

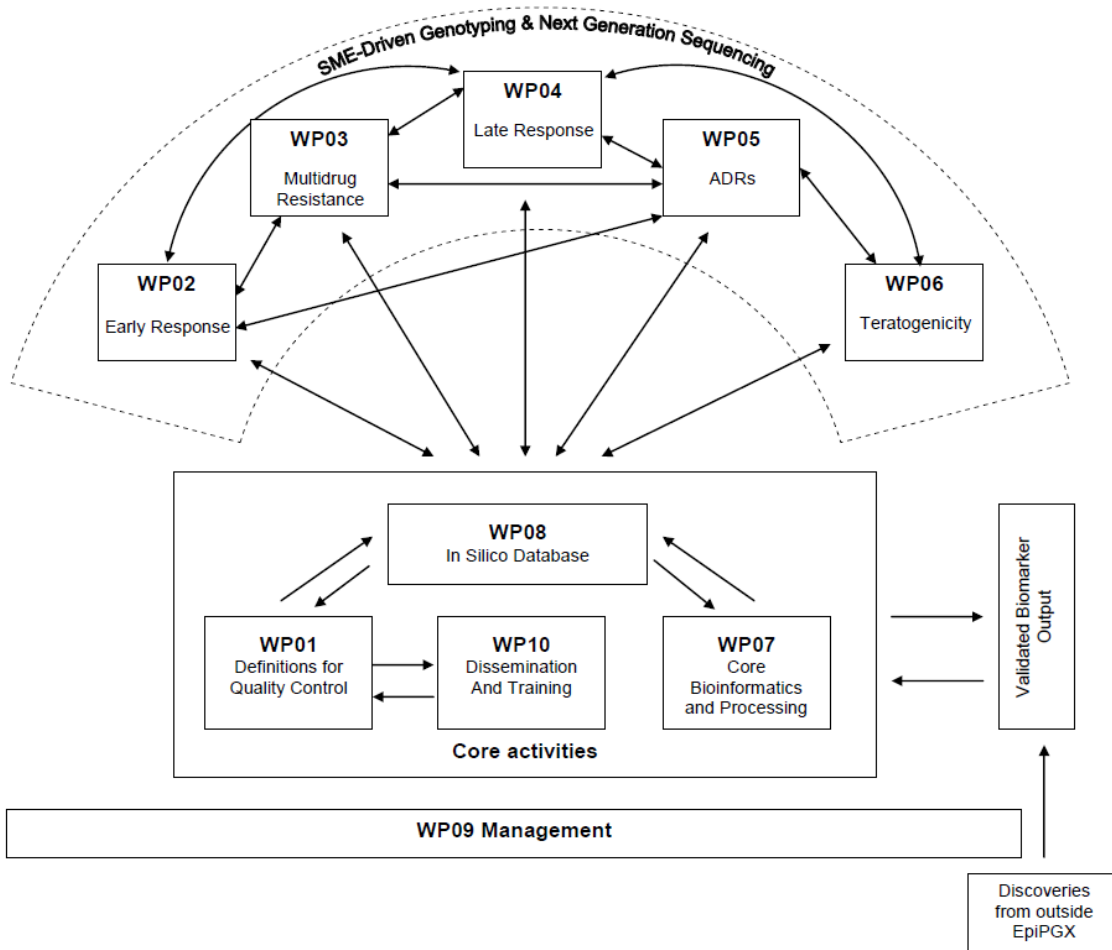
Predictors of adverse reactions to AEDs

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EpiPGX - context



- Goal is to identify (BEST glossary):
 - Safety Biomarkers
- Biobanked data from >12,000 people with epilepsy, across 14 sites.
- Data includes:
 - over >40,000 individual drug trials and outcomes
 - >11,000 GWAS
 - >3,200 exomes

Approach for adverse drug reactions..

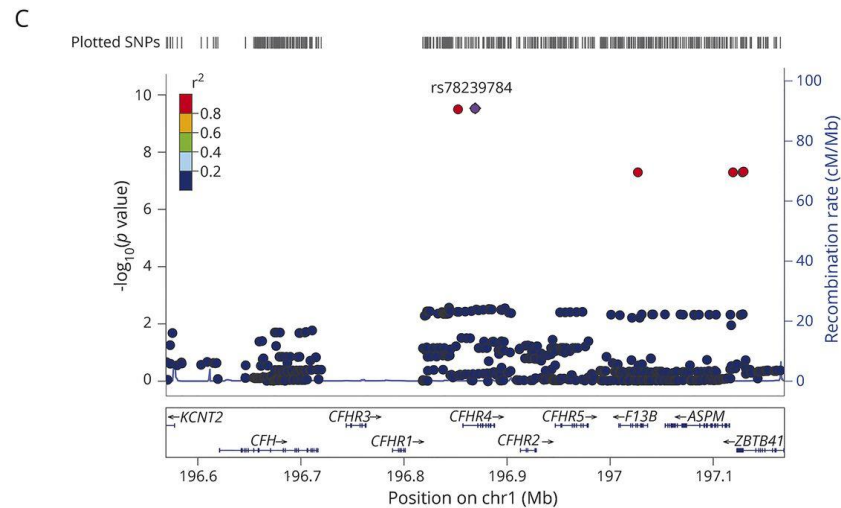
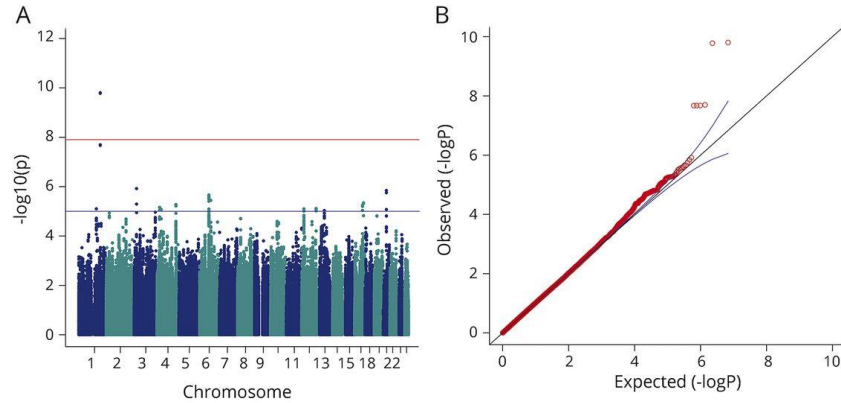


To be attributed to the AED in question the ADR should:

1. Occur within 6 months of initiation of AED (not for visual field defects)
2. Lead to dose reduction or withdrawal of AED where appropriate
3. Reverse or improve after dose reduction or withdrawal, where appropriate (not for visual field defects)
4. Not be attributed to another cause by treating/phenotyping clinician.

| ADR | cases | Screened controls |
|--------------------------------------|----------------------|-------------------|
| Cutaneous ADRs | 369 | |
| MPE | 323 | 2153 |
| HSS/SJS/TEN | 46 | |
| Weight change (VPA) | 151 | 1357 |
| Neutropenia | 28 | 376 |
| Hyponatremia | 397/1141 | 234 |
| Thrombocytopenia | 16 | 353 |
| Tremor (VPA) | 42 | 1357 |
| Hepatic dysfunction | 24 | 121 |
| Behavioural disorder (LEV) | 126 | 1322 |
| Psychosis (LEV) | 21 | 1322 |
| Cognitive impairment (TPM) | 68 | 710 |
| Speech Disorder (TPM) | 15 | 710 |
| Visual fields (VGB) | 194 | na |
| Total (excluding misc events) | 2,245 (1,061) | |

Results: A predictor of phenytoin-induced skin rash..



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Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients

Mark McCormack, Hongsheng Gui, Andrés Ingason, Doug Speed, Galen E.B. Wright, Eunice J. Zhang, Rodrigo Secolin, Clarissa Yasuda, Maxwell Kwok, Stefan Wolking, Felicitas Becker, Sarah Rau, Andreja Avbersek, Kristin Heggeli, Costin Leu, Chantal Depondt, Graeme J. Sills, Anthony G. Marson, Pauls Auce, Martin J. Brodie, Ben Francis, Michael R. Johnson, Bobby P.C. Koelmann, Pasquale Striano, Antonietta Coppola, Federico Zara, Wolfram S. Kunz, Josemir W. Sander, Holger Lerche, Karl Martin Klein, Sarah Weckhuysen, Martin Krenn, Lårus J. Gudmundsson, Kári Stefánsson, Roland Krause, Neil Shear, Colin J.D. Ross, Norman Delanty, for the EPIGEN Consortium; Munir Pirmohamed, Bruce C. Carleton, for the Canadian Pharmacogenomics Network for Drug Safety; Fernando Cendes, Iscia Lopes-Cendes, Wei-ping Liao, Terence J. O'Brien, Sanjay M. Sisodiya, for the EpiPGX Consortium; Stacey Cherny, Patrick Kwan, Larry Baum, for the International League Against Epilepsy Consortium on Complex Epilepsies; and Gianpiero L. Cavalleri

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Table 1 Breakdown of antiepileptic drug (AED)-induced maculopapular exanthema (MPE) cases and AED-tolerant controls in discovery dataset

| Ethnicity | All aromatic AEDs | | CBZ | | LTG | | PHT | |
|--------------------------|-------------------|----------------------|------------|--------------|------------|------------|-----------|------------|
| | MPE ^a | Control ^b | MPE | Control | MPE | Control | MPE | Control |
| European | 259 | 979 | 95 | 869 | 118 | 812 | 52 | 472 |
| Han Chinese ^c | 116 | 342 | 85 | 197 | 16 | 32 | 22 | 58 |
| Subtotal | 375 | 1,321 | 180 | 1,066 | 134 | 844 | 74 | 530 |

Abbreviations: CBZ = carbamazepine; ILAE = International League Against Epilepsy; LTG = lamotrigine; PHT = phenytoin.

^a Individual participant counts only, despite 16 patients being cross-reactive to more than 1 AED.

^b A total of 1,321 controls were tolerant to all 3 of CBZ, LTG, and PHT.

^c Fifty-two carbamazepine-induced MPE cases from Guangzhou were available for analysis of human leukocyte antigen serotype data only.

Challenges/bottlenecks identified..



- **Biomarker Discovery:**
 - Case ascertainment & retrospective phenotyping
 - Relatively limited 'omic & environmental data
- **Biomarker Translation:**
 - Lack of prospective studies
 - Access to cost-effective testing infrastructure
 - Limited genomic literacy



Next steps, to move forward



- Consolidate *centralized* data storage and analytical platforms
 - Collation of epilepsy data in a pan EU ecosystem
- A pan-European, prospective epilepsy biobank?
 - This should be *patient-driven* and *clinician-informed*
 - Linked to electronic health records with appropriate safeguards

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- Wolfgang Kunz
- + All other members



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