Polygenic epilepsies

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Epilepsy Genetics Update 2020

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Today we know with high confidence about 30 – 100 genes associated with Epilepsy – Neurodev. disorder with seizures.

The number of known genes for rare (monogenic) epilepsies is growing.
All types of causal variants

Modified from McCarthy et al., 2008
PMID: 18398418
All types of causal variants

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PMID: 18398418
Monogenic vs. polygenic epilepsies

Overall frequency

From Dhiman, 2017
PMID: 28615892
Genes known to cause Mendelian forms of epilepsy play only minor roles for common forms of epilepsy.

There is an unmet need for predictive genetic markers for the common epilepsies.
The utility of PRS as biomarkers has been demonstrated virtually all complex traits and diseases, including neuropsychiatric disorders.
Polygenic risk scores

- The utility of PRS as biomarkers has been demonstrated virtually all complex traits and diseases, including neuropsychiatric disorders.
ILAE2 Genetic Generalized Epilepsy (GGE) GWAS – 3708 cases vs. 24218 controls

Per person

\[
\text{PRS} = \frac{\text{Number (Alleles)} \times \log(\text{OR}_{\text{SNP}_1}) + \text{Number (Alleles)} \times \log(\text{OR}_{\text{SNP}_2}) + \text{Number (Alleles)} \times \log(\text{OR}_{\text{SNP}_3})}{\text{Number SNP}_i} = \sum \left[ \log(\text{OR}_i) \times \text{N}_{\text{allele}i} \right] / \text{Number SNP}_i
\]

In other words:

PRS aggregate the effects of many SNPs

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera, Mark Chaffin, Krishna G. Aragam, Mary E. Haas, Carolina Roselli, Seung Hoan Choi, Pradeep Natarajan, Eric S. Lander, Steven A. Lubitz, Patrick T. Ellisn & Sekar Kathiresan

Nature Genetics
Letter | Published: 13 August 2018

2p24.1
2q42.3
PCDH7

-6q22.3

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations
Polygenic risk scores are normally distributed

From https://www.genome.gov
Evaluation of the Polygenic Risk Scores

Polygenic score for relative risk stratification

Modified from Liu and Kiryluk, 2018
PMID: 30279535
Can epilepsy PRS be used as genetic biomarkers?
PRS are derived from a GWAS and can only be generated in independent samples.

1. Genome-wide association study (GWAS) for risk score generation

**ILAE 2018 analysis**
12,803 cases
24,218 controls

**GWAS:**
Genetic Risk
variants

**Epi25-EUR**
♀ = 5,705
♂ = 620

**Cleveland-EUR**
♀ = 20,435
♂ = 449

**EUR controls**
♀ = 620
♂ = 20,435

**Epi25-FIN**
♀ = 449
♂ = 1,559

**FINRISK**
♀ = 1,559
♂ = 20,435

**UK biobank (UKB)**
♀ = 459
♂ = 383,197

**Vanderbilt biobank (BioVU)**
♀ = 829
♂ = 48,670

**BioBank Japan (BBJ)**
♀ = 324
♂ = 168,356

8,386 people with epilepsy and 622,217 population controls available across six cohorts.
Polygenic risk scores for focal (FE) and generalized (GE) epilepsy

PRS = Polygenic risk score; GE = Generalized epilepsy; FE = Focal epilepsy; T2D = Type 2 diabetes; CC = Cleveland Clinic cohort, Epi25 = Consortium cohort
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How are the PRS distributed

- Few patients with very high PRS burden
- Slight shift toward higher PRS burden in all patients
Individuals with GE are enriched in the extreme tail of the PRS distribution.
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Individuals with GE are enriched in the extreme tail of the PRS distribution.

- **Top 0.5%**
  - OR = 4.6
  - \( P = 2.60 \times 10^{-15} \)
  - Sensitivity: 0.024
  - Specificity: 0.997

**Graphical representation:**
- **Polygenic risk score**
  - Low → 20375 (GE) vs. 2202 (Controls)
  - High → 60 (GE) vs. 54 (Controls)
- **Legend:**
  - Red: Generalized epilepsy
  - Teal: Controls
Polygenic risk score in large datasets
To learn more about genetics of complex disorders

PLOS ONE

Pleiotropy of polygenic factors associated with focal and generalized epilepsy in the general population

Costin Leu, Tom G. Richardson, Tobias Kaufmann, Dennis van der Meer, Ole A. Andreassen, Lars T. Westlye, Robyn M. Busch, George Davey Smith, Dennis Le

Published: April 28, 2020 • https://doi.org/10.1371/journal.pone.0232292
UK Biobank

Socio-demographics and lifestyle factors
Brain imaging (MRI)
Cognitive tests
Hearing and eyesight measures
Linked to:
Electronic health records
Death register
Cancer register

Physical activity monitoring
Heart and lung function measures
Heart and body imaging (MRI)
Whole body dual-energy X-ray absorptiometry of bones and joints
Body size and impedance measures

Genomics
Biological samples (blood, saliva, urine)
Biochemical markers

Markers within genomic regions of interest
~47,000
Markers relevant to specific phenotypes
~45,000

Rare and coding variation
~125,000

UK Biobank Axiom genotype array

Genome-wide coverage for improved performance of array-based imputation
~630,000

biobankuk
Improving the health of future generations
PRS brain-focused PheWAS in the UKB

UK biobank (UKB)

= 334,398 without epilepsy

PRS for generalized and focal epilepsy

with

42 conditions, categorized six groups:
1. Educational attainment
2. Neuroticism
3. Mood [affective] disorders
4. Substance use/abuse/dependence
5. Diseases of the nervous system
6. Nonpsychotic mental disorders
Educational attainment

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<tr>
<td>GE</td>
<td>-0.014</td>
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<tr>
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<tr>
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<tr>
<td>GE</td>
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<tr>
<td>FE</td>
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Significant association if $P<5.95\times10^{-4}$
**Neuroticism**

Significant association if $P<5.95 \times 10^{-4}$
Polygenic risk score to evaluate clustering algorithms for improved patient classification

Polygenic risk heterogeneity among focal epilepsies
Gramm*, Leu* et al., 2020 (accepted)
Cluster analysis can improve classifications

**A Study cohort**

- **Cleveland Clinic**
  - 414 individuals with focal epilepsy (FE)
    - Phenotype data
    - Genotype data
    - European ancestry

- **20,435 population controls**
  - Genotype data
  - European ancestry

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**Known etiology (n=204)**

**Unknown etiology (n=210)**

**Early seizure onset (n=254)**

**Late seizure onset (n=160)**

**Psychiatric Comorbidity (n=210)**

**No psychiatric comorbidity (n=204)**
Summary

• Most epilepsy cases are not monogenic

• Polygenic factors are shown for other diseases to confer risk equivalent to monogenic risk variants

• **Polygenic risk factors also play a role in epilepsy and can be measured**

• Polygenic risk factors for epilepsy are associated with neurological and psychiatric traits in healthy individuals

• Polygenic risk factors can be used to test and potentially improve the genetic homogeneity within phenotype subgroups
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http://epi-25.org