Genetics And Neural Plasticity After Stroke

Steven C. Cramer, MD

Professor, Depts. Neurology, Anatomy & Neurobiology, and PM&R
Clinical Director, Sue & Bill Gross Stem Cell Research Center
Associate Director, Institute for Clinical & Translational Science

University of California, Irvine
Disclosures

Dr. Cramer has served as a consultant for MicroTransponder, Dart Neuroscience, and Toyama.
“Genetic variation, stress, and functional outcomes after stroke rehabilitation”

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stroke@uci.edu
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Genetic variation

Measures of neural plasticity

Studies of genetic polymorphisms related to stroke recovery
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Genetics—what are the variables?

**Human DNA**
- 23 pairs of chromosomes
- ~6.3 billion base pairs
- ~20,000 protein-encoding genes

**Alleles**
- Different forms of the same gene [*Sickle cell disease*]
- Generally, each person has 2 alleles for a given gene
Classifying genetic variation

**Genetic mutation**: rare, causes significant functional change \([HD]\)  

**Genetic polymorphism**: not rare (frequency \(\geq 1\%\)), relatively small effect on behavior or phenotype \([blood\ type]\)  

Many types of polymorphism, e.g., single nucleotide polymorphisms (SNP) \([BDNF\ val^{66}met]\), variable number of tandem repeats, insertions/deletions, etc  

**Numerous classes of genetic variation**, e.g., can have translocations of large amounts of DNA, frameshift, copy number variations  

**Epigenetics**: changes in the regulation of gene activity and expression not dependent on primary gene sequence
Interaction with another gene

*Epistasis:* when the expression of one gene is modified by another gene
Understanding genetic variation via interactions

Interaction with another gene

*Epistasis:* when the expression of one gene is modified by another gene

Interaction with chemical state
Understanding genetic variation via interactions

Interaction with another gene

*Epistasis*: when the expression of one gene is modified by another gene

Interaction with chemical state

Interaction with experience
Approaches to studying genetic association

--Candidate gene approach, examine key genes

--Genome-wide association study, assesses massive number of polymorphisms

--Gene score, examine group of genes across one system

--Many other possible approaches, e.g., exome sequencing, epigenetics, transcriptomic variation
Stroke Genetics Network (SiGN)

Meschia et al, Stroke 2013;44:2694-2702
Stroke Genetics Network (SiGN) Study
Design and Rationale for a Genome-Wide Association Study of Ischemic Stroke Subtypes

James F. Meschia, MD; Donna K. Arnett, PhD; Hakan Ay, MD; Robert D. Brown Jr, MD; Oscar R. Benavente, MD; John W. Cole, MD, MS; Paul I.W. de Bakker, PhD; Martin Dichgans, MD; Kimberly F. Doheny, PhD; Myriam Fornage, PhD; Raji P. Grewal, MD; Katrina Gwinn, MD; Christina Jern, MD; Jordi Jimenez Conde, MD, PhD; Julie A. Johnson, PharmD; Katarina Jood, MD; Cathy C. Laurie, PhD; Jin-Moo Lee, MD, PhD; Arne Lindgren, MD; Hugh S. Markus, FRCP; Patrick F. McArdle, PhD; Leslie A. McClure, PhD; Braxton D. Mitchell, PhD; Reinhold Schmidt, MD; Kathryn M. Rexrode, MD; Stephen S. Rich, PhD; Jonathan Rosand, MD, MSc; Peter M. Rothwell, MD; Tatjana Rundek, MD; Ralph L. Sacco, MD; Pankaj Sharma, MD; Alan R. Shuldiner, MD; Agnieszka Slowik, MD; Sylvia Wassertheil-Smoller, PhD; Cathie Sudlow, MD; Vincent N.S. Thijs, MD; Daniel Woo, MD; Bradford B. Worrall, MD, MSc; Ona Wu, PhD; Steven J. Kittner, MD; on behalf of the NINDS SiGN Study

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Studies of genetic polymorphisms related to stroke recovery
Cellular & molecular events underlying stroke recovery

**Ipsilesional changes**
- inflammatory markers
- growth-associated proteins
- cell cycle proteins
- growth factors
- GABA receptor downregulation
- NMDA receptor binding
- angiogenesis
- hyperexcitability & facil’ n of LTP
- synaptogenesis
- dendrite branching/spine density
- neuronal sprouting
- extracellular matrix remodelling
- cortical thickness

**Contralesional changes**
- inflammatory markers
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_Nudo, Curr Op Nbio, 99; Cramer & Chopp, TINS, 00; Wieloch & Nikolich, Curr Op Nbio 06_
Cellular & molecular events underlying stroke recovery

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There are also extra-neural processes of interest that affect stroke recovery, e.g., stress, inflammation, metabolism.

*Nudo, Curr Op Nbio, 99; Cramer & Chopp, TINS, 00; Wieloch & Nikolich, Curr Op Nbio 06*
The Volume of the Spleen and Its Correlates after Acute Stroke

Nina L. Chiu, BS,* Brian Kaiser, DO,* Y Vien Nguyen, DO,†
Susan Welbourne, BSN, RN,‡ Chandana Lall, MD,† and Steven C. Cramer, MD*§

Stroke recovery at the bedside

Fig. 2. Plot of means and 1 SD of Fugl-Meyer upper extremity after stroke.

Change in Fugl-Meyer scale over time after stroke

Duncan et al, Neuropharmacology; 39:835-841
A Standardized Approach to Performing the Action Research Arm Test

Nuray Yozbatiran, PT, PhD, Lucy Der-Yeghiaian, MA, OTR/L, and Steven C. Cramer, MD

Measuring extent of corticospinal tract injury to stratify patients

Riley et al, Stroke; 2011
A standardized approach to measuring corticospinal tract injury in a clinical study

Extent of corticospinal tract injured predicts treatment response.

This measure is a better predictor than infarct volume, baseline behavioral status, or demographic measures (n = 23)

Riley et al, Stroke; 2011
A standardized approach to measuring neurophysiology in a clinical study

Methods for an International Randomized Clinical Trial to Investigate the Effect of Gsk249320 on Motor Cortex Neurophysiology using Transcranial Magnetic Stimulation in Survivors of Stroke

Matt P. Malcolm\textsuperscript{1*}, Lori Enney\textsuperscript{2} and Steven C Cramer\textsuperscript{3}
Genetic variation

Measures of neural plasticity

Studies of genetic polymorphisms related to stroke recovery
The influence of genetic factors on brain plasticity and recovery after neural injury

Kristin M. Pearson-Fuhrhop\textsuperscript{a}, Erin Burke\textsuperscript{a}, and Steven C. Cramer\textsuperscript{a,b}
Transl Stroke Res, 2016 Apr 25. [Epub ahead of print]

Spontaneous and Therapeutic-Induced Mechanisms of Functional Recovery After Stroke.

Cassidy JM¹, Cramer SC²,3,4,5.
Clinicians might study genetics in order to better

• Inform therapeutic decision-making, e.g., Rx choice or Rx dose
• Understand biology and pathogenesis of disease
• Estimate individual risk, prognosis, tendencies
• Stratify enrollees in a clinical trial
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**BDNF val^{66}met SNP:** an endophenotype of brain function and spontaneous stroke recovery

**ApoE4 polymorphism:** predicts motor learning, mood, impulsiveness, response to L-Dopa

**Dopamine polygene score:**
Persons taking clopidogrel (Plavix) who have CYP2C19 loss-of-function alleles have a higher rate of cardiovascular events compared to those who do not.

Shuldiner et al, JAMA. 2009; 302:849-858
Endophenotype: a measurement (behavioral, imaging, biochemical, etc) linked to a genotype that is useful for distinguishing biological subgroups that look the same clinically.
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An endophenotype is a component of a complex phenotype that is more directly related to the underlying genotype.

Examples: OCD symptoms in certain autism spectrum disorder subgroups; or premotor cortex activation in certain Parkinson’s-related genotypes.
42 patients with chronic stroke received arm motor robot therapy
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Kim et al, Phys Therapy, 2016
Motor cortex activation varied significantly per BDNF genotype.

Same result as was seen in our prior study of healthy controls (McHughen et al, Cerebral Cortex 2010; 20:1254-1262)
Motor cortex activation varied significantly per BDNF genotype.

But: differences in cortical function not related to baseline FM or to change in FM with therapy (wrong motor task during fMRI?)

Kim et al, Phys Therapy, 2016
Genotype predicts gains in a clinical trial

Among 241 subjects in the GAIN trials, the percentage of subjects with minimal/no disability (modified Rankin Scale score 0-1) was lower when the ApoE4 genotype was present (*p = 0.01).

Cramer and Procaccio, Eur J Neurol; 2012
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Getting iv tPA instead of placebo: ARR = 13%

Getting ApoE4 (-) instead of ApoE4 (+): ARR = 17%

NINDS tPA trial; NEJM, 1995

Cramer and Procaccio, Eur J Neurol; 2012
Most genetic effects have RR in range of 1.1-1.4, effect of any single gene generally small--ApoE is a major exception
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Thus interest in combining the effect of many genes in polygenic models or panels…that assigns points for the presence of various risk alleles and calculates an overall risk of disease
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Thus interest in combining the effect of many genes in polygenic models or panels…that assigns points for the presence of various risk alleles and calculates an overall risk of disease

For example, in a study of 5 SNPs associated with prostate cancer, the investigators expressed the risk of disease associated with the increasing presence of risk alleles: they found an OR of 1.6 with risk allele at 1 SNP and up to 4.5 with risk alleles at 4 SNPs

Dopamine gene score

Constructed a gene score based on the genotype of 5 biologically active polymorphisms related to dopamine
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Hypothesized subjects with lower dopamine neurotransmission would have:
  - less learning
  - greater boost in learning with L-Dopa
  - more depression
  - poorer impulse control, greater improvement with Ropinirole
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Genetic Variation in the Human Brain Dopamine System Influences Motor Learning and Its Modulation by L-Dopa

Kristin M. Pearson-Fuhrhop¹, Brian Minton¹, Daniel Acevedo¹, Babak Shahbaba², Steven C. Cramer¹,³

¹ Department of Anatomy & Neurobiology, University of California Irvine, Irvine, California, United States of America, ² Department of Statistics, University of California Irvine, Irvine, California, United States of America, ³ Department of Neurology, University of California Irvine, Irvine, California, United States of America
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Legend

- TMS
- Baseline assessments
- Pill intake
- Skilled task practice

Day 1 2 3 4 5

2 week washout

Day 6 7 8 9 10
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Dopamine Genetic Risk Score Predicts Depressive Symptoms in Healthy Adults and Adults with Depression

Kristin M. Pearson-Fuhrhop, Erin C. Dunn, Sarah Mortero, William J. Devan, Guido J. Falcone, Phil Lee, Avram J. Holmes, Marisa O. Hollinshead, Joshua L. Roffman, Jordan W. Smoller, Jonathan Rosand, Steven C. Cramer
Lower dopamine gene scores, i.e. lower dopamine neurotransmission, associated with greater depression scores.

Pearson-Fuhrhop et Dunn et al PLOS-ONE 2014
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Dopamine Gene Profiling to Predict Impulse Control and Effects of Dopamine Agonist Ropinirole

Hayley J. MacDonald¹, Cathy M. Stinear¹, April Ren¹, James P. Coxon², Justin Kao³, Lorraine Macdonald³, Barry Snow³, Steven C. Cramer⁴, and Winston D. Byblow¹
On placebo: lower dopamine gene scores (lower dopamine neurotransmission) associated with poorer impulse control.

On the dopamine agonist Ropinirole: lower dopamine gene scores showed improved response inhibition, while higher gene scores with trend towards worsened response inhibition.

MacDonald et al, Journal of Cognitive Neuroscience (in press)
On the one hand, large consortia, big questions, big data.
  --Always with precise definitions and measures of phenotype

On the other hand, continue targeted studies of candidate genes.
  --Esp those with highest therapeutic implications
  --Need mechanistic insights, biomarkers that capture repair events of interest to optimize hypothesis testing
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