Pharmacogenetics & Epilepsy
From a Clinical Perspective

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Pharmacogenetics

The study of the consequences of genetic variations on drug effects

The genotype is used to predict clinical outcome:

- drug response
- adverse reactions
Pharmacogenetics

Pharmacokinetics
  Drug transport
  Drug metabolism

Pharmacodynamics
  The antiepileptic effect
  Adverse reactions
Absorption  
Transporter polymorphisms

Distribution

Blood brain barriere

CNS
Target polymorphisms

Metabolism / Elimination
Polymorphic enzymes
Absorption
CNS
Metabolism / Elimination
Distribution
Blood brain barriere
Transporter polymorphisms
Target polymorphisms
Polymorphic enzymes
Multidrug transporters
Absorption

CNS Metabolism / Elimination

Distribution

Blood brain barriere

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Polymorphic enzymes

Multidrug transporters
Multidrug transporters

The multidrug resistance gene (MDR1) encodes the Permeability glycoprotein (P-gp), which may influence absorption, distribution and elimination of drugs.

Studies have shown associations between MDR1 polymorphisms and refractory epilepsy.
Permeability glycoprotein (P-gp)

- Activates ATPase pump in the plasma membrane
- MDR1 overexpression -may explain pharmacodynamic variability -cause of drug resistant epilepsy?
- Inhibitors: probenecid, indomethacin, verapamil
Absorption → CNS → Metabolism / Elimination

- Blood brain barrier
- Distribution
  - Absorption
    - Transporter polymorphisms
  - CNS
    - Target polymorphisms
  - Metabolism / Elimination
    - Polymorphic enzymes
      - CYP 450
CYP 2C9 and 2C19

Responsible for PHT metabolism (90%)

Polymorphisms may result in significant differences in PHT dose-concentration ratio, particularly when both isoenzymes are affected

Therapeutic Drug Monitoring is important
Pharmacogenetics

Pharmacokinetics
- Drug transport
- Drug metabolism

Pharmacodynamics
- The antiepileptic effect
- ADNFLE
- Adverse reactions
- Valproate hepatotoxicity
- Skin reactions
Pharmacodynamics

Antiepileptic effect
- ADNFLE
- Tuberous Sclerosis
- SCNA1-related epilepsies

Adverse reactions
- Rett syndrome
- Valproate hepatotoxicity
- Skin reactions
Absorption

CNS

Distribution

Blood brain barriere

Absorption

Transporter polymorphisms

CNS

Target polymorphisms

Distribution

Metabolism / Elimination

Polymorphic enzymes

Receptor mutations

pathophysiologic mechanisms
Pharmacodynamics

Antiepileptic effect

ADNFLE

Tuberous Sclerosis

SCNA1-related epilepsies

Adverse reactions

Rett syndrome

Valproate hepatotoxicity

Skin reactions
A missense mutation in the neuronal nicotinic acetylcholine receptor α4 subunit is associated with autosomal dominant frontal lobe epilepsy

Steinlein O, Mulley JC, Propping P, Wallace RH, Phillips HA, Sutherland GR, Scheffer IE, Berkovic
Nature Genet 1995;11:201-3

The gene for ADNFLE maps to chromosome 20 q 13.2-q13.3 in an Australian kindred.

A missense mutation replacing serine with phenylalanine at codon 248 (Ser 248 Phe) was found.
ADNFLE

Wide phenotype variability

What factors influence

• penetrance
• onset age
• severity
• fluctuations
• remissions
Nicotine as an antiepileptic agent in ADNFLE: an N-of-one study

Willoughby JO, Pope KJ. Eaton V
Epilepsia 2000;41:529-35

Open and double blind trials in one single patient with ADNFLE (Ser248Phe) showed that nicotine patches were effective
Tobacco habits in ADNFLE

22 subjects in two ADNFLE pedigrees:

• 10 of 14 tobacco consumers were seizure free

• 3 of 4 obligate asymptomatic carriers used tobacco

• All 8 non-smokers had persistent seizures

• In several, fluctuations and remissions corresponded with change in tobacco habits

Brodtkorb, Picard F, Epilepsy Behav 2006;9:515-20
<table>
<thead>
<tr>
<th>Tobacco habits in ADNFLE</th>
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<tr>
<td>Persistent seizures</td>
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<tr>
<td>Tobacco use</td>
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<tr>
<td>No tobacco use</td>
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P = 0.024

Brodtkorb E, Picard F, Epilepsy Behav 2006;9:515-20
Tobacco habits modulate the clinical course of ADNFLE
Pharmacodynamics

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Tuberous Sclerosis complex
Autosomal dominant, multisystem disorder associated with mutations in the TSC1 and TSC2 gene
The neurobiological mechanism of Tuberous Sclerosis

The gene products of TSC 1 and 2, tuberin and hamartin, form a complex which inhibits the kinase mTOR which regulates protein synthesis, proliferation and cell overgrowth.

Deficient mTOR pathway causes abnormalities in many tissues, such as brain, skin, kidneys etc.
mTOR: A Central Regulator of Cell Proliferation, Angiogenesis, and Cell Metabolism

mTOR regulates cell proliferation, angiogenesis, and cell metabolism by activating or inhibiting protein synthesis upon receipt of appropriate biochemical signals.

EGF = epidermal growth factor
ER = estrogen receptor
IGF = insulin-like growth factor
TSC1 = tuberous sclerosis complex 1 (hamartin)
TSC2 = tuberous sclerosis complex 2 (tuberin)
VEGFs = vascular endothelial growth factors
Do we have a treatment for Tuberous Sclerosis?

Maybe soon
Rapamycin (Sirolimus)

- an established immunosuppressant

- a macrolid, such as tacrolimus

- an antiproliferative profile
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Rapamycin in Tuberous Sclerosis

A successful cascade of translational research leading to a potential mechanistic treatment

1) TSC 1 and 2 mutations identified in patients

2) In-vitro studies revealed the mTOR mechanism

3) Pharmacological studies in knock-out mouse models

4) Clinical studies in patients
Clinical studies of Rapamycin in TS

1 year observational study: Diminished size of renal angiomyolipomas

Improved pulmonary function in lymphangioleiomyomatosis

Shrinkage of tubers and subependymal astrocytomas

Improved seizure control in a 10 year old girl

Crino PB, Epilepsy Curr 2008;8:159-62
Clinical studies of Rapamycin in TS

Vision:
Multicenter controlled studies

1) To document an effect on seizures, cognition and autism
1) To study the risk/benefit profile in TS
2) To determine the duration of treatment
Pharmacodynamics

Antiepileptic effect

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Adverse reactions

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- Skin reactions
SCN1A-related epilepsies

> 100 mutations – wide phenotype spectrum

- Generalized epilepsy with Febrile Seizures +
  Inherited missense mutations: channel activity↑

- Dravet syndrome (previously Severe Myoclonic Epilepsy of Infancy) and borderline conditions
  De novo mutations with loss of function
Dravet syndrome

• What causes hyperexcitability?
  Selective loss of Na current and action potential firing of GABAergic inhibitory neurons

• What causes ataxia?
  Selective loss of Na current and action potential firing of GABAergic Purkinje neurons
Pharmacodynamics

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Rett Syndrome

- MECP2 mutations in one X-chromosome
- Adverse reactions to VPA are common.
- Hyperacetylation of histones results from the mutation
- VPA is an inhibitor of **histone deacetylase** and causes hyperacetylation

- May VPA aggravate the disorder?
Pharmacodynamics

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Valproate hepatotoxicity

VPA

- glucuronidation: 50%
- ω-oxidation: 15%
- ω-1-oxidation: 10%
- dehydrogenation: 0.3%

4-en-VPA

- β-oxidation: 24%

microsomal

mitochondrial
Valproate hepatotoxicity

VPA

- glucuronidation 50%
- ω-oxidation 15%
- ω-1-oxidation 10%
- dehydrogenation 0.3%
- 4-en-VPA

microsomal

mitochondrial

β-oxidation 24%
Valproate hepatotoxicity

Microsomal induction

VPA

Mitochondrial inhibition

glucuronidation

ω-oxidation

ω-1-oxidation

dehydrogenation

4-en-VPA

β-oxidation

Mitochondrial inhibition
Clonally expanded mitochondrial DNA mutations in epileptic individuals with mutated DNA polymerase gamma


In 5 pediatric patients with severe myoclonic epilepsy and valproic acid-induced liver failure, we identified 1 novel and 4 previously described pathogenic mutations in the linker region of this enzyme.
Mitochondriopathy with POLG mutation

- Nuclear mutations in the gene coding for the mitochondrial DNA polymerase γ

- Recessive transmission pattern

- Carrier frequency has been estimated as high as 1:50 in the Norwegian population
  (Winterthun et al., 2005)
POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection


• Epilepsy was first symptom in 12/19 patients
• Partial seizures with visual components and focal occipital EEG discharges were common
• Status epilepticus occurred in all, usually of focal motor type (epilepsia partialis continua)
• Valproate was associated with liver failure in 5 patients and should be avoided.
POLG disorder

Very wide phenotypic variation:

• Epilepsy
• Headache (migraine-like)
• Progressive cerebellar ataxia
• Peripheral neuropathy
• Liver involvement
• Cognitive symptoms
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Skin reactions
Hapten Hypothesis

Drug

Bioactivation

Detoxification

Metabolite or Drug + Protein

T-cell effector: CD8+

CD4+

Stevens Johnson

TEN

Rash

Hypersensitivity Syndrome
Cross reactivity of rash from aromatic AEDs

Alvestad, Lydersen, Brodtkorb, Epilepsy Res 2008; 80:194-200
Hapten Hypothesis

Drug

Bioactivation

Detoxification

SKIN REACTION

Genes

Environment

Hormones
Association between HLA-B* 1502 and CBZ-induced skin reactions

- High association with Stevens Johnson/ TEN in the Asian population
- No association with simple rash or hypersensitivity syndrome
- Studies in Caucasian population did not show the same association
FDA ALERT [12/12/2007]:

Dangerous or even fatal skin reactions that can be caused by CBZ therapy, are significantly more common in patients with a particular HLA allele, HLA-B*1502.

This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians.

Genetic tests for HLA-B*1502 are already available.
Conclusion

A pharmacogenetic approach is useful in an increasing number of patients.

The pharmacokinetic side
Drug transporters: of potential importance
Metabolizing enzymes: Therapeutic Drug Monitoring

The pharmacodynamic side
Mechanistically directed treatment can compensate for defects or prevent adverse reactions.