Genomics as an Informational Tool in Neurorehabilitation

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Disclosures
Dr. Cramer serves as a consultant for MicroTransponder, Dart Neuroscience, Roche, NeuroLutions, Regenera, Abbvie, SanBio, and TRCare.

Genetics and Stroke Recovery/Rehab
Types of genetic variation
Stroke recovery, neurorehabilitation, and neural plasticity
Genetic variation in relation to recovery, rehab, and plasticity

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 [Color blindness]
- 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 ≥ 1%), relatively small effect on behavior or phenotype [blood type]

Many types of polymorphism, e.g., single nucleotide polymorphisms (SNP) [BDNF val<sup>66</sup>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 chemical state

Interaction with experience

Smoking and Parkinson disease

Evidence for gene-by-smoking interactions

Approaches to studying genetic association

--Candidate gene approach, examines key genes
--Genome-wide association study, assesses massive # polymorphisms
--Gene score, examines group of genes across one system
--Many other possible approaches, e.g., exome sequencing, epigenetics, transcriptomic variation

Types of genetic variation

Stroke recovery, neurorehabilitation, and neural plasticity

Genetic variation in relation to recovery, rehab, and plasticity

What is stroke recovery, rehabilitation, and neural plasticity?
Potential human restorative therapies

- **Small molecules** eg, SSRIs, amphetamine, levodopa, niacin, memantine, etc
- **Growth factors** eg, EPO, hCG, G-CSF, b-FGF, OP-1, etc
- **Monoclonal Ab**, other large molecules eg, anti-MAG Ab
- **Stem cells**
- **Brain stimulation** eg, TMS, tDCS, tACS, epidural stim, deep brain stim; vagal nerve stim
- **Telemedicine**
- **Intensive physiotherapy, robotics, other training**
- **Lesion bypass** eg, BCI, nerve transfer
- **Motor imagery, observation, environmental enrichment, other cognitive Rx**

What is stroke recovery, rehabilitation, and neural plasticity?

Use of these terms is usually far too broad for their measurement to connect with specific gene-based hypotheses.

Cellular & molecular events underlying stroke recovery

<table>
<thead>
<tr>
<th>Ipsilesional changes</th>
<th>Contrallesional changes</th>
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<tr>
<td>inflammatory markers</td>
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<td>growth-associated proteins</td>
<td>growth-associated proteins</td>
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<td>cell cycle proteins</td>
<td>GABA receptor downregulation</td>
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<td>NMDA receptor binding</td>
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<tr>
<td>GABA receptor downregulation</td>
<td>neuronal hyperexcitability</td>
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<td>hyperexcitabil'y &amp; facil'n of LTP</td>
<td>synaptogenesis</td>
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<td>synaptogenesis</td>
<td>cortical thickness</td>
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<td>dendrite branching/spine density</td>
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<tr>
<td>neuronal sprouting</td>
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<td>extracellular matrix remodelling</td>
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<tr>
<td>cortical thickness</td>
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Laterality of brain function and stroke recovery

<table>
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<tr>
<th>Control</th>
<th>Recovered stroke patient</th>
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<tr>
<td>R finger tap</td>
<td>L finger tap</td>
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Less lateralized (more bilaterally organized) with larger infarct worse deficits over time

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Cramer et al, Stroke 97; Marshall et al, Stroke 01; Cramer et al, Exp Br Res 05

Less lateralized (non-dominant side infarct) over time

Cramer et al, Stroke 97; Marshall et al, Stroke 01; Cramer et al, Exp Br Res 05
**Site of brain activation and stroke recovery:**
posterior shift for some tasks

61 y/o RHM
6 mo after R pre-central gyrus embolus

**Network activation and spontaneous stroke recovery**

**Brain activation and treatment-related stroke recovery**

**Brain function (EEG) predicts treatment-related recovery**

256 leads
Data collection feasible in ER, ICU, rehab unit, etc
From “hello” to start data collection in 5 minutes
Current methods require only 3 minutes of data collection

**Brain function (EEG) predicts treatment-related recovery**

EEG (β coherence) predicted change in Fugl-Meyer score across 4 weeks of telerehab

**Behavioral recovery after stroke**


Molecular
Systems
Behavior
Behavioral recovery after stroke

The Case for Modality-Specific Outcome Measures in Clinical Trials of Stroke Recovery-Promoting Agents
Steven C. Cramer, MD; Walter J. Kowshetz, MD; Seth P. Finklestein, MD

Stroke. 2007;38:1393-1395.

Types of genetic variation
Stroke recovery, neurorehabilitation, and neural plasticity

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Why would clinicians study genetics?

Clinicians might study genetics in order to better
• Inform therapeutic decision-making, e.g., Rx choice or Rx dose; adverse event risk

Genetics and therapeutic decision-making

Cytochrome P450 enzymes metabolize many drugs; polymorphisms can alter drug levels, e.g., for clopidogrel, codeine, or azathioprine.

Vitamin K epoxide reductase complex reduces vitamin K; SNPs account for 25% of the variance in warfarin dosing.

Stevens Johnson syndrome from carbamazepine is substantially more common with even one copy of certain HLA alleles: B*1502 (Asian populations) and A*3101 (Europeans).
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- Understand biology and pathogenesis of disease
- Estimate individual risk, prognosis, tendencies
- Stratify enrollees in a clinical trial

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- **BDNF val66met SNP**: endophenotype
- **ApoE4 polymorphism**: spontaneous stroke recovery
- **Dopamine polygene score**: predicts motor learning, mood, impulsiveness, response to L-Dopa

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**Stroke Recovery Genetics**

- Arne Lindgren, MD, PhD; Jane Maguire, RN, PhD

- Understand biology and pathogenesis of disease
- Estimate individual risk, \( \text{Stroke. 2016;47:2427-2434} \)
- Stratify enrollees in a clinical trial

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**Genetics of motor cortex plasticity**

Kleim et al, 2006; Nat Neurosci
val<sup>66</sup>met BDNF polymorphism associated with reduced short-term, activity-dependent motor cortex plasticity

Kleim et al. 2006, Nat Neurosci


Kim DY, Quinlan EB, Gramer R, Cramer SC. BDNF val<sup>66</sup>met polymorphism is related to motor system function after stroke. Phys Ther. 2016;96:533-539

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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—other compensatory process?—wrong motor task during fMRI?—endophenotype?


Endophenotype: a measurement (behavioral, imaging, biochemical, etc) linked to a genotype that is useful for distinguishing biological subgroups that look the same clinically. An endophenotype is an inherited trait marker, a component of a complex phenotype that is more directly related to the underlying genotype.

Examples:
- Decreased pre-symptomatic hippocampal volume in certain genetic forms of Alzheimer's disease
- Increased error-related negativity (an EEG measure of cingulate activity following an error) in subjects with OCD
- Increased pre-symptomatic activation and connectivity in premotor cortex of certain genetic forms of Parkinson's disease

Genetic factors & brain atrophy after stroke

Genetic variation has been associated with differences in brain atrophy in many settings—is this true after stroke?

“Endophenotypes are typically quantitative and lie in the causal pathway to the disease but are closer to the gene action than the clinical phenotype...”

Variants in specific genes have been associated with several imaging endophenotypes of—white matter hyperintensities—covert brain infarcts by MRI—Virchow-Robin spaces—cerebral microbleeds—carotid intima/media thickness—atrial fibrillation

Genetic variation has been associated with differences in brain atrophy in many settings—is this true after stroke?

Volume of the ventricles and the brain were measured in stroke survivors enrolled in ICARE trial.\(^\text{1}\)

Brain atrophy expressed as the Ventricle-Brain Ratio (VBR).

VBR was then examined in relation to the two genotypes of interest, BDNF val66met and ApoE \(\varepsilon4\).

\[^{1}\text{Winstein et al. JAMA. 2016; 315:571-581.}\]

Mean ventricle volume=30.8 cc; brain volume=1,166 cc; and VBR=0.027.

VBR as a function of BDNF val66met carrier status, p=0.014
ApoE \(\varepsilon4\) carrier status, p=0.53

Mean VBR increases 1.97-fold (97\%) when the BDNF val66met polymorphism is present compared to absent.

BDNF val66met polymorphism assoc with 97\% greater atrophy.

But BDNF val66met not related to behavior at enrollment or 12 month change.

Suggests VBR is an endophenotype for val66met status
Genetic factors and brain atrophy after stroke

BDNF val<sup>66</sup>met polymorphism assoc with 97% greater atrophy.

But BDNF val<sup>66</sup>met not related to behavior at enrollment or 12 month change.

Suggests VBR is an endophenotype for val<sup>66</sup>met status.

VBR association with atrophy but not behavior might reflect short time interval examined, no measure of brain function (reserve); younger group enrolled, or that patients had mild-moderate deficits.

Insights into biology of inter-subject differences in brain anatomy after stroke might inform restorative therapy and clinical trials.

Genotype predicts gains in a clinical trial

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

Getting iv tPA instead of placebo: ARR = 13%
Getting ApoE4 (-) instead of ApoE4 (+): ARR = 17%

Polygene score

Most genetic effects have RR in range of 1.1-1.4; effect of any single gene is generally small—ApoE is a major exception.
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Thus interest in combining effect of many genes in polygenic models that assign points for the presence of risk alleles and calculates an overall risk of disease.

Example: in a study of 5 SNPs associated with prostate cancer, risk of disease associated with increasing # risk alleles:

- OR = 1.6 with risk allele at 1 SNP,
- OR = 4.5 with 4 risk alleles

The many proteins of the dopamine system

Dopamine gene score

Constructed a gene score based on the genotype of 5 biologically active polymorphisms related to dopamine.

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-Fuhrhop, Brian Minton, Daniel Acevedo, Babak Shahbaba, Steven C. Cramer

Pearson-Fuhrhop et al PLOS-ONE 2013

Hand training for 2hr/day x 2 mo in 33 children with cerebral palsy
Gains in Assisting Hand Assessment scores varied by gene score

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Dopamine gene score

Dopamine Genetic Risk Score Predicts Depressive Symptoms in Healthy Adults and Adults with Depression

Kristin M. Pearson-Fuhrhop1,2,3, Eric C. Denn1,4,5, Sarah Munter5, William J. Devan5, Guido J. Falcoz5, PhD, Lee1,6,7,8,4, Jolene J. Holmes9,10, Marissa O. Hellmeck9,10, Joshua L. Hoffman9, Jordan W. Smoller1,4,9, Jonathan Rosand1,11, Steven M. Cramer7,9,11.

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Dopamine gene score and depression

Lower dopamine gene scores, i.e. lower dopamine neurotransmission, associated with greater depression scores.

Pearson-Fuhrhop 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. Stinegar1, April Bea1, James P. Cosner2, Justin Kao3, Lorraine Macdonald3, Barry Snow3, Steven C. Cramer4, and Winston D. Bylow5

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 had trend towards worsened response inhibition.


Moving forward

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.
Stroke, Stress, Rehabilitation, and Genetics Study

The STRONG Study
www.STRONG-study.com

What is The STRONG Study?
STRONG Study will evaluate how stress and genetics can affect recovery after stroke. The goal is to understand:
1. How common are stress reactions in people after stroke?
2. Do stress reactions affect brain function?
3. How do stress reactions affect recovery from stroke?
4. Do stress reactions change over time?

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