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Precision medicine in women with epilepsy: the challenge, systematic review and future direction

Yi Li, M.D. Ph.D.[1,*], **Sai Zhang, Ph.D.**[2], **Michael P. Snyder, Ph.D.**[2], **Kimford J. Meador, M.D.**[1]

[1]Department of Department of Neurology & Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA

[2]Stanford Center for Genomics and Personalized Medicine, Department of Genetics, Stanford University School of Medicine, Stanford CA, 94305, USA

Abstract

Epilepsy is one of the most prevalent neurologic conditions, affecting almost 70 million people worldwide. In the United States, 1.3 million women with epilepsy (WWE) are in their active reproductive years. WWE face gender specific challenges such as pregnancy, seizure exacerbation with hormonal pattern fluctuations, contraception, fertility and menopause. Precision medicine, which applies state-of-the art molecular profiling to diagnostic, prognostic, and therapeutic problems, has the potential to advance the care of WWE by precisely tailoring individualized management to each patient's needs. For example, antiseizure medications (ASMs) are among the most common teratogens prescribed to women of childbearing potential. Teratogens act in a dose-dependent manner on a susceptible genotype. However, the genotypes at risk for ASM-induced teratogenic deficits are unknown. Here we summarize current challenging issues for WWE, review the state-of-art tools for clinical precision medicine approaches, perform a systematic review of pharmacogenomic approaches in management for WWE, and discuss potential future directions in this field. We envision a future in which precision medicine enables a new practice style that puts focus on early detection, prediction and targeted therapies for WWE.

Keywords

Epilepsy; Pregnancy; Precision medicine; genomics; women

[*]**Corresponding author:** Yi Li, MD, PhD, Clinical Assistant Professor, Department of Neurology & Neurological Sciences, Stanford University School of Medicine, Stanford Neuroscience Health Center, 213 Quarry Road, Palo Alto, CA 94304-5979, Tel: 650-725-6648, lyi@stanford.edu.

Contributions:

Yi Li: Study concept and design, literature review, data analysis, drafting and revising the manuscript

Sai Zhang: Literature review, critical revision of manuscript for intellectual content

Michael Snyder: Study concept and design, critical revision of manuscript for intellectual content

Kimford Meador: Study concept and design, critical revision of manuscript for intellectual content

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The authors declare no competing interests.

1. Introduction:

Epilepsy is one of the most prevalent neurologic conditions and an important cause of disability. It has been estimated to affect almost 70 million people worldwide. In the United States, 1.2% of the population has epilepsy as an active diagnosis, including over one million women of childbearing age.[1] Women with epilepsy (WWE) face specific challenges throughout their lifespan, such as special reproductive and general health concerns.

Recent biotechnological advances have led to a rapid acceleration of disease-relevant molecular information, with the potential to greatly advance patient care. The idea of "precision medicine" highlights the fundamental goal of coupling state-of-the art molecular profiling with clinical indexes to precisely tailor diagnostic, prognostic, and therapeutic strategies for each patient's requirements.[2]

In this review, we provide a brief overview of the unique challenges for WWE, elaborate potential approaches of precision medicine, perform a systematic review of pharmacogenomics in this regard, and discuss future directions.

2. Special challenges of WWE

2.1 WWE and pregnancy outcomes

Over 90% of pregnancies in WWE proceed without any apparent complications.[3] However, WWE are considered at high risk in pregnancy due to increased maternal and fetal risks. They face particular challenges during their pregnancy, such as spontaneous abortion, antepartum hemorrhage, gestational hypertension, preeclampsia, breech position, induction of labor, cesarean section, and preterm birth.[4] Further, increased clearance of several anti-seizure medications (ASMs) during pregnancy can lower ASM blood levels and increase the risk of seizures.[4]

Beyond obstetric risks, WWE are also at higher risk regarding fetal outcomes. WWE are often more concerned about the negative influence on their fetus from both the epilepsy, comorbid disorders, and fetal exposure of ASMs. So far, only a few commonly used ASMs have been investigated systematically (Figure 1) for malformation and neurodevelopmental risks. The profiles for most ASMs still remain unclear. A meta-analysis including 65,533 pregnancies in WWE exposed to carbamazepine, lamotrigine, phenobarbital, phenytoin, or valproate showed that overall incidence of congenital malformations in children born of WWE is approximately threefold that of healthy women (7.08% vs. 2.28%), with the highest incidence for ASM polytherapy (16.78%).[3] Further, children's long-term neurodevelopment outcomes can be affected by ASM exposures, notably valproate, resulting in lower IQ scores[5] and behavioral problems such as autism spectrum disorders[6] However, the risks for most ASMs and the reasons for individual variability in outcomes are unknown.[7]

2.2 WWE and special challenges outside pregnancy

Other than pregnancy, there are still many special challenges faced by WWE. Effective contraception is a commonly encountered issue, since it is complicated by enzyme-inducing ASMs causing lower levels of hormone contraceptives (especially, carbamazepine, phenobarbital, phenytoin, primidone, and also eslicarbazepine, felbamate, oxcarbazepine, perampanel, topiramate). In addition, some ASMs are affected by contraceptive medications (i.e., lamotrigine). These changes by ASMs exhibit inter-individual variation, and understanding the pharmacogenomic variation is still limited at the current stage. Some WWE also face special challenges due to periodic hormonal changes over time, such as catamenial epilepsy,[8] worsening seizures during perimenopause,[9] and higher rate of osteoporosis and risk of fractures than men[10] which further exacerbated by enzyme-inducing ASMs.[11] In addition, there are many commonly encountered problems in WWE (e.g., migraines, mental health) that largely overlap with men suffering from epilepsy, but these topics are not included in this review.

3. Precision Medicine Approaches:

This review section is tailored to neurologists and other clinicians who are less familiar with rapid developments in genomic medicine. From discovery of the double helix to the assembly of the human genome's 3 billion nucleotides over the past decades, genomic medicine has undergone persistent rapid development. Recent advancements with next generation sequencing technique have improved the quality of sequencing while tremendously reducing the cost as well. Clinical practitioners have started to utilize this rich genetic information to guide treatment and management for patients in many fields, and this approach has also been advocated in epilepsy patients.

3.1 Chromosome microarray analysis (CMA)

CMA is performed with either comparative genomic hybridization or a single nucleotide polymorphism array. It works by detecting submicroscopic imbalances, often referred to as copy number variants (CNVs), which are as small as 50–100 kilobases (kb), resulting in more than 100-fold increase in resolution compared to traditional karyotyping that only detects imbalances greater than 7–10 million bases.[12] CMA hence offers the benefit of more sensitive detection of pathogenic microdeletions or microduplications, cryptic unbalanced chromosome rearrangements; with the caveat that it cannot detect truly balanced chromosome rearrangements, nor does it give positional information.

Molecular karyotyping using CMA has been utilized in prenatal diagnosis and in the evaluation of products of conception. Prenatal studies have shown that the rate of clinically significant abnormal amniotic CMA results is 4.7%, which is twice that of karyotypic abnormalities in pregnancies with various abnormal ultrasonographic findings.[13] In prenatal diagnostic samples with a normal karyotype, CMA could diagnose a clinically significant subchromosomal deletion or duplication in approximately 1% of structurally normal pregnancies and 6% with a structural anomaly. CMA has been shown to be a valuable diagnostic tool in prenatal genetic diagnosis of central nerve system anomalies, and is currently extensively used to explore chromosomal aberrations in the postnatal population

with neurodevelopmental disorders such as autism, intellectual disability, epilepsy, and congenital anomalies.

3.2 Next-generation exome sequencing (NGS)

In the 1970s, Sanger sequencing, one of the classic first-generation sequencing methods, was developed utilizing DNA polymerase. It carries limitation of low throughput due to DNA template preparation as well as relatively high cost. Since around 2006, various NGS techniques have been developed they may differ in details but usually follow a similar general paradigm in DNA sequencing: DNA sample fragmentation, clonal amplification, and massively parallel sequencing reactions. NGS can bypass the tedious process of identifying a causal mutation via linkage analysis and fine-mapping by Sanger sequencing. Compared to first generation sequencing, the advantages of NGS include higher throughput with parallel sequencing, faster turnaround time and higher sensitivity to rare variants. These benefits have brought the genomic research to a different era and have substantially improved the prediction of phenotypic outcomes.

Various approaches with next generation exome sequencing techniques such as trio sequencing with both proband and their parents, post-zygotic (somatic) de novo mutation study, targeted high coverage candidate gene panel studies, and assessment of the contribution of rare and ultra-rare genetic variations in common diseases have advanced not only our understanding of epileptogenesis, but also increased the detection yield of prenatal diagnoses.

3.3 Whole genome sequencing

With the falling costs of NGS technology as well as the advance of bioinformatic analysis, the paradigm of precision medicine is shifting from microarray-based genotyping studies to whole exome sequencing (WES), and eventually to whole genome sequencing (WGS). WES targets protein-coding genes, which only account for 2% of the entire human genome. It is known that DNA variations outside the exomes could affect gene activity and protein function, which WES would certainly miss but can be captured by WGS. The sequencing cost of WES is less than half of WGS, so the clinical application of WES currently is more prevalent. WGS, on the other hand, uses a more unbiased approach to investigate not only protein-coding genes, but also other potential genetic causes such as non-coding variants, structural variations, repeat expansions, and complex chromosomal rearrangements.

WGS has been used to help augment prenatal karyotyping using customized whole-genome jumping libraries.[14] It may also become a promising tool in the analysis of intellectual developmental disorders such as autism spectrum disorder.[15] Although many more genetic changes can be identified with whole genome sequencing than with WES, their functional effects and the associations with diseases largely remain unclear, greatly challenging the clinical interpretation and utility. (Table 1)

3.4 Multi-Omics profiling

Recent advances in multi-omics analyses, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and other omics areas, have provided further

insight into the molecular mechanisms contributing to the certain phenotypes in epilepsy, as well as in the identification of biomarkers for clinical risk predictions. Besides the advent of genomics with genome sequencing methods described above, *epigenomics* depicts epigenomic changes such as DNA methylation and chromatin modifications that have also been shown to modulate gene expression. As an illustration, DNA methylation could be utilized for long-term epigenetic silencing of imprinted genes which can either increase or decrease the level of transcription, depending on whether the methylation inactivates a negative or positive regulatory element. Epigenetic modulation indeed has been shown to affect seizure-induced neurogenesis and cognitive decline.[16] Different from genomic and epigenomic studies, *transcriptomics* focuses on quantifying the dynamic change of transcriptome, which is a complete set of RNA transcripts in cells, at a specific developmental stage or physiological condition. RNA-sequencing is the current method of choice for approach to transcriptome profiling that has advantages of high accuracy for mapping and quantifying transcriptomes, as well as a very low background signal. *Proteomics* and *metabolomics*, on the other hand, are the studies of the complete set of proteins or metabolites present in cells, organ, or organism, including their abundance, modification, and interaction. The number of human protein products, including splice variants and essential posttranslational modifications, has been estimated to be close to one million.[17] Metabolites are the substrates and products of metabolism that drive essential cellular functions. In addition to being produced directly by the host organism, it can also derive from other exogenous sources such as medications, food, microbiota that inhabit the body, and the environment. Various methods have been applied in the proteomics and metabolomics studies including mass spectrometry, protein arrays and nuclear magnetic resonance. Detailed methodology of different omics approaches is beyond the scope of current review. Multi-omics approaches have been applied to a wide range of biological problems; and multi-omics profiling has been heralded as the key to better understand the underlying mechanisms of epilepsy and to identify biomarkers that may be used to either diagnose epilepsy or predict the risks of comorbidities (Figure 2).

4. Systematic review of current pharmacogenomic approaches in treatment for WWE

Personalized treatment for WWE has long been advocated; it is complex and challenging, but the pharmacogenetic approach could be an important instrument. Here we provide an updated systematic review of studies that utilize pharmacogenetics to inform the management for WWE.

4.1 Methods

4.1.1 Literature searches, eligibility criteria, and study selection—In our initial approach, we conducted a systematic literature review employing search terms used in the previously published AAN Practice Parameter: “update management issues for women with epilepsy focus on pregnancy”[18] except that we added the terms “women or female” as well as “pharmacogenomics, pharmacogenomics, pharmacogenetics, pharmacogenetic, pharmacogenomic, GWAS, genome-wide, gene association study, polymorphism, polymorphisms, allele, gene variant, and alleles”, and constraining the

search to human subjects, English language, and between January, 1985 and June, 2020. The literature search yielded a total of 491 abstracts; however, the majority of abstracts were unrelated to the questions addressed in the topic of the proposed review, and thus were excluded from further analysis. Twenty studies were extracted for full article review from this initial search strategy. In addition to our primary analysis, we carried out a broader systematic literature search for studies from January, 1985 to June, 2020 with pharmacogenomics and WWE. Our two search strategies are depicted in Figure 3, which includes the selection and exclusion criteria. The search was again confined to articles using human subjects, including all languages for which there was an abstract in English in the same period of time as first search strategy from January, 1985 to June, 2020. In this primary search strategy, we identified a total of 1450 articles in the PubMed database. After reviewing titles and abstracts, 51 articles were included based on criteria presented in Figure 3. Combined, the two searches yielded 51 studies total abstracted for full literature review. An additional 38 studies were excluded after full-length review, and 13 studies were included with findings summarized in Table 2. The review follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) system of reporting. [19] Ethical approval was not required.

4.1.2 Data abstraction—

Authors YL and KM defined the key words and search strategy as well as the search logistics. Author YL performed the first round of titles and abstract screening. For all the 51 studies that required full article review, authors YL and KM reviewed the studies from the papers and selected the studies to be included and excluded, summarized in Figure 3 and Table 2. All authors YL, SZ, MS, and KM reviewed the final extracted findings and agreed they are pertinent to the objective of the review and should be included in the description summary tables. As described in 3.1.1, most of the individual studies were small to moderate cohorts and conducted in patients with specific ethnicity, hence are often limited in application to the general population. Due to the scarcity of the research done on pharmacogenomics in WWE, no meta-analysis, data synthesis or bias analysis within the studies was performed.

4.2 Summary and discussion

In general, there is a remarkable shortage of research focusing on pharmacogenomics for WWE. For issues of WWE outside pregnancy, nine articles were identified, six of them were investigating the role of genetic variants in ASM drug response for seizure control in WWE, mainly focused on the variants located on the ABC transporter genes ABCB1[20–22] and ABCC2,[23] as well as gene CYP1A1[24, 25] which is related to sex hormone metabolism. One study examined the adverse effects of ASM in young WWE and indicated that CYP2C19 polymorphism was associated valproate-induced weight gain in young female patients with epilepsy.[26] Two of the investigations focused on the association of epilepsy diagnosis and targeted genetic variation in WWE, showing that polymorphism of MTHFR (rs1801133)[27] and PRNP (rs1799990) gene [28] are more commonly found in WWE. These could be potential biomarkers in the future for establishing epilepsy diagnosis in WWE after further validation studies.

Data on pregnancy related issues in WWE and pharmacogenetics is more scarce. Four studies have been identified from the literature search. One study focused on the lamotrigine clearance during pregnancy and identified that UGT polymorphisms as well as gender of fetus are associated with the variability of lamotrigine clearance during pregnancy.[29] In addition, two other studies sought to understand the differential teratogenic impact of ASMs in WWE. One study showed that the maternal EPHX1 genotype may be associated with fetal major craniofacial abnormalities in WWE taking phenytoin.[30] Another study based on an Indian population indicates the possibility that ABCB1 and Cyp2C19 may play a pivotal role in the ASM induced teratogenesis, independently of the nature of the malformation.[31] Currently, there are nearly 30 available FDA approved medications to treat epilepsy, but malformation risks have been investigated for only a few commonly used ASMs. (Figure 1) The genetic contributions to ASM-induced malformation risks for most ASMs still remain uncertain. In addition, even for the ASMs that are viewed as relatively safe for WWE during pregnancy, good outcomes are not universal for every case. For example, lamotrigine at higher dose is associated with a higher rate of major congenital malformations.[32] Developing strategies of combining genomic information to identify the WWE who will be more susceptible to adverse outcomes for themselves or their offspring would be very helpful to guide clinical management. A recent trio-based WES study explored the association of maternal ASM exposure and their offspring's de novo variants load, and found that prenatal ASM exposure does not increase the burden of de novo variants.[33] These investigations provide an exciting new direction that could ultimately help with clinical decision-making regarding the optimal management for WWE.

5 Future directions-precision medicine approach for care of WWE

5.1 Biomarker identification for personalized treatment regimen

Prevalence of ASM use for pregnant women has increased from 15.7 per 1000 deliveries in 2001 to 21.9 per 1000 deliveries in 2007 in the United States, primarily driven by a 5-fold increase in the use of newer ASMs. This increase includes women beyond WWE, as ASMs are also commonly used in patients with psychiatric or pain disorders.[34] The general rule in clinical practice is to use an ASM with the least severe side effects profile such as lamotrigine or levetiracetam, and to avoid valproate if possible due to known higher incidence of congenital malformations and worse cognitive and behavioral outcomes. Nevertheless, after more than 50 years since its introduction, valproate still remains a valuable treatment option for many patients with epilepsy.[35] In addition, even though lamotrigine has been deemed to have relatively low risk for WWE, it is not risk-free, and offspring outcomes are not uniformly optimal in every exposed case. Further, there is great uncertainty for most of the other ASMs.

Responses to ASM vary across people with epilepsy, and genetic variations including genes affecting drug pharmacokinetics or drug pharmacodynamics are probably a significant contributing factor.[36] The rapid progress in genomic medicine is in turn advancing our understanding of the genetic underpinnings of epilepsy regarding drug responses and disease susceptibility.[37] In addition, the idea of population-based pharmacokinetic-pharmacodynamic models to determine the optimal concentration of ASM according to

the clinical characteristics of each patient has been experimentally studied with the aim to provide personalized pharmacological therapy for epilepsy.[38] However, such precision medicine approaches have barely been explored in pregnancy and fetal complications of WWE. Here, we describe what has been investigated in this field and also potential targets for further research.

5.1.1 Potential biomarkers for ASM dosing during pregnancy in WWE—

Maintaining ASM plasma level within the therapeutic range during pregnancy is important, not only to avoid breakthrough seizures that could be harmful to mother and fetus, but also to avoid adverse side effects due to toxicity. Substantial pharmacokinetic changes occur with many ASMs during pregnancy, due to multiple physiological changes during pregnancy including increased volume of distribution, increased renal elimination, altered hepatic enzyme activity, and decreased plasma protein concentrations.[4] Interindividual variability has necessitated therapeutic drug monitoring during pregnancy in clinical practice. The majority of this variability is probably due to differences in the pharmacokinetics of drug metabolism. Some key enzymes that are involved in metabolic variation include (1) the CYP450 family enzymes involved in phase 1 drug metabolism and (2) various phase 2 enzymes involved in acetylation, glucuronidation, sulfation and methylation. Genetic variations, such as those seen in SNPs (single nucleotide polymorphisms) of these enzymes, as well as SNPs associated with receptor modification, may lead to the various effects seen in clinical setting.[39] Pharmacogenetics studies have explored candidate genes and their SNP differences in an effort to explain interindividual variability during pregnancy. Here, we summarize the relevant findings for lamotrigine and levetiracetam, which are the two most commonly prescribed ASMs for pregnant women with epilepsy. Hopefully with further investigation and validation studies, there will be a better tool to help predict response and dosing adjustment of ASM during pregnancy in the near future.

Lamotrigine (LTG): LTG is almost exclusively hepatically metabolized by glucuronidation catalyzed by UDP-glucuronosyltransferase (UGT) isoenzymes, hence the major enzyme responsible for LTG elimination. The activity of these UGT isoenzymes is encoded by UGT genes, and it has been found that UGT1A4*3 (142T > G, L48V), UGT1A4*2 (70C > A, P24T) and UGT 2B7*2 (802C > T, H268Y) are the most common gene variants that affect LTG metabolism in non-pregnant patients.[40, 41] During pregnancy, there is a substantial interindividual variability in the magnitude of the LTG clearance. The majority of the women (77 %) displayed a marked increase in LTG clearance, whereas 23 % had a minimal increase in LTG clearance from baseline, with a 10-fold rate difference.[42] A recent study explored the relationship of UGT polymorphisms and LTG clearance during pregnancy.[29] It compared the percentage LTG concentration/dose ratio (C/D ratio) reductions during pregnancy within UGT1A4 T142G genotype variants, and found that heterozygous carriers (TG) had a lower C/D ratio reduction in 3rd trimester of pregnancy than the wild type (TT), when compared with levels in pre-pregnancy. In addition, homozygous carriers of UGT2B7 C802T (TT) had a more pronounced LTG clearance in the first and third trimester than heterozygous variant.[29] Another study found that during pregnancy, the UGT1A4 expression is upregulated by 17-beta-estradiol through estrogen receptor α and transcription factors specificity protein-1.[43] These results suggest that additional pharmocogenomic

information could be used as a potential biomarkers to guide individualized lamotrigine dosing during pregnancy, though we should also keep in mind that validation studies are needed for different ethnicity groups.

Levetiracetam (LEV): Serum concentrations of LEV have pronounced interindividual variability, especially in the third trimester of pregnancy. There have not been any genomic studies investigating potential genetic variants linked with this phenomenon. In nonpregnant epilepsy populations, accumulation of the SNP rs9305614 G-allele has been associated with resistance to LEV in temporal epilepsy patients,[44] while HLA-A*11:01 was found at a higher frequency in patients who had adverse events related to LEV.[45] These data suggest that genetic factors may be part of the explanation of the variability seen in individuals' response to LEV, and it will be an important area for further studies in WWE. A recent study using high-resolution mass spectrometry investigated the metabolome-wide association of ASMs in WWE who received LEV or LTG.[46] It revealed changes in metabolites and metabolic pathways important to maternal health and fetal neurodevelopment, including changes in one-carbon metabolism, neurotransmitter biosynthesis and steroid metabolism. Further understanding of the ASM pharmacometabolomic framework may facilitate the development of biomarkers to predict adverse ASM effects during pregnancy.

5.1.2 Potential biomarkers for fetal adverse outcomes in WWE—

The intricacies of ASM management during pregnancy continues to present clinicians and WWE with difficult decisions, especially when facing the questions about potential adverse effects of fetal exposure. ASMs are among the most commonly used medicines with potential teratogenic effects in women of childbearing age. Teratogens act in a dose-dependent manner on a susceptible genetic substrate. Variability in outcomes exists not only across ASMs, but also across individual children who were exposed to the same ASM at similar dosages. Differences in genetic susceptibility may result in greater damage from a teratogenic exposure in one individual than in another. ASMs are metabolized by several common hepatic enzymes such as Cyp2C9, Cyp2C19 and Cyp3A4 and transported by ABCB1. A study conducted with the aim of finding risks for certain gene polymorphisms for these enzymes found an absence or reduction in the level of enzyme activity is associated with a higher risk of teratogenicity.[31] It could be one of the future directions to develop genotyping assays for WWE to uncover genetic factors predisposing to poor pregnancy outcomes.

Previous experimental studies have supported the hypothesis that individual WWE and their embryos have a genotype that is either sensitive or resistant to ASM-induced teratogenesis, which may contribute to variability seen in clinical settings.[47] One potential target is the folate pathway, as maternal folate exposure is critical for fetal brain development,[48] and several commonly used ASMs are known to interfere with folate metabolism.[49] As a coenzyme, folate is important in the biosynthesis of purine and pyrimidine nucleotides and therefore crucial for synthesis of DNA Maternal folic acid exposure has been shown to alter gene expression in their offspring.[50] Deficiency of MTHFR, one of the key enzymes for folate metabolism, is also associated with impaired short-term memory and increased hippocampus apoptosis in animal studies.[51] Recent investigations suggested that folate has

protective effects against fetal ASM-induced language delay as well as autistic traits.[52, 53] Periconceptional folate exposure at doses >=400 mcg/day has also been associated with better neurodevelopmental scores across a variety of long-term cognitive variables in children of WWE at 6 years old.[54, 55] It is an interesting question whether genes associated with the folate pathway may influence susceptibility to teratogenic effects of ASM on cognitive outcomes in offspring of WWE, and deserves further investigations.

Another valuable candidate biomarker is epigenetic dysregulation in WWE associated with offsprings' cognitive outcomes. The methylation pattern of maternal glucocorticoid response genes has been shown to be related to the degree of infants' inability to adapt to the stresses in the postnatal environment, indicating aberrant methylation of glucocorticoid response genes may affect infant neurobehavioral outcomes, which could have implications for long-term mental health and cognitive outcomes for children of WWE.[56] In addition, studies have demonstrated that WWE using various ASMs have excessive oxidative stress, and those with unfavorable pregnancy outcome (e.g., malformation and miscarriage) were associated with higher level of oxidative stress.[57, 58] Whether gene regulation related to oxidative stress pathways could be used as one of the candidate biomarkers deserves further research.

5.1.3 Potential biomarkers to optimize bone health in WWE—Patients with epilepsy have been reported to have 2–6 times increased risk of fractures, which is higher in women than in men.[10, 59] These fractures cause long lasting disability and dependence, as well as high financial burden. Multiple risk factors for osteoporosis have been identified, of which heredity is one of the strongest factors.[60] Nearly 20% of U.S. adult women have at least one family member affected with osteoporosis,[61] and positive family history is a powerful risk factor for osteoporotic fractures, suggesting genetic factors contribute.[62] There is only scarce research about genetic susceptibility in WWE to higher risk of osteoporosis. Lambrinoudaki *et al.* showed bone mineral density was significantly associated with the genotype of vitamin D receptor in both men and premenopausal women.[63] Although the sample size of this study was small (n=72), this finding emphasizes the need to further elucidate possible mechanisms of genetic predisposition of WWE to osteoporosis. Furthermore, the advances in genomic technologies have broadened the understanding of the genetic architecture and biological mechanisms in the field of osteoporosis. Currently, more than 500 loci are found to be associated with bone marrow density through GWAS studies, which details have been summarized in other papers and beyond the scope of current review.[64] In addition to susceptibility loci identified in GWAS studies, advances in genomics, transcriptomics, epigenomics, proteomics and metabolomics, have all been applied to dissect the pathogenesis of osteoporosis.[65] These have provided a valuable road map which could be potentially integrated for illuminating the biomarkers for WWE that can help to predict who will be at higher risk of osteoporosis, and also help to develop individualized treatment with prediction of response to different treatment regimen.

5.2 Noninvasive cell-free fetal DNA prenatal analysis of pregnancy complication risk and fetal outcome

Cell-free DNA describes short fragments of extra-cellular DNA found circulating in blood plasma. Cell-free fetal DNA (cffDNA) is genetic material that is released by the placenta and circulates in the pregnant woman's blood. From about four weeks' gestation, a small amount of fetal DNA is released from the placenta, making up 5–20% of the total circulating cell-free DNA in maternal plasma and increases throughout pregnancy. cffDNA reflects the genetic makeup of the fetus and serves as a new biomarker that can provide information about the placenta and potentially be used to predict clinical problems. The test has been used clinically to identify certain chromosome disorders in fetus with PCR following restriction enzyme digest or relative haplotype dosage approach, including the presence of extra chromosomes (trisomies), as well as some paternally inherited dominant disorders, or recessive and X-linked conditions.[66]

As the cost of sequencing falls and technology develops further, there may well be applications of exome and whole genome sequencing cffDNA from the maternal plasma as part of personal care for WWE and their unborn fetus, one of the advantages being safer prenatal testing.[67] NGS with cffDNA could further help our understanding of the genotype-phenotype prenatally of certain complex disorders such as developmental delay and intellectual disability in children of WWE. In addition, researches have demonstrated the potential of cell-free fetal transcriptomic and methylomic analysis to assess and monitor pregnancy-associated pathologies such as preeclampsia, intrauterine growth restriction, and risk of preterm birth.[68] This technique could also be utilized in the near future for WWE since they are deemed as high risk pregnancy populations in general. These approaches could help enable more informative counseling during pregnancy on prognosis for the fetus and recurrence risk for future pregnancies for WWE.

5.3 Integrative personal omics profile monitoring for WWE

Integration of multiple omics technologies has emerged as an important approach for personalized medicine. These include but are not limited to genomics data, transcripts, proteins, metabolites, cytokines, microbes profiling, as well as single cell analysis, actigraphy using wearable sensors and clinical phenotypes. This meta-dimensional multiomics approach provides a more comprehensive view of disease and helps capture the complexity of the molecular indexes that may act as causal variants, by combining heterogeneous database at various biological levels.[69] This approach has been used in a variety of scenarios from common diseases to exposure under extreme situation,[70–72] which may provide a valuable roadmap of the putative risks for human diseases.

A recent metabolome-wide association study of ASM treatment in WWE during pregnancy showed ASMs were associated with changes in metabolites and metabolic pathways that are important to maternal health and linked to fetal neurodevelopment.[46] A transcriptomic approach has also been used to investigate the developmental toxicity for the ASM valproic acid in cell models.[73] In addition, with easy and popular access of various wearable monitoring devices for patients, including pregnancy women, physiomes tracking has provided useful information regarding physiological changes and personal health care.[74]

For example, a larger circadian variation in diastolic blood pressure in pregnant women, rather than a difference in the mean value of systolic or diastolic blood pressure, has been found to be statistically significantly associated with intrauterine growth retardation.[75] This study suggests that digital health for WWE might help recognize situations with elevated risk. Although still far from routine clinical practice, there is great promise for future research incorporating longitudinal multi-omics profiling to provide a powerful tool to assess potential fetal adverse outcomes in WWE, and detect early signs of obstetrical complication in order to initiate preventive treatment when possible.

6 Ethics of genetic testing

Precision medicine offers hope for patients, and in particular it has been applied fairly routinely in the field of oncology.[76] Hopefully, we will also expand the approach of precision medicine to our epilepsy patients including WWE. Emerging genetic information and the availability of genetic testing in current clinical neurology practice, which even in the absence of active genetic modifications, can raise important ethical concerns. [77] A previous study has shown in apparently healthy adults of European descent who received whole exome testing, that approximately 2% were found to have genetic variations that are pathogenic or likely pathogenic.[78] These are incidental findings deemed medically actionable and medical intervention is possible to ameliorate the effects of the disease. In the United States in 2008, the Genetic Information Nondiscrimination Act (GINA) was passed to protect Americans from discrimination based on their genetic information in both health insurance and employment. However, according to NIH Human Genome Research Institute, GINA's health insurance protections do not cover long-term care insurance, life insurance, or disability insurance, though some states have state laws that offer additional protections against genetic discrimination along these lines. In addition, the consideration of incidental genetic findings may be important not only to patients, but also to their family members who may inadvertently become aware of these mutations, despite possibly having chosen to avoid knowing this information. Hence, patients with epilepsy and their families should receive appropriate genetic counseling before and after genetic testing to ensure that they understand the predictive value and clinical utility of the test, limitation of test results (e.g., variants of unknown significance), and the ethical, legal and social implication of genetic testing, so they can make informed decisions in the context of their personal health, families and even their religious belief.[79] While we are trying to fulfill the vaunted promise of precision medicine and better care to our patients, we should also uphold the ethical ideals of medicine.

7 Conclusion

In summary, in this era of medicine where epileptologists provide care using trial and failure to reduce the seizure burden, often at significant expense from continued seizures and from medication-related adverse effects and comorbidities of epilepsy such as adverse pregnancy and fetal outcomes, suboptimal bone health, as well as decreased quality of life; we envision a future in which precision medicine enables the emergence of new practice style shifting towards early detection, prediction, and targeted treatments which incorporate multi-omics approaches.

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Highlights

- Women with epilepsy (WWE) face specific challenges throughout their lifespan.
- With the advance of genetic sequencing, precision medicine approach has been advocated in WWE.
- Review of current pharmacogenomic research in WWE highlights the need for further investigations.

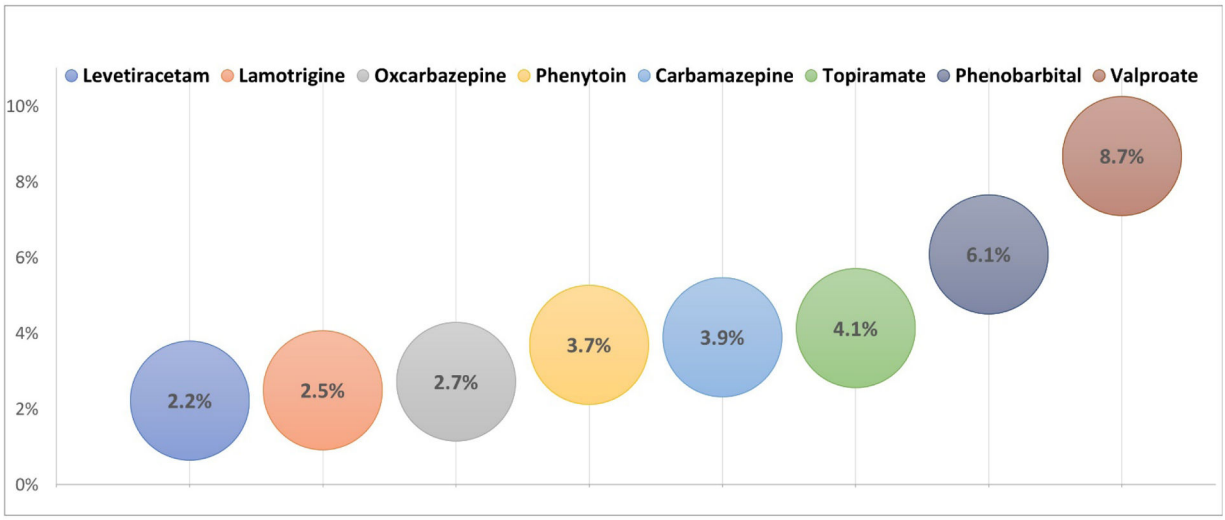

Figure 1: Prevalence of major congenital malformations for different anti-seizure medication monotherapies.

Prevalence of major congenital malformation for different anti-seizure medication monotherapies: we performed a pooled analysis (data shown above) with data extracted from the summary table 1 of the 2019 international league against epilepsy task force on women and pregnancy report, which was originated from the data published from recent 3 major registries: The North American Antiepileptic Drug Pregnancy Registry, UK Epilepsy and Pregnancy Registry, and EURAP international registry.[80] The x axis reflects different anti-seizure medications. The y axis reflects the percentages of major congenital malformation.

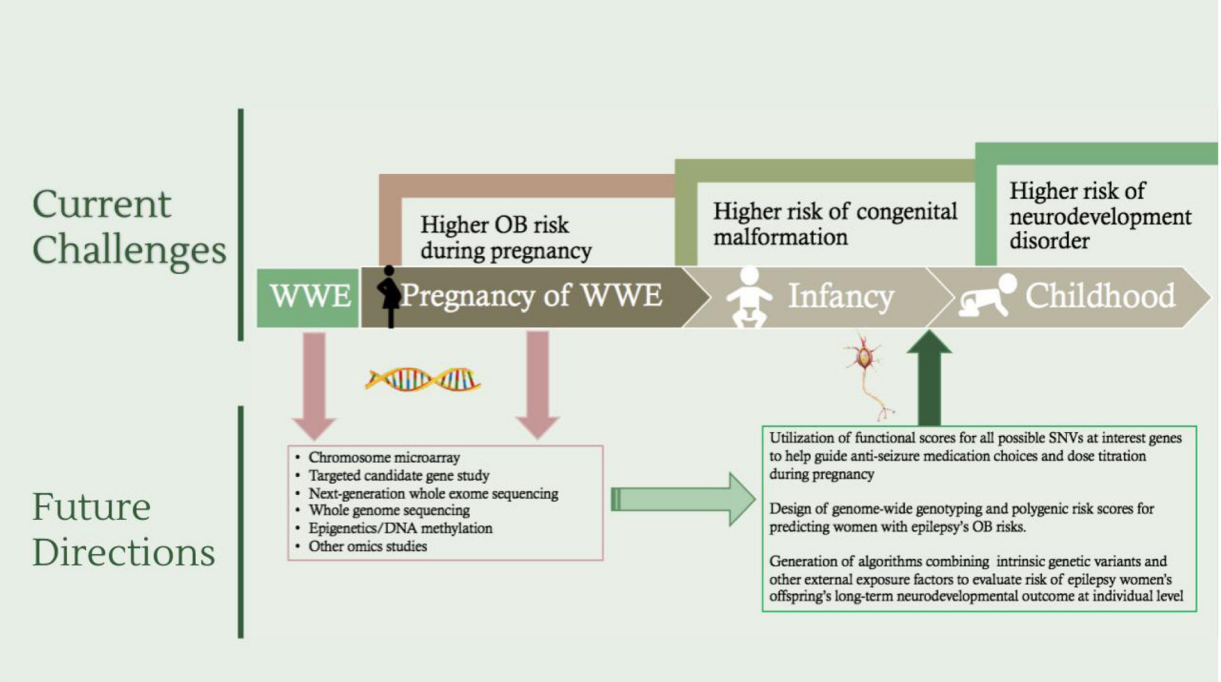

Figure 2: Current challenges and future directions of precision medicine for WWE during epilepsy.

The top panel of the figure shows examples of major challenges that WWE and their children might encounter. The bottom panel of the figure lists current diagnostic tools to help facilitate precision medicine (pink box) and conceptualized examples of future research approaches utilizing precision medicine to help predict the risk of adverse events associated with pregnancy for WWE (green box). WWE: women with epilepsy. SNV: single nucleotide variant. OB risks: obstetric risks.

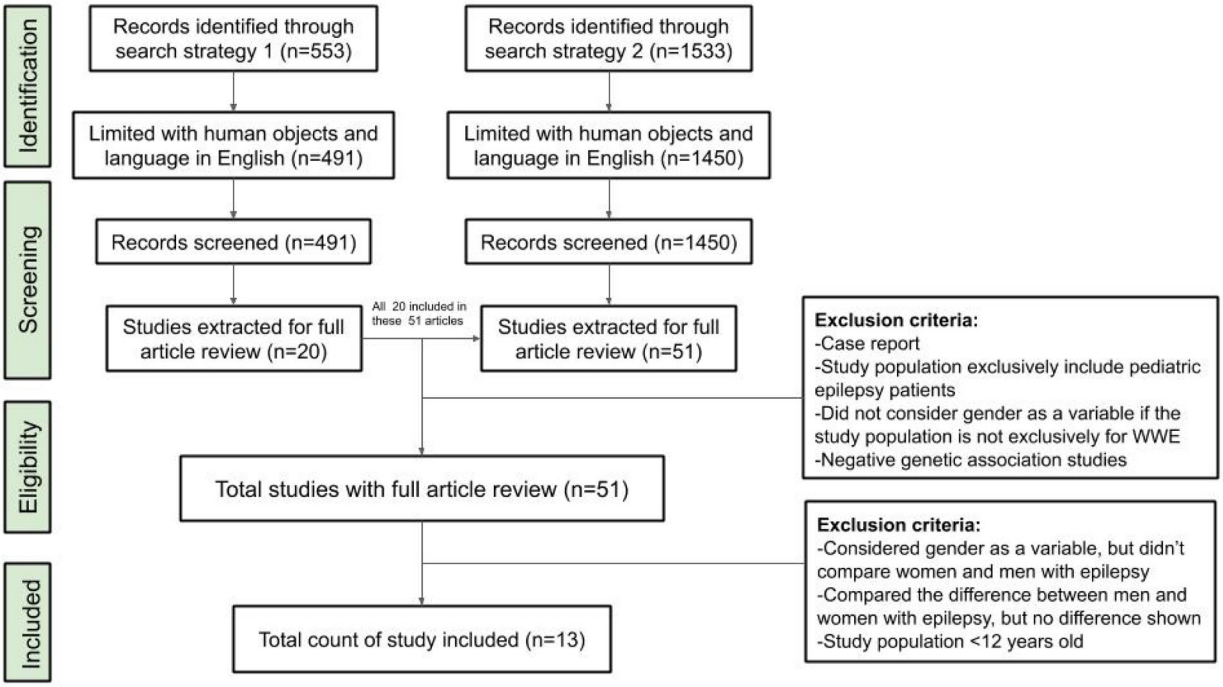

Figure 3: Flow diagram of identification and selection of pharmacogenomic studies in WWE.

In this systematic review, studies were included if they investigated WWE using pharmacogenetic approach, and we used two search strategies in PubMed database with details below as initial inclusion criteria for screening. Search strategy 1: (((women OR woman OR female) AND (seizure OR epilepsy)) AND ("pharmacogenomics" [All Fields] OR "pharmacogenetics"[All Fields] OR "pharmacogenetic"[All Fields] OR "pharmacogenomic"[All Fields] OR "GWAS"[All Fields] OR "genome-wide"[All Fields] OR "gene association study"[All Fields] OR "polymorphism"[All Fields] OR "polymorphisms"[All Fields] OR "allele"[All Fields] OR "gene variant"[All Fields] OR "alleles"[All Fields])) AND (((catamenial AND epilepsy) OR (pregnancy OR anticonvulsants OR antiepileptic OR teratogenesis OR (birth AND defects) OR (pregnancy AND registry) OR (cognitive AND outcome) OR (vitamin AND K) OR folate OR (folic AND acid) OR breastfeeding OR (oral AND contraceptives) OR (polycystic AND ovary AND syndrome) OR (hormone AND replacement AND therapy) OR menopause OR perimenopause OR fertility)), with limit of year =1985–2020. Search strategy 2: (("epilepsy"[All Fields] OR "seizure"[All Fields]) AND ("women"[All Fields] OR "female" [All Fields]) AND ("pharmacogenomics"[All Fields] OR "pharmacogenetics"[All Fields] OR "pharmacogenetic"[All Fields] OR "pharmacogenomic"[All Fields] OR "GWAS"[All Fields] OR "genome-wide"[All Fields] OR "gene association study"[All Fields] OR "polymorphism"[All Fields] OR "polymorphisms"[All Fields] OR "allele"[All Fields] OR "gene variant"[All Fields] OR "alleles"[All Fields])), with limit of year =1985–2020. We excluded articles that: (1) were not written in the English language, (3) were not using human being as study objects, (2) were case reports, (4) studied on study population merely < 12 years old, (5) study population were neither specific in WWE, nor epilepsy

patients with further stratified analysis performed between women and men with epilepsy (6) negative genetic association studies.

Table 1:

Clinical utilization and limitations of current genetic tests.

Methods	Clinical utilization	Limitations
Karyotype	Detect apparently balanced rearrangements which could be missed by microarray analysis	Limited to imbalances greater than 7–10 million bases
	Useful especially when suspicion is aneuploidy (such as trisomy) or ring chromosome syndromes (such as ring 20 syndrome)	
Chromosome microarray analysis	Detect submicroscopic imbalance as small as 50–100 kb range, which is more than 100-fold magnification when compared to karyotyping, hence has more sensitive detection of pathogenic microdeletions or microduplications, cryptic unbalanced chromosome rearrangements	Cannot detect truly balanced chromosome rearrangements
	Often first choice of genetic test for patients with epilepsy plus cases, such as concomitant developmental delay, autism or congenital anomalies	Does not give positional information
Whole exome sequencing (WES)	Sequencing protein coding regions of the genome	Investigates only ~2% of whole human genome
	Detect the variants at nucleotide-level	
Whole genome sequencing (WGS)	Sequencing whole genome, including additional information such as non-coding variants, repeat expansions, small non-coding regulatory RNAs, and complex chromosomal rearrangements when compared to WES	Significance for much of the information from WGS data remains to be determined
	Limited use in clinical practice due to high cost	
On the horizon:		
DNA methylation	One of the most widely assessed epigenomic features in clinic studies, especially in cancer detection, prognostic prediction and treatment recommendation	Usually cell type or tissue specific, and the sensitivity is not optimized when using non-invasive measurement
RNA sequencing (RNA-seq)	Analysis on transcriptome level, and can be used to detect transcript variations and interpret splicing events	Cell type or tissue specific and also dynamic to environmental conditions. Usually need longitudinal measurement for more accuracy
Proteomics and metabolomics	Closer to phenotypes and easier to interpret, rapid response to external factors	Limitation similar to RNA-seq

Table 2:

Summary of pharmacogenomic studies in WWE.

Ref #	Study population	Summary of key findings	Study cohort sample size	Genotyping of polymorphisms studied	Ethnicity / Country
1. Drug Response in WWE					
[20]	Drug-responsive epilepsy patients, drug-resistant epilepsy patients and healthy controls	The risk of drug resistance was higher in WWE with 1236CC or CT genotype than in those with TT genotype of ABCB1 gene.	332 epilepsy patients(157 females) and 200 healthy controls	T129C(rs2188524) and T1236C(rs1128503) of ABCB1	Iranian
[21]	Drug-responsive epilepsy patients, drug-resistant epilepsy patients and healthy controls	WWE with a C/C genotype at position 3435 of the ABCB1 gene have a higher risk of resistance to antiepileptic drugs.	Same as above	G2677(rs2032581) and T2677(rs2032581) of ABCB1 gene	Iranian
[22]	Epilepsy patients on monotherapy of either CBZ or VPA for at least 12 months	rs3789243T allele carriers of Malay females with symptomatic epilepsy were more resistant to either CBZ or VPA than C allele carriers.	685 patients which include 309 WWE	ABCB1 rs3789243 C > T, C1236T, G2677T/A, rs6949448 C > T, and C3435T haplotypes polymorphisms	Chinese, Indian, and Malay
[23]	Nonpregnant women with epilepsy	Functionally relevant promoter polymorphisms from ABCC2: c.−1549G>A and c.−1019A>G either considered alone or in haplotype and diplotype combinations were observed for a significant association with seizure control in WWE.	216 patients of WWE	26 single nucleotide polymorphisms (SNPs) from ABCB1, 32 SNPs from ABCC1, and 40 SNPs from ABCC2	North Indian
[24]	Epilepsy patients on phenobarbitone, phenytoin, CBZ, VPA or their combinations for at least 12 months	An intronic SNP,rs2606345 in the CYP1A1 gene is one of the factors determining drug response to first-line AEDs in WWE.	127 males and 101 females	g. −4404C>T (rs7495708), IVS1 +606C>A (rs2606345), IVS1 −728C>T (rs4646421), Ex2 +160G>A (rs4646422) and Ex7 +131A>G (rs1048943)	North Indian
[25]	Same as above	A validation study of earlier finding	351 epilepsy patients which include 157 WWE, and 552 healthy controls	SNP rs2606345 of CYP1A	24 different ethnic groups in India
2. ASM dosing during pregnancy for WWE					
[29]	WWE during pregnancy	Genetic polymorphism in UGT1A4 and UGT2B7, as well as gender of foetus, are associated with LTG clearance changes during pregnancy.	40 women with 47 pregnancies	UGT1A4 142T > G, L48V (*3), UGT1A4 70C > A, P24T (*2) and UGT2B7 802C > T, H268Y (*2)	Danish
3. Outcome in offspring of WWE					
[30]	WWE and their offspring	Maternal EPHX1 genotype may be associated with risk of fetal anomalies among pregnant women taking phenytoin.	174 pregnancies in 155 women	CYP2C9 R144C (rs1799853), CYP2C9 I395L (rs1057910), EPHX1 Y113H (rs1051740) and EPHX1 H139R (rs2234922)	Not specified
[31]	WWE and their offspring	CC genotype of Ex07 + 139C/T iin ABCB1 and allele *2 genotype of CYP2C219 was significantly higher in in WWE with malformation	143 WWE whose children had malformation and 123 WWE who had normal offspring	CYP2C9(rs 1799853, rs1057910) CYP2C19 (rs4244285, rs4986893) MRHFR (rs1801133, rs 1801131), ABCB1(Pro129T/C, Ex03–1G/A, Ex07 + 139C/T, Ex13 1236C/T, Ex18–76T/A, Ex22 2677G/T and Ex27 3435C/T).	Indian
[33]	Offspring exposed or not exposed to ASMs	Prenatal ASM exposure does not increase the burden of de novo variants	76 child-parent trios	Whole exome sequencing data from child-parent trios were interrogated for	Australian

Ref #	Study population	Summary of key findings	Study cohort sample size	Genotyping of polymorphisms studied	Ethnicity / Country
				de novo single-nucleotide variants/indels	
4.Diagnosis and comorbidities					
[26]	Epilepsy patients treated with either VPA or CBZ for more than 6 months, and started at age <18 years old	Loss-of-function CYP2C19 polymorphisms are associated with an increased BMI gap and a high prevalence of becoming overweight during VPA therapy in WWE	85 VPA (include 30 WWE) and 93 CBZ (include 39WWE) treated epilepsy patients	CYP2C19*2 (c.681G>A; rs4244285) and CYP2C19*3 (c.636G>A; rs4986893)	Japanese
[27]	Women taking ASMs	The frequency of the MTHFR 677TT genotype was significantly higher in women with idiopathic generalized epilepsy when compared to controls	174 women taking ASM (170 WWE and 4 bipolar) and 312 healthy control	MTHFR 677C>T,MTHFR 1298A>C, cytosolic SHMT1 1420C>T,MTR 2756A>G,MTRR 66A>G	Scottish
[28]	Drug-responsive epilepsy patients	The 129V allele was highly represented only in women with TLE compared with controls	289 patients)include 162 WWE) and 272 controls	rs2606345 of CYP1A	Southern Italy

Ref #: reference number. ASM: anti-seizure medication. CBZ: carbamazepine. LTG: lamotrigine. VPA: valproic acid. WWE: women with epilepsy.