92– | 81 | 14 |
| phTPH3 | 1-333 | –333 | 79 | n.d. |
| phTPH6 | 1-408 | –408 | 87 | 1.3 |
| phTPH11 | 92-408 | 92–408 | 77 | n.d. |
| phTPH17 | 92-425 | 92–425 | 79 | 0.5 |

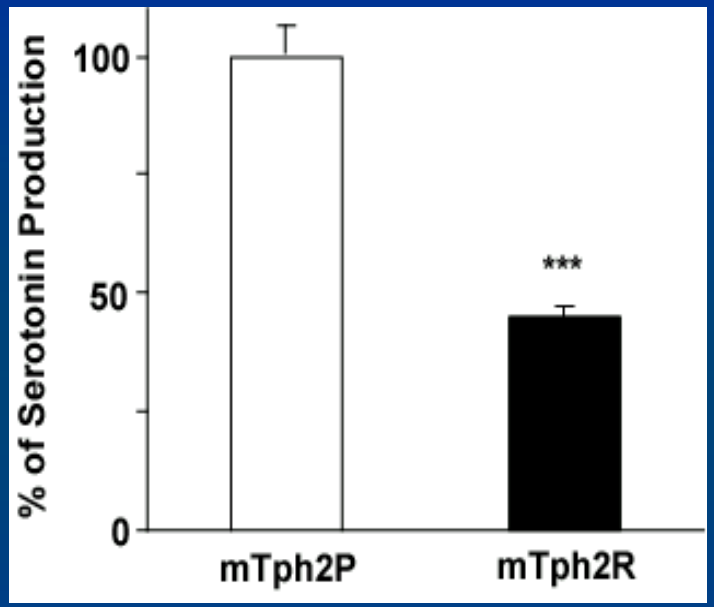
*Proc. Natl. Acad. Sci. USA* **91**, 6659-6663 (1994)

# Expression of mTph2P and mTph2R in PC12 cells




**mTph2P: P447**

**mTph2R: R447**



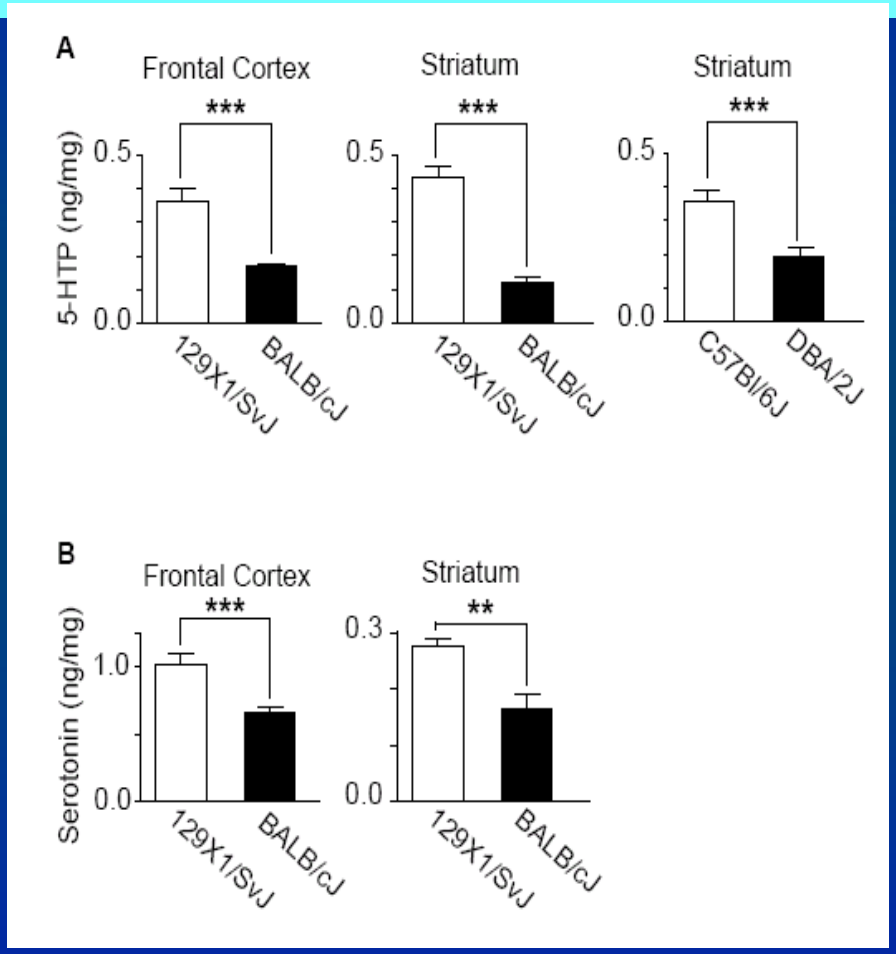

- PC12 cells endogenously express TH, AADC, VMAT and DBH.
- PC12 cells synthesize dopamine and norepinephrine and store neurotransmitters in vesicles.

# SNP genotyping in different inbred mouse strains

| Source | Strain | N | Allele | | |
|---|---|---|---|---|---|
| | | | C/C | C/G | G/G |
| Jackson Laboratory | C57BL/6J | 116 | + | | |
| | 129X1/SvJ | 31 | + | | |
| | BALB/cJ | 27 | | | + |
| | DBA/2J | 9 | | | + |
| Charles River | C57BL/6NCrlBR | 25 | + | | |
| | BALB/cAnNCrlBR | 5 | | | + |
| | DBA/2NCrlBR | 5 | | | + |
| Harlan | C57BL/6NHsd | 5 | + | | |
| Hilltop | C57BL/6NHlaCVF | 5 | + | | |
| | BALB/cHlaCVF | 5 | | | + |

mTph2P: C-allele, mTph2R: G-allele

# Brain serotonin tissue content and rate of synthesis in mice



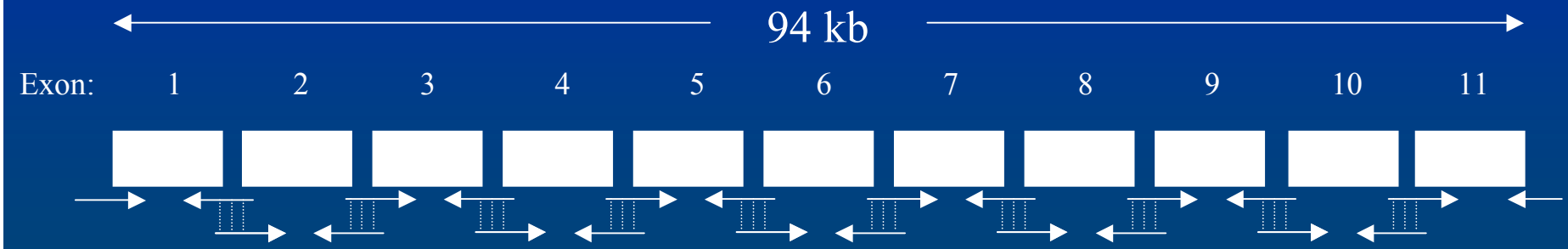

129X1/SvJ, C57Bl/6J: mTph2$^{C/C}$, mTph2P

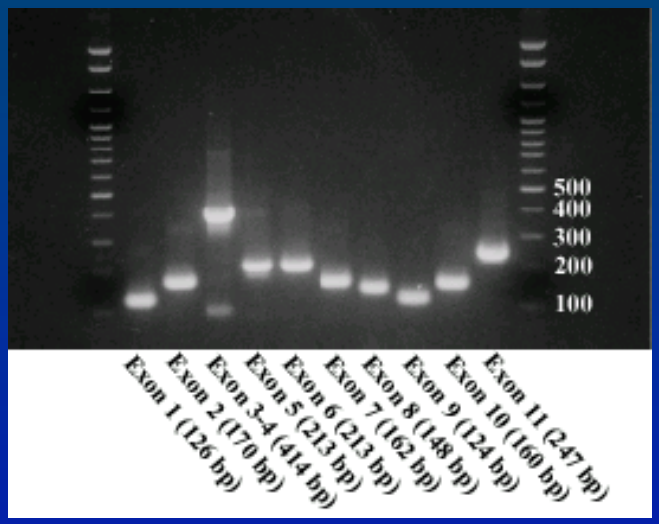
BALB/cJ, DBA/2J: mTph2$^{G/G}$, mTph2R

# Summary

- **We have identified a (C1473G) SNP in the coding region of neuronal-specific Tph2 in inbred mouse strains.**
- **mTph2 (P447R) significantly decreases serotonin synthesis *in vitro* and *in vivo*.**
- **This is the first evidence that serotonin synthesis in CNS is mediated by Tph2.**

# Cloning of *hTph2*



# Initial Screening for SNP in *TPH2*

## Objectives:

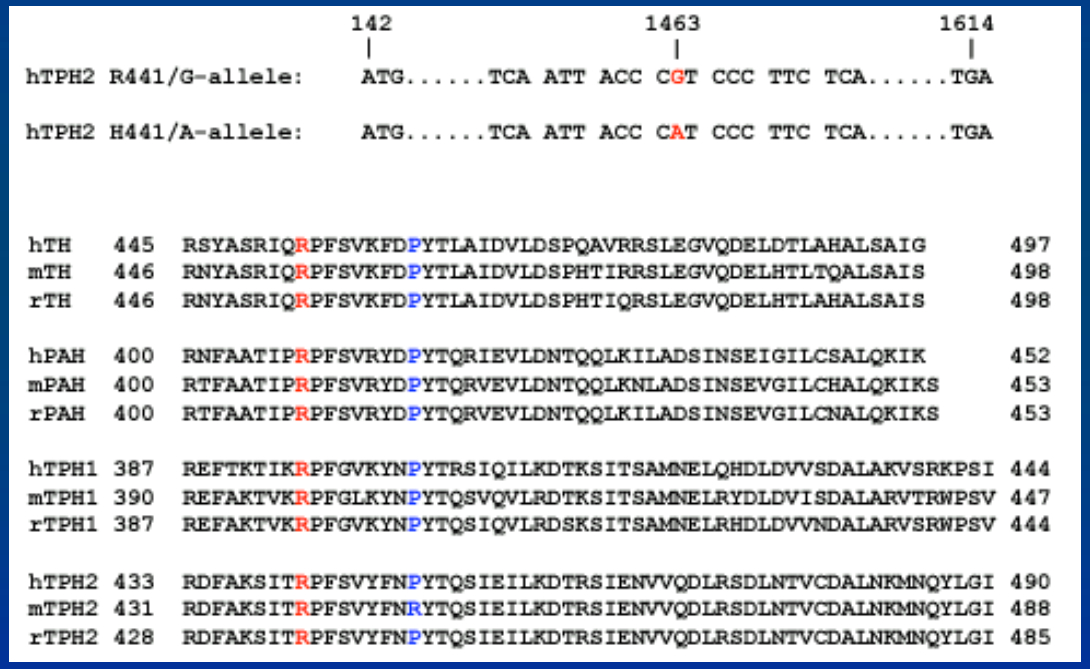
- **Search for (C1486G) SNP (Pro449Arg) in human *TPH2***
- **Sequence all 11 exons to identify additional SNPs**

## Study Group:

- ~300 adults without psychiatric disorders
- recruited from the community for participating in a study of psychosocial and behavioral risk in lower social-economical characteristic study groups
- aggressive behavior
- low 5-hydroxyindoleacetic acid (5-HIAA), a major serotonin metabolite, in the cerebrospinal fluid (CSF)

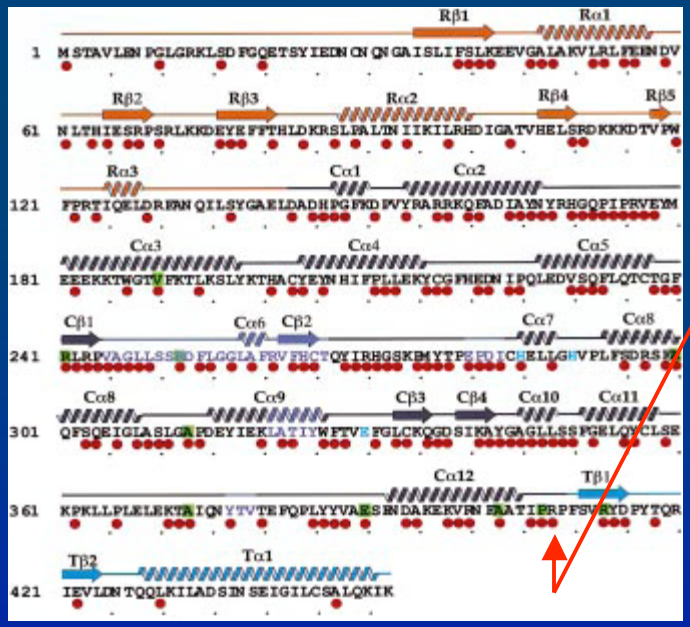
R. B. Williams *et al., Neuropsychopharmacology* **28,** 533 (2003).

# Identification of (G1463A) SNP in *hTPH2*



# Mutations in *PAH* that lead to phenylketonuria (PKU)

- one of the most common inherited disorders
- a genetic condition associated with mutations in the *PAH* gene
- 477 mutations to date (302 missense mutations)

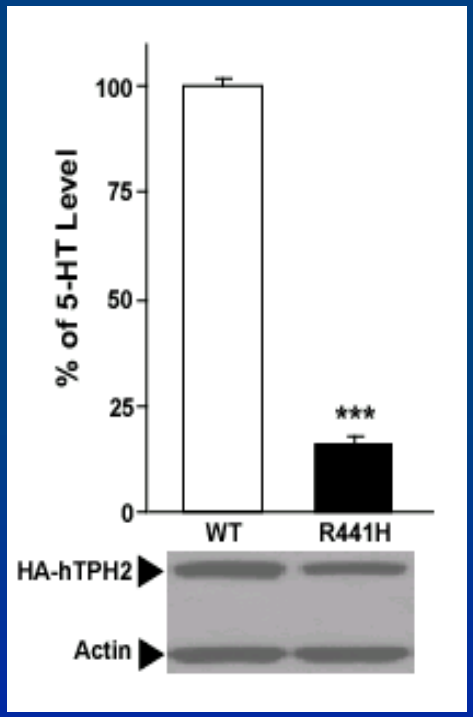


PKU Database http://www.pahdb.mcgill.ca/

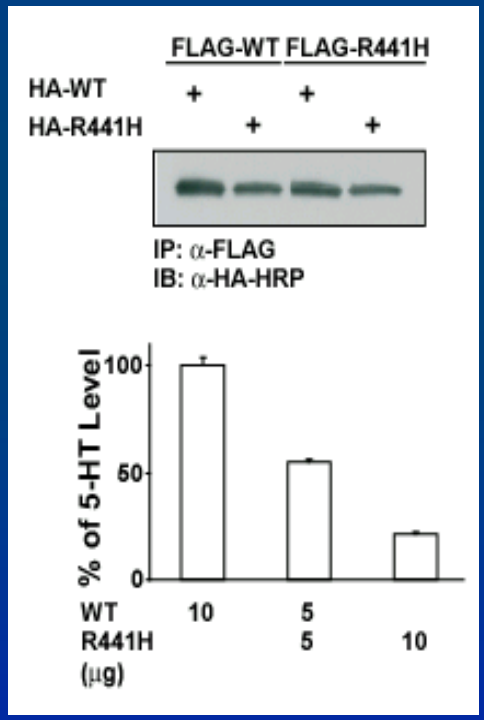
- **R408W is the most common mutations in hPAH (~9%) and represents the most severe form of PKU.**
- **R408W affects PAH protein folding, causing complete loss of protein expression and enzyme activity.**

# Biochemical characterization of TPH2 (R441H)

## Serotonin synthesis in PC12 cells




## Oligomerization




## Dominant-negative Effect

**Table 1. Summary of Subjects Carrying Functional (G1463A) SNP in *hTPH2* .**

| Unipolar Major Depression Patients | Patient I.D. | Sex | Age | Allele | Family History | Suicidality | Anxiety | SSRI Response | Note |
|---|---|---|---|---|---|---|---|---|---|
| N=87 | 1202 | F | 72 | A/A | - | + | - | + | Sertraline 200 mg |
| | 1294 | M | 80 | G/A | + | + | - | - | ECT |
| | 1496 | M | 74 | A/A | - | - | + | + | Sertraline 100 mg |
| | 1745 | M | 71 | G/A | + | - | + | - | ECT |
| | 1747 | M | 82 | G/A | + | + | - | - | ECT |
| | 1839 | F | 69 | G/A | + | - | - | - | Bupropion |
| | 1851 | F | 65 | G/A | + | + | - | - | ECT |
| | 1902 | F | 77 | A/A | + | + | + | - | Bupropion |
| | 1541 | F | 80 | G/A | + | | - | | Mild depression |
| | 1996 | F | 75 | G/A | + | | - | | Mild depression |

Family history: family history for mental illness, drug and alcohol abuse
Suicidality: suicidal ideation or attempt
Anxiety: three or more anxiety symptoms
All patients listed above were Caucasians except subject 1541 who was Arican American.
Mutant (1463A) allele was not found in a cohort of 60 bipolar disorder patients.

# Summary

- **We have identified the first functional (G1463A) SNP (Arg441His) in the coding region of neuronal-specific TPH2 in patients with unipolar major depression.**

- **TPH2 (R441H) exhibits ~80% loss-of-function when expressed in cell culture systems.**

- **This is the first direct evidence of the role of serotonin synthesis in neuropsychiatric disorders .**

- **Functional SNPs in *TPH2* can be used as genetic markers for the diagnosis and effective treatment of serotonin-related neuropsychiatric disorders.**

# Acknowledgements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David Schwartz

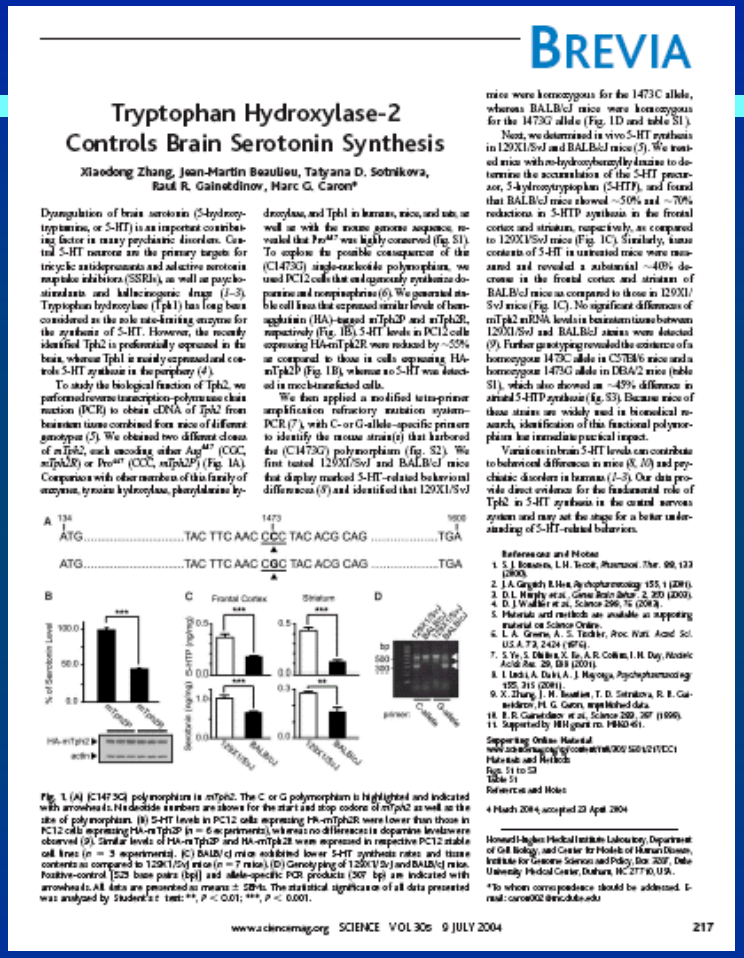
Lauranell Burch

Tony Church

Center for Human Genomics

Marcy Spear

Alison Ashley-Koch



BREVIA

# Tryptophan Hydroxylase-2 Controls Brain Serotonin Synthesis

Xiaodong Zhang, Jean-Martin Beaulieu, Tatyana D. Sotnikova, Raul R. Gainetdinov, Marc G. Caron*

Dysregulation of brain serotonin (5-hydroxytryptamine, or 5-HT) is an important contributing factor in many psychiatric disorders. Central 5-HT neurons are the primary targets for tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), as well as psychostimulants and hallucinogenic drugs (*1*–*3*). Tryptophan hydroxylase (Tph1) has long been considered as the sole rate-limiting enzyme for the synthesis of 5-HT. However, the recently identified Tph2 is preferentially expressed in the brain, whereas Tph1 is mainly expressed and controls 5-HT synthesis in the periphery (*4*).

To study the biological function of Tph2, we performed reverse transcription–polymerase chain reaction (PCR) to obtain cDNA of *Tph2* from brainstem tissue combined from mice of different genotypes (*5*). We obtained two different clones of *mTph2*, each encoding either Arg$^{447}$ (CGC, *mTph2R*) or Pro$^{447}$ (CCC, *mTph2P*) (Fig. 1A). Comparison with other members of this family of enzymes, tyrosine hydroxylase, phenylalanine hydroxylase, and Tph1 in humans, mice, and rats, as well as with the mouse genome sequence, revealed that Pro$^{447}$ was highly conserved (fig. S1). To explore the possible consequences of this (C1473G) single-nucleotide polymorphism, we used PC12 cells that endogenously synthesize dopamine and norepinephrine (*6*). We generated stable cell lines that expressed similar levels of hemagglutinin (HA)–tagged mTph2P and mTph2R, respectively (Fig. 1B). 5-HT levels in PC12 cells expressing HA-mTph2R were reduced by ~55% as compared to those in cells expressing HA-mTph2P (Fig. 1B), whereas no 5-HT was detected in mock-transfected cells.

We then applied a modified tetra-primer amplification refractory mutation system–PCR (*7*), with C- or G-allele–specific primers to identify the mouse strain(s) that harbored the (C1473G) polymorphism (fig. S2). We first tested 129X1/SvJ and BALB/cJ mice that display marked 5-HT–related behavioral differences (*8*) and identified that 129X1/SvJ mice were homozygous for the 1473C allele, whereas BALB/cJ mice were homozygous for the 1473G allele (Fig. 1D and table S1).

Next, we determined in vivo 5-HT synthesis in 129X1/SvJ and BALB/cJ mice (*5*). We treated mice with *m*-hydroxybenzylhydrazine to determine the accumulation of the 5-HT precursor, 5-hydroxytryptophan (5-HTP), and found that BALB/cJ mice showed ~50% and ~70% reductions in 5-HTP synthesis in the frontal cortex and striatum, respectively, as compared to 129X1/SvJ mice (Fig. 1C). Similarly, tissue contents of 5-HT in untreated mice were measured and revealed a substantial ~40% decrease in the frontal cortex and striatum of BALB/cJ mice as compared to those in 129X1/SvJ mice (Fig. 1C). No significant differences of mTph2 mRNA levels in brainstem tissue between 129X1/SvJ and BALB/cJ strains were detected (*9*). Further genotyping revealed the existence of a homozygous 1473C allele in C57BL/6 mice and a homozygous 1473G allele in DBA/2 mice (table S1), which also showed an ~45% difference in striatal 5-HTP synthesis (fig. S3). Because mice of these strains are widely used in biomedical research, identification of this functional polymorphism has immediate practical impact.

Variations in brain 5-HT levels can contribute to behavioral differences in mice (*8*, *10*) and psychiatric disorders in humans (*1*–*3*). Our data provide direct evidence for the fundamental role of Tph2 in 5-HT synthesis in the central nervous system and may set the stage for a better understanding of 5-HT–related behaviors.



Fig. 1. (A) (C1473G) polymorphism in *mTph2*. The C or G polymorphism is highlighted and indicated with arrowheads. Nucleotide numbers are shown for the start and stop codons of mTph2 as well as the site of polymorphism. (B) 5-HT levels in PC12 cells expressing HA-mTph2R were lower than those in PC12 cells expressing HA-mTph2P ($n = 6$ experiments), whereas no differences in dopamine levels were observed (*9*). Similar levels of HA-mTph2P and HA-mTph2R were expressed in respective PC12 stable cell lines ($n = 3$ experiments). (C) BALB/cJ mice exhibited lower 5-HT synthesis rates and tissue contents as compared to 129X1/SvJ mice ($n = 7$ mice). (D) Genotyping of 129X1/SvJ and BALB/cJ mice. Positive-control [529 base pairs (bp)] and allele-specific PCR products (367 bp) are indicated with arrowheads. All data are presented as means ± SEMs. The statistical significance of all data presented was analyzed by Student's *t* test: **, $P < 0.01$; ***, $P < 0.001$.

References and Notes
1. S. J. Bonasera, L. H. Tecott, *Pharmacol. Ther.* **88**, 133 (2000).
2. J. A. Gingrich, R. Hen, *Psychopharmacology* **155**, 1 (2001).
3. D. L. Murphy et al., *Genes Brain Behav.* **2**, 200 (2003).
4. D. J. Walther et al., *Science* **299**, 76 (2003).
5. Materials and methods are available as supporting material on *Science* Online.
6. L. A. Greene, A. S. Tischler, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 2424 (1976).
7. S. Ye, S. Dhillon, X. Ke, A. R. Collins, I. N. Day, *Nucleic Acids Res.* **29**, E88 (2001).
8. I. Lesch, A. Dell, A. J. Hayoya, *Psychopharmacology* **155**, 315 (2001).
9. X. Zhang, J. M. Beaulieu, T. D. Sotnikova, R. R. Gainetdinov, M. G. Caron, unpublished data.
10. R. R. Gainetdinov et al., *Science* **283**, 397 (1999).
11. Supported by NIH grant no. MH60451.

Supporting Online Material
www.sciencemag.org/cgi/content/full/305/5681/217/DC1
Materials and Methods
Figs. S1 to S3
Table S1
References and Notes

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Report

# Loss-of-Function Mutation in Tryptophan Hydroxylase-2 Identified in Unipolar Major Depression

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## Summary

Dysregulation of central serotonin neurotransmission has been widely suspected as an important contributor to major depression. Here, we identify a (1463A) single nucleotide polymorphism (SNP) in the rate-limiting enzyme of neuronal serotonin synthesis, human tryptophan hydroxylase-2 (*hTPH2*). The functional SNP in *hTPH2* replaces the highly conserved Arg441 with His, which results in ~80% loss of function in serotonin production when hTPH2 is expressed in PC12 cells. Strikingly, SNP analysis in a cohort of 87 patients with unipolar major depression revealed that nine patients carried the mutant (1463A) allele, while among 249 controls, three subjects carried this mutation. In addition, this functional SNP was not found in a cohort of 80 bipolar disorder patients. Identification of a loss-of-function mutation in hTPH2 suggests that defect in brain serotonin synthesis may represent an important risk factor for unipolar major depression.

## Introduction

The neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) has been implicated in a variety of physiological functions in both peripheral and central nervous systems (CNS) (Lucki, 1998; Veenstra-VanderWeele et al., 2000; Malhotra et al., 2004). Many neuropsychiatric disorders, such as depression (Lesch, 2004; Malhotra et al., 2004), schizophrenia (Veenstra-VanderWeele et al., 2000), autism (Veenstra-VanderWeele and Cook, 2004), aggression and suicidal behavior (Arango et al., 2005), and attention-deficit/hyperactivity disorder (ADHD) (Gainetdinov et al., 1999; Quist and Kennedy, 2001), are considered to be related to dysfunction in serotonergic neurotransmission in the CNS. Therefore, the brain 5-HT system is a major target for tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and psychostimulants (Lucki, 1998; Gainetdinov and Caron, 2003; Blier and Abbott, 2001; Gordon and Hen, 2004; Malhotra et al., 2004). Numerous studies have suggested associations between various neuropsychiatric disorders and genes that modulate central serotonergic neurotransmission, such as the 5-HT transporter (SERT, 5-HTT) (Lesch et al., 1996; Caspi et al., 2003; Murphy et al., 2003), 5-HT receptors (Lucki, 1998; Arango et al., 2003; Bonsenes and Teeori, 2000; Gordon and Hen, 2004; Malhotra et al., 2004), and monoamine oxidases (Shih et al., 1999), as well as the rate-limiting enzymes in 5-HT synthesis, tryptophan hydroxylases (TPH1 and TPH2) (Arango et al., 2003; Harvey et al., 2004).

TPH1 and TPH2 belong to the superfamily of aromatic amino acid hydroxylases, which also includes tyrosine hydroxylase (TH) and phenylalanine hydroxylase (PAH). These four enzymes share considerable structural similarity and require the same cofactors for function (Fitzpatrick, 1999; Jiang et al., 2000). In contrast to TPH1, which controls most of peripheral 5-HT synthesis (Cote et al., 2003; Walther et al., 2003), TPH2 was recently discovered and found to be neuronal specific and predominantly expressed in brain serotonergic neurons originating from raphe nuclei (Walther et al., 2003; Patel et al., 2004). We have previously identified a functional (1473G) single nucleotide polymorphism (SNP) which results in the replacement of proline with arginine at position 447 in mouse Tph2 (Zhang et al., 2004). Expression of mutant Tph2 (P447R) in PC12 cells revealed an ~55% decrease in 5-HT levels as compared to wild-type Tph2. Moreover BALB/cJ and DBA/2 inbred mice carrying the homozygous mutant (1473G) alleles showed 50%–70% reduction in the rate of synthesis of cortical and striatal 5-HT accompanied by ~40% reduction in 5-HT tissue content when compared to C57BL/6 and 129X1/SvJ inbred mice carrying homozygous wild-type (1473C) alleles. Interestingly, these strains of mice display significantly different behaviors and responses to antidepressants (Lucki et al., 2001). These observations provided direct evidence for the fundamental role of Tph2 in brain 5-HT synthesis (Zhang et al., 2004) and raised the interesting possibility that similar mutations in human *TPH2* (*hTPH2*) may affect brain 5-HT homeostasis in certain neuropsychiatric conditions.

Here we report the identification of a functional (1463A) SNP in *hTPH2*, which replaces a highly conserved Arg441 with His and results in an ~80% reduction in activity when expressed in cell culture systems. Furthermore, we identified nine subjects carrying this functional SNP in a cohort of 87 unipolar major depression patients. These data provide a potential molecular mechanism for aberrant 5-HT function in neuropsychiatric disorders.

## Results

In order to explore whether functional SNP(s) could be identified in *hTPH2*, we screened 11 exons of *hTPH2* by sequence analysis in 48 genomic DNA samples randomly selected from a cohort of ~300 individuals from a study of psychosocial and behavioral risk in lower

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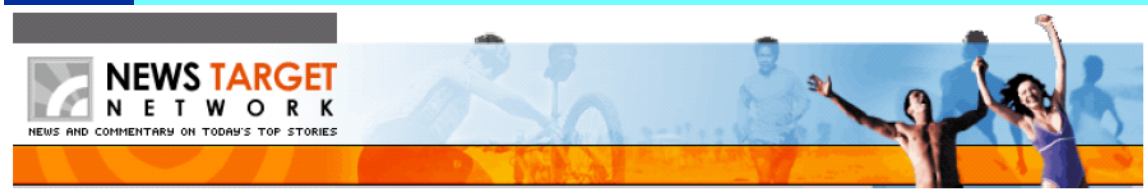
*Science* **305**, 217 (2004)

*Neuron* **45**, 11-16 (2005)

# *News Target Brings You The Real Story Behind The News*




Tuesday, January 04, 2005 commentary:

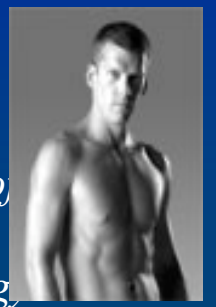
**Health researchers try to blame depression on genes**

Tuesday, January 04, 2005 commentary:

**Mass media continues to distort health sciences with misleading headlines like 'happiness is controlled by your genes'**

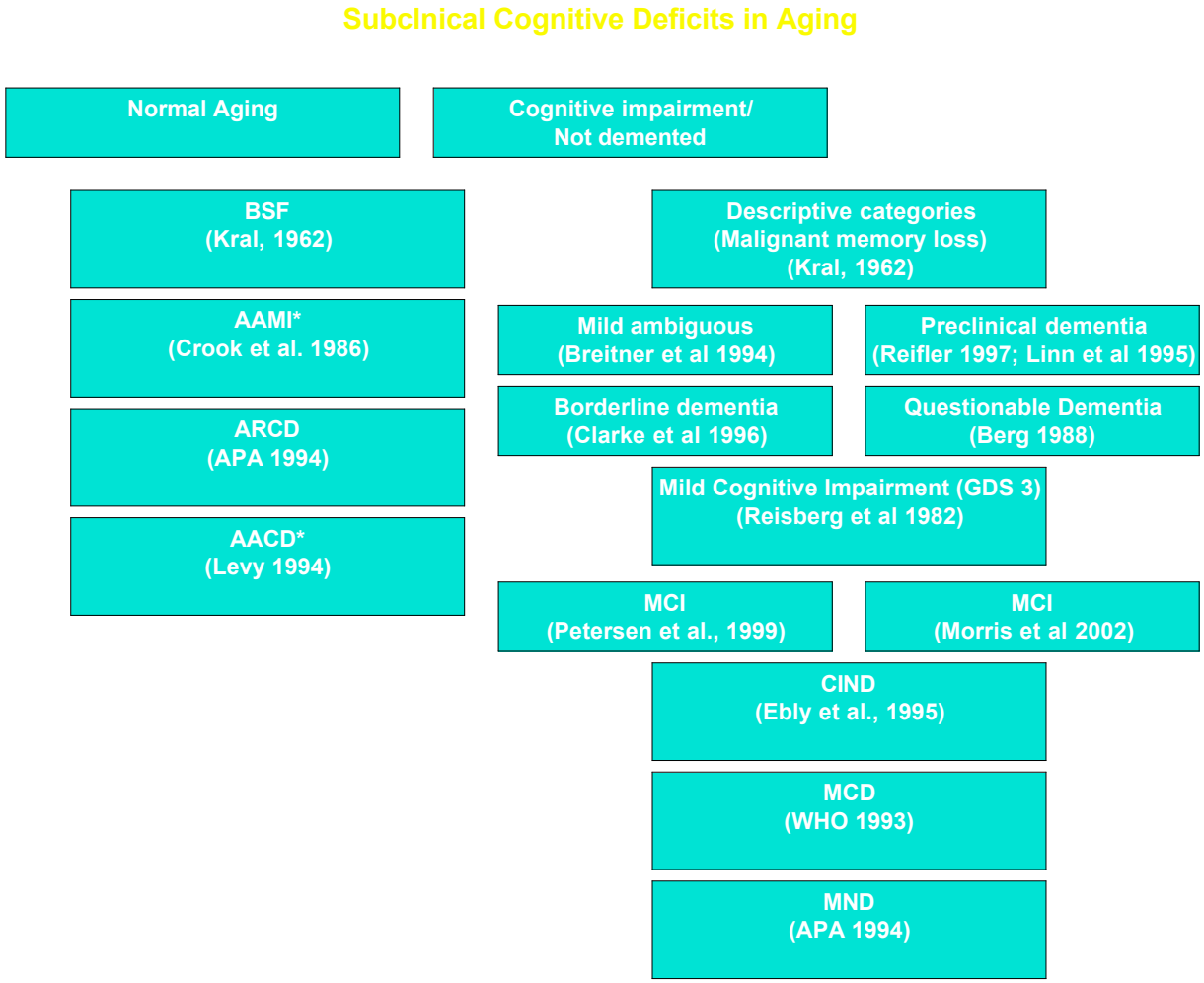
"It's the same old story by conventional medicine: focus on the genes, the drugs, and surgical procedures. Meanwhile, ignore all the other factors that don't generate profits such as natural sunlight -- a powerful anti-depressant treatment. …. That is, unless you think we were somehow pre-programmed to be depressed because it's in our genetic code.
It's a preposterous idea, actually. You'd have to be insane to think our evolutionary path somehow favored genes that actually cause mental depression."

**About the author:**



*Author Mike Adams is a holistic nutritionist with over 4,000 hours of study on nutrition, wellness, food toxicology and the true causes of disease and health. He is well versed on nutritional and lifestyle therapies for weight loss and disease prevention / reversal. … In his spare time, Adams engages in pilates, cycling, strength training, gymnastics and comedy improv training. In the technology industry, Adams is president and CEO of a well known email marketing software company.*

# Historical Context MCI



# MILD COGNITIVE IMPAIRMENT CRITERIA

- **MEMORY COMPLAINT**
- **MEMORY IMPAIRED FOR AGE**
- **NORMAL GENERAL COGNITIVE FUNCTION**
- **NORMAL ACTIVITIES OF DAILY LIVING**
- **NOT DEMENTED**

# Mild Cognitive Impairment Amnesic (MCI-a)

(Petersen et al., 1995;1999; 2001)

- Report of cognitive decline/ complaint
- Normal IADLs (CDR 0.5)
- MMSE in normal range (24+)
- Abnormal memory for age (1.5 sd below age/ed adjusted mean)
- Otherwise normal cognition
- Not demented
- No neurological/ medical explanation
- No psychiatric disorder

# Cognitive Impairment No Dementia (CIND)

(Ebly et al., 1995; Graham et al., 1997)

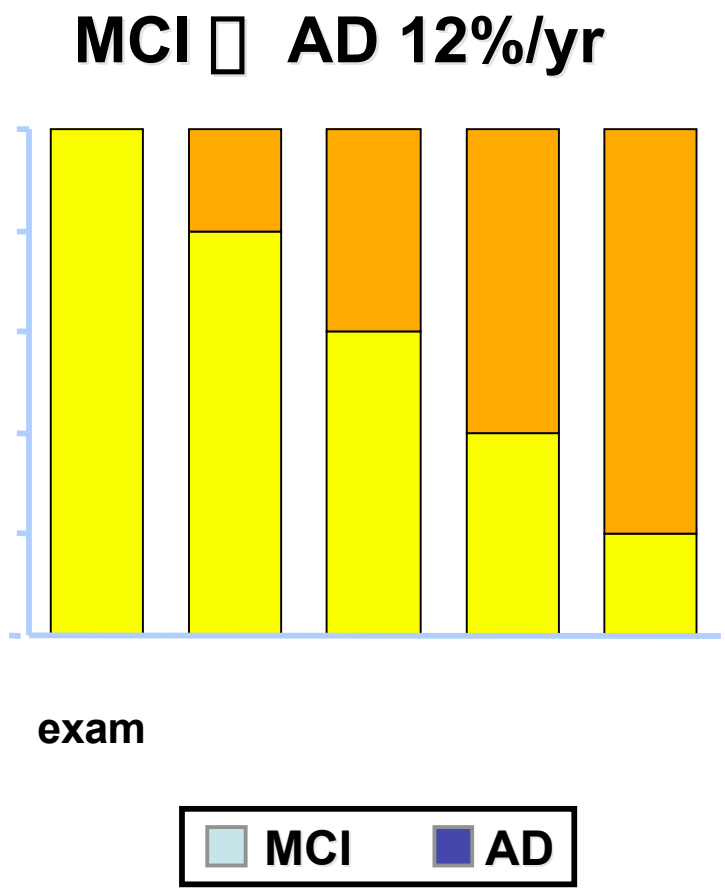
- Report of cognitive decline
- Objective evidence of difficulty in at least one of the following (1.5 sd):
  - Memory
  - Executive function
  - Language
  - Visuospatial
- May be due to systemic illness, cerebral disease, psychiatric disturbance
- Excludes frank dementia

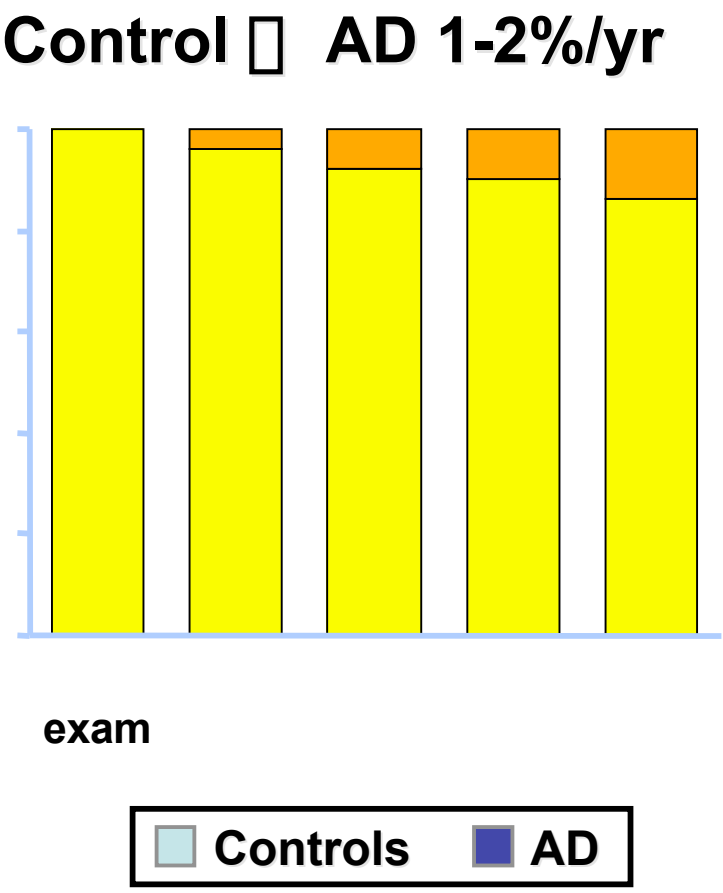
# Prevalence of Mild Cognitive Syndromes

- Rates vary across studies from 3.2%- 27%, underscoring the effect of criteria and their operationalization:
  - 3.2% MCI (Ritchie et al., 2001)
  - 5.3% MCI (Hanninen et al., 1996)*
  - 6.0% MCI (Lopez, et al., 2003)
  - 10.7% CIND (DiCarlo et al., 2000)
  - 16.8% CIND (Graham et al., 1997)
  - 18.8% MCI/CIND (Lopez et al., 2003)
  - 20.9% AACD (Ritchie et al., 2001)
  - 23.4% CIND/AACD (Unverzagt et al., 2001)
  - 23.5% AACD (Schroder et al., 1998)
  - 26.6% AACD (Hanninen et al., 1996)**

***Older sample*

# Mild Cognitive Impairment (MCI)




Petersen RC et al: Arch Neurol 56:303-308, 1999

# Conversion Rates to Dementia

- Higher rates of conversion to dementia compared to controls
  - 10%-15% year compared
  - 1-2% in controls (e.g. Petersen et al., 1999)
  - Rates <10%  reported for BSF, AAMI, GDS=3, MCD
  - Rates>10% found for MCI, AACD,CIND

# Conversion Rates to Dementia

- In epidemiological samples, the rates are somewhat variable depending on a number of factors, including but not limited to:
  - the outcome (dementia, AD)
  - criteria for syndrome (MCI, CIND etc)
  - operationalization of inclusion criteria (1.0 vs 1.5 sd)
  - Consideration of exclusionary factors (e.g. medical explanations)
  - intervals of follow-up (1 yr, 18 mo, 3yrs etc)

# Conversion Rates to Dementia

| Category | Interval | Conversion | Citation |
|---|---|---|---|
| MCI<br>AACD | 3 yrs | 0%-11%<br>18%-29% | Ritchie et al (2001) |
| MCI | 1 yr | 8.3%* | Larrieu et al. (2002) |
| CIND/AACD<br>Vascular<br>Subsyndromal | 1.5 yrs | 26%<br>43%<br>34% | Unverzagt et al (2002) |
| MCI<br>AACD | 2.6 yrs | 33%<br>36%-47% | Busse et al. (2003) |
| CIND | 5.0 yrs | 47% | Tuokko et al., 2003 |

* Convert to AD

# Stability of Syndromes

- Data across studies, indicate considerable instability in the diagnostic groupings over time.
- Possibly due to depression or other medically illnesses that remit over the interval
- Or artifacts of measurement (e.g. regression to the mean & ‘test-retest effect’)
- Bottom line for inferences about modifiability, need to keep in mind that some subjects will revert to ‘normal” without intervention

# Modifiable?
# Risk Factors for MCI

- Suggested risk factors for MCI include but are not limited to:
  - APOE
  - low education
  - cerebrovascular disease
  - low cognitive test scores
  - *depression*

(e.g. Lopez et al.,2003; Archives of Neurology)

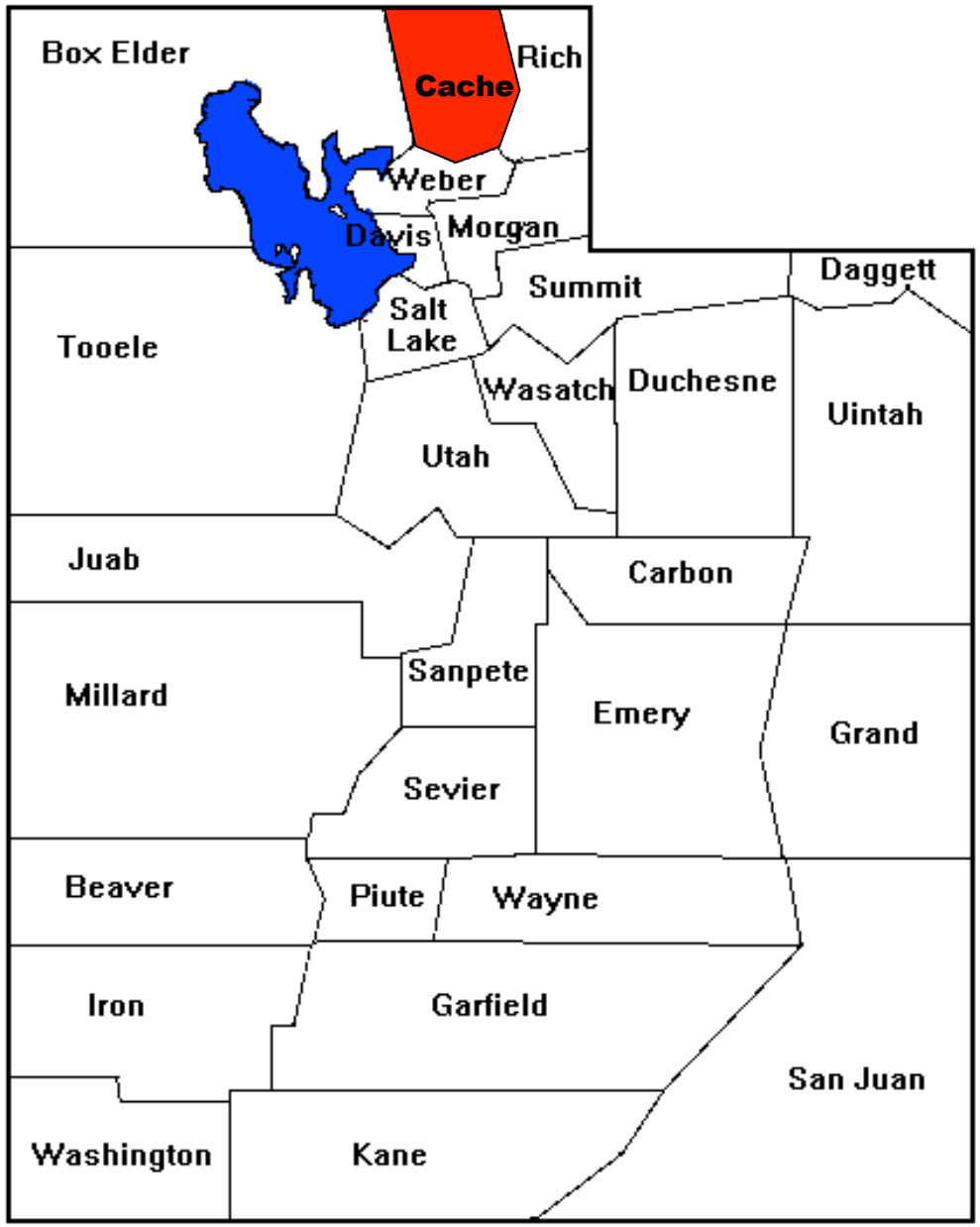
# Challenges/ Issues

- Group definition (MCI,CIND) and endpoints
  - cognitive change
  - dementia
- How to operationalize
  - which measures to select
  - required change (1, 1.5 sd)
  - how many tests impaired
  - required metric

# Challenging Issues

- Etiological considerations when designing metrics
  - sensitive to vascular, AD
- Methods to study progression
  - multiple time points over extended interval
  - reliable change metrics
- Sample differences:
  - clinic, community, population
- Effects of selective attrition

# Study in Cache County, Utah



# Risk Factors for MCI

- Other antecedent exposures that affect AD risk may also potential exert a relationship in MCI & cognitive change.
  - Data from Cache County suggest hormone therapy (Carlson et al., 2002 Neurology) and some cardiovascular risk factors- diabetes, MI (Garrett et al., JINS, 2003) affect decline.
- To the extent that some of these factors can be modified may affect rates of  conversion of MCI to dementia

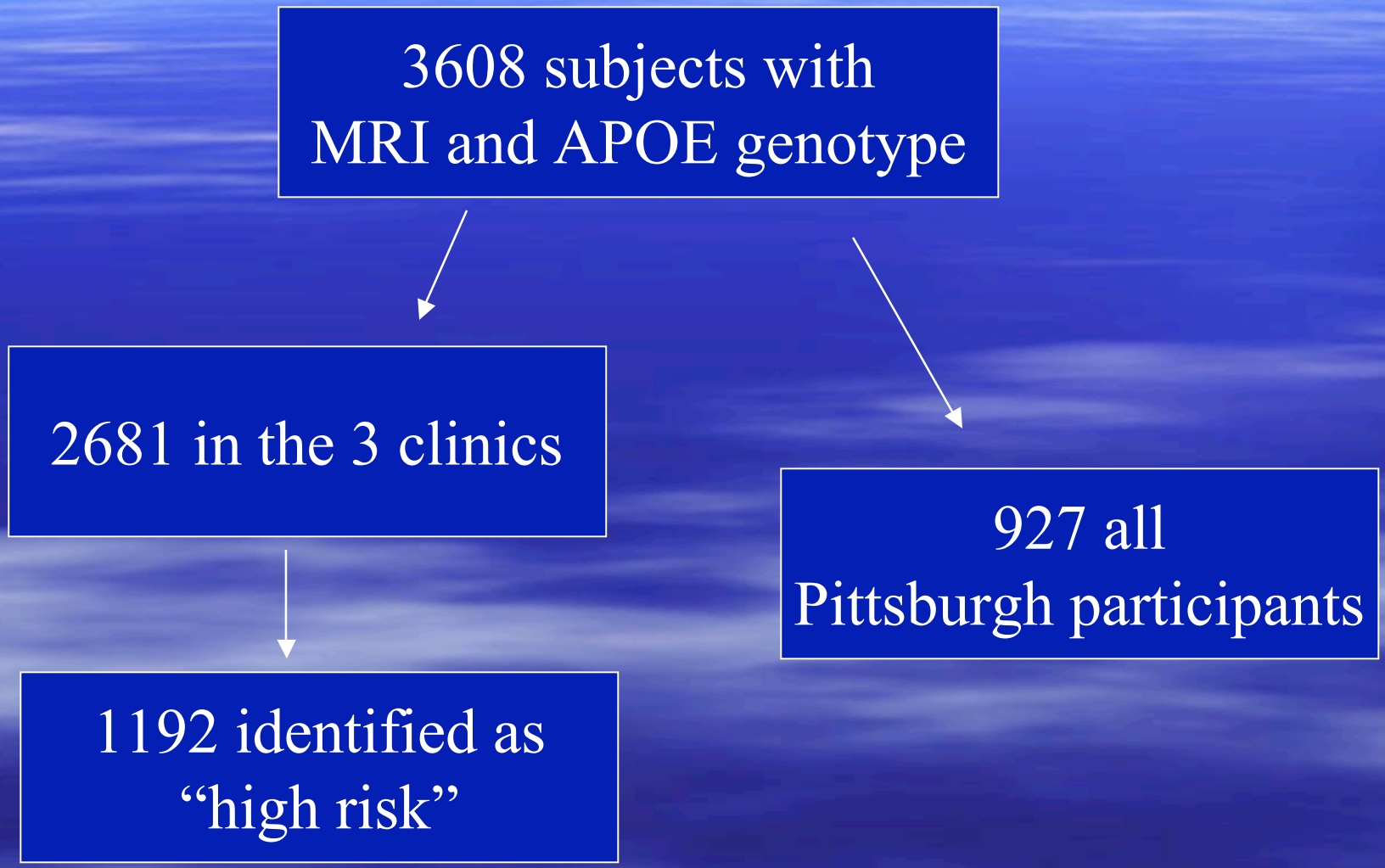
# Progression to dementia: The Cache County Study
## (Tschanz et al., JINS 2003)

- Sample of 4475 subjects categorized into one of three groups by clinicians (not operationalized criteria) based on multi-screen assessment protocol:
  - Noncase
  - MA/MCI -amnesic
  - Other Cognitive Impairment (CIND)
- Same protocol three years later for assessment of incident dementia

# RESULTS
# Demographics

| | MA/MCI amnesic | Other Cognitive Impairment | Non-Case |
|---|---|---|---|
| **Males** | **33** | **62** | **1844** |
| **Females** | **51** | **58** | **2427** |
| **Mean Age (S.D.)** | **83.46 (6.87)** | **80.12 (7.37)** | **74.58 (6.64)** |
| **Mean Education (S.D.)** | **12.81 (3.10)** | **12.85 (3.02)** | **13.27 (2.87)** |
| **3-Yr. Follow-up (% of Baseline Participants)** | **44 (52%)** | **68 (57%)** | **3228 (76%)** |
| **3-Yr. Conversion to Dementia (%)** | **17 (42.5%)** | **23 (35.4%)** | **106 (3.4%)** |

# CHS Cognition Study



# MCI Diagnostic Classification

- MCI amnestic-type
- MCI Multiple cognitive domain-type

# MCI Amnestic-type

- Memory deficits, defined as performance >1.5 below that of individuals of comparable age, and education.
- Other domains are normal.
- The memory impairment represent a decline from previous level of functioning.

# MCI multiple cognitive domain-type

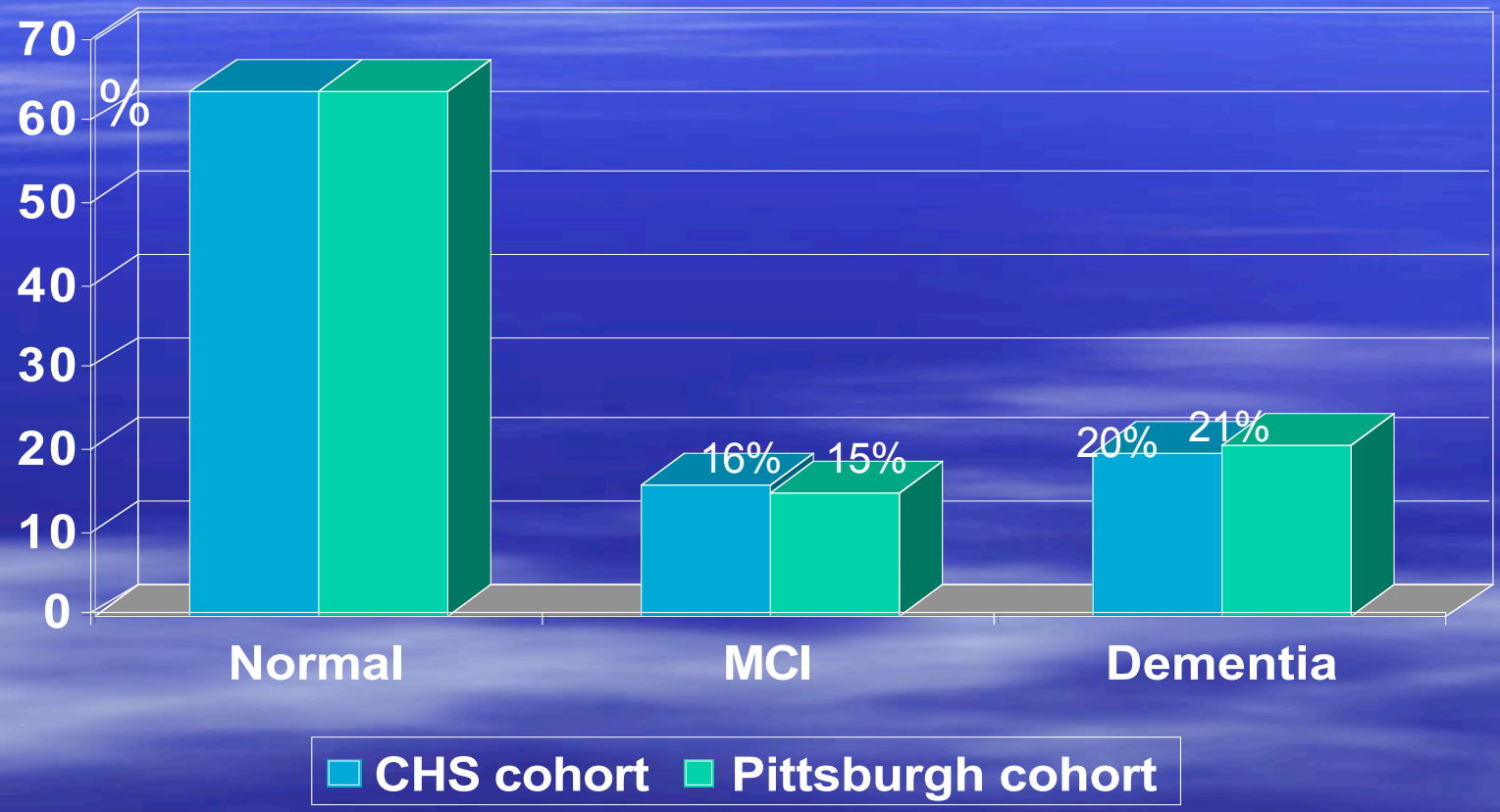
- Deterioration in at least one cognitive domain (not including memory).

  OR

  One abnormal test in at least two domains without sufficiently severe cognitive function impairment, or loss of IADLs to constitute dementia.

- The cognitive impairment represent a decline from previous level of functioning.

# Proportion of participants with MCI and dementia in the CHS Cognition Study



# Risk Factors for MCI

1. Age*
2. Education level
3. Gender
4. Race
5. APOE-4 allele
6. Neuropsychological measures: 3MSE, and DSST*.
7. Cardiovascular risk factors:
   - Heart disease*
   - Diabetes mellitus*
   - Hypertension*
9. Depression Measures (CES-D)*
10. MRI findings (1992-94)

*Closest to MRI. CES-D: Center for Epidemiological Studies Depression Scale

# Risk factors for MCI in the CHS cohort

(Multivariate analysis)

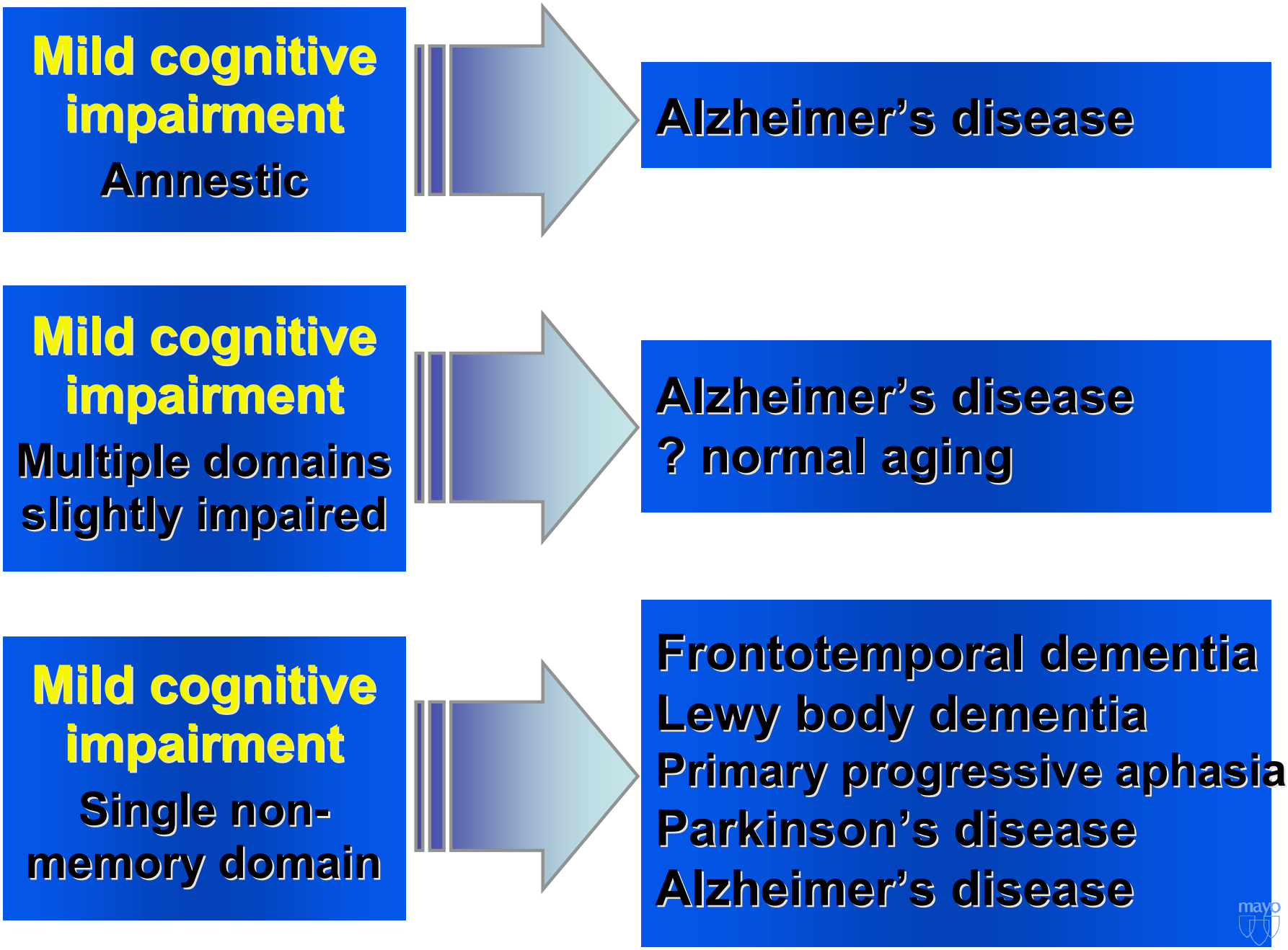
| | Odds Ratio | 95% CI |
|---|---|---|
| African-Americans: | 4.4 | 3.2 – 5.8 |
| <High school | 0.8 | .61 - .99 |
| MRI-identified infarcts: | 1.4 | 1.1 – 1.9 |
| Cortical atrophy grade >5: | 1.5 | 1.1 – 1.8 |
| DSST closest to MRI | 1.0 | .97 - .99 |
| 3MSE closest to MRI | 0.9 | .90 - .95 |
| CES-D >8 closest to MRI | 1.5 | 1.1 – 1.9 |

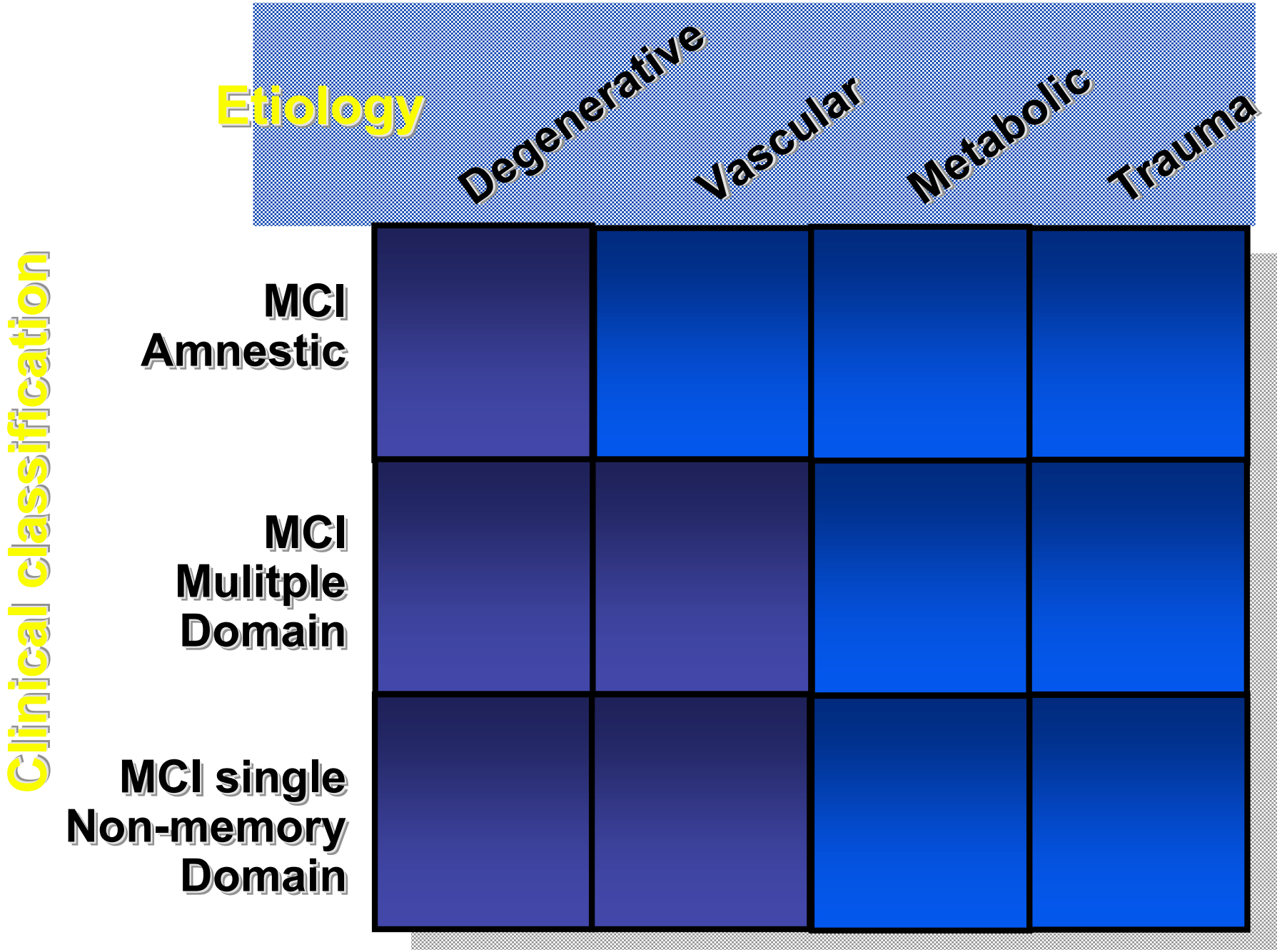
CES-D: Center for Epidemiological Studies Depression Scale

# Risk Factors for MCI subgroups

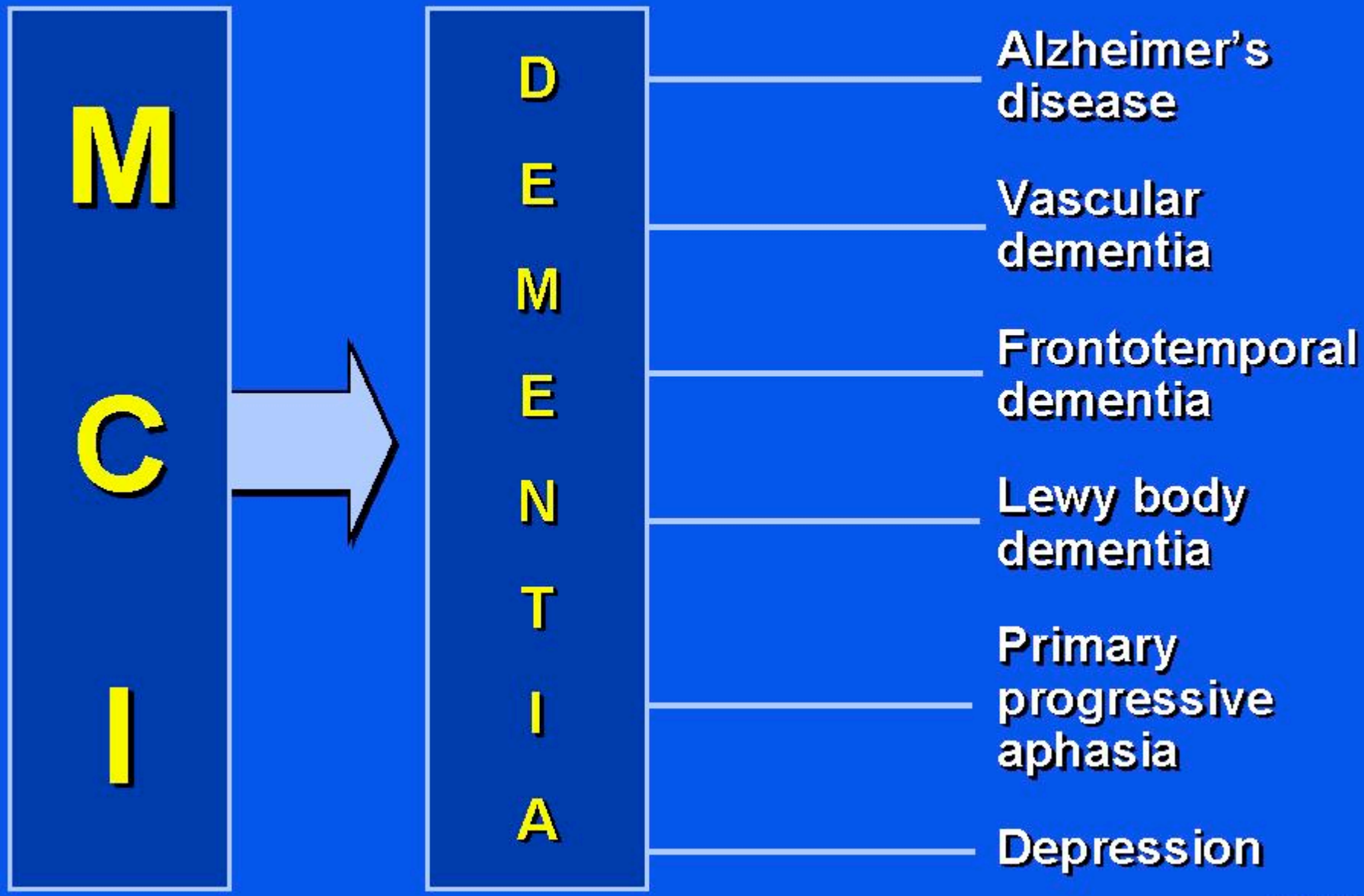
(Multivariate analysis)

| | MCI-AT<br>OR (95% CI) | MCI-MCDT<br>OR (95% CI) |
|---|---|---|
| APOE-4 allele | 2.5 (1.13 – 5.69) | NA |
| MRI-identified infarcts | 2.3 (1.07 – 5.02) | NA |
| 3MSE scores | .9 (.82 - .96) | .9 (.82 - .91) |
| DSST scores | NA | 1.0 (.93 - .99) |


Mild cognitive impairment
Amnestic
Alzheimer's disease
Mild cognitive impairment
Multiple domains slightly impaired
Alzheimer's disease
? normal aging
Mild cognitive impairment
Single non-memory domain
Frontotemporal dementia
Lewy body dementia
Primary progressive aphasia
Parkinson's disease
Alzheimer's disease


Etiology
Degenerative
Vascular
Metabolic
Trauma
Clinical classification
MCI Amnestic
MCI Mulitple Domain
MCI single Non-memory Domain

# Progression of Mild Cognitive Impairment



# MCI Tenets

- Not all MCI represents AD
- All AD patients go through an MCI stage
- AD symptoms progress from MCI to greater severity of dementia
  - "Conversion" (MCI to AD) is a clinical construct inconsistent with pathobiology
- Clinical methods accurately identify MCI-AT
- Quality of clinical information (informants) and labelling threshold of clinician determine dx