GWAS of Fatigue: Use of the UK Biobank for Genetic Discovery

Richa Saxena
Massachusetts General Hospital, Harvard Medical School
Disclaimer
This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure
This certifies that I, Richa Saxena, have no financial relationship that is relevant to the subject matter of this presentation.
Fatigue is multi-factorial and amenable to genetics

- Gene discovery unbiased to known biology
- Biological and pathophysiological insights
- New therapeutic hypotheses

Example
CFS prevalence: 0.2%
heritability: 10-40%

Strategies: GWAS, exome/genome seq
The UK Biobank: population-based prospective study and health resource (n ~500,000)

Data on UK Biobank participants

- Lifestyle, medical history, sociodemographic
- Physical measures
- Environmental measures
- Urinary biomarkers
- Genetic data via the EGA (500,000)
- Cognitive function and hearing tests
- Health outcome data
- Genotyping & imputation (n = 500,000)
- Web-based questionnaire data (~200,000)
- Physical activity monitor (100,000)
- Imaging (15,000+)

Age 40-70 years, 94% European ancestry
GWAS of sleep quality, quantity, timing, sleepiness, tiredness
UK Biobank phenotypic resources to study fatigue

2006-2010 Baseline assessment
- self-reported clinical diagnosis of CFS
- N=502,000 (1,825 cases)
- 1 tiredness, 7 sleep questions

2010-2014 Activity monitoring
- N=100,000

2020 Online pain questionnaire
- 7 CFS questions
- 9-item Fatigue Severity scale
- N=167,219 (2,723 cases)

Ongoing EHR Diagnosis Code
- Ongoing extraction from health records
- CFS (1,229 cases)
Genetic risk factors of ME/CFS: a critical review

Joshua J. Dibble¹, Simon J. McGrath² and Chris P. Ponting¹,*

Human Molecular Genetics, 2020, Vol. 29, No. R1

GWAS of Chronic Fatigue Syndrome in UK Biobank

Self-report of diagnosis

1,825 cases
~300,000 controls

<table>
<thead>
<tr>
<th>DNA variant chromosome nearby gene</th>
<th>Minor allele freq (gnomAD)</th>
<th>P (Neale) female</th>
<th>P (Neale) male</th>
<th>P (Neale) both</th>
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<tbody>
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<td>rs7337312</td>
<td>13</td>
<td>2.6 × 10⁻⁸</td>
<td>0.74</td>
<td>4.0 × 10⁻⁶</td>
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<tr>
<td>SLC25A15</td>
<td>0.54</td>
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SLC25A15 is a mitochondrial transporter key for urea cycle.

Dibble, HMG 2020

Main symptom (acute or chronic encephalopathy) is related to high protein intake, increased catabolism, infections or stress.

**Medical & Science**

**hhh**

**hyperornithinemia**
**hyperammonemia**
**homocitrullinuria syndrome**

by acronymsminterq.com

**Nurses:**
- Poor feeding
- Lethargy
- Loss of reflexes
- Seizures

**Temperature lability**
**Hyperventilation**
**Respiratory acidosis**
**Intracranial hemorrhages**
**Progressive encephalopathy**

**Infants and children**
- Failure to thrive
- Feeding problems
- Nausea, vomiting

**Episodic encephalopathy**
**Ataxia**
**Convulsions**

**Adolescents and adults**
- Chronic neurologic symptoms
- Chronic psychiatric symptoms

**Episodic encephalopathy**
**Behavioral problems**
Phewas: SLC25A15 associates with immune cell traits

~2,000 illness codes
UK Biobank

~3,000 disease, biomarker, behavioral traits in
UK Biobank
Broader phenotype classification - Fatigue and dysautonomia

Leveraging UK Biobank EHR data

ICD10 codes for fatigue and dysautonomia
- Dysautonomia
- POTS
- CFS

13,549 cases and 435,365 controls
ADRA2A in fatigue and dysautonomia

Ollila lab

Samuel Jones

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Hanna Ollila
GWAS to biology: leverage multi-omics and physiologic characterization for systems level insights

- Multilevel data integration (Oomics-wide association study, OWAS)
- Genetic architecture (Number, Effect, Pleiotropy, Epistasis, Environmental interaction)

Schematic adapted from Du et al., *Front.Plant.Sci* 2019
Cross-phenotype genetic analysis can highlight shared biology and identify heterogeneous underlying mechanisms.

Individual variants cluster into subtypes of disease
Wang, Nat. Comm 2019

Genetic overlap across sleep traits
Posthuma, Nat Genet 2019

Mendelian Randomization
Vitamin D levels & Tiredness
Havdahl, Sci Rep 2019
Exome-sequencing at scale pinpoints rare coding variation

3,817 phenotypes with gene-based and single-variant testing across 281,852 individuals with exome sequence data from the UK Biobank
Global Biobanks will enhance gene discovery, risk prediction, subtyping of disease and help to prioritize therapeutic targets.
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