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Genetics of Photosensitivity (Photoparoxysmal Response): A Review

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Summary: We present a review of phenotype–genotype correlation and the genetics of photosensitivity. The photoparoxysmal response in EEG (PPR) is still one of the best paradigms for exogenously triggered brain responses based on a genetic predisposition. The definition of the PPR phenotype requires multiple, precise methodologic guidelines. Individual factors such as age and gender but also other, unknown factors influence the expression of the PPR. For example, PPRs occur during adolescence and can disappear at a later age. As a consequence, it is difficult to assign nonaffected disease status correctly. Autosomal dominant inheritance has been found in clinical studies of relatives of PPR-positive epilepsy and nonepilepsy subjects. Genetic heterogeneity of the PPR is obvious because the PPR also can be evoked in a number of autosomal recessive diseases. PPR is most commonly associated with idiopathic generalized epilepsies (IGEs) such as juvenile myoclonic epilepsy (JME). This comorbidity suggests that a genetic factor involved in photosensitivity also may influence the susceptibility for JME. Finding the gene for PPR also might represent a step forward in unraveling the genetic background of JME. The search for the genetic factors causing PPRs should focus on the genes affected in such epilepsies, such as genes (coding) for ion channels and neurotransmitters and their receptors. The expression of defined proteins with as-yet-undetermined functions, is changed in a few types of epilepsies with a mendelian mode of inheritance. These additional genes and the human equivalents of the genes found to be mutated in animal models also are candidates for molecular genetic studies of the PPR. **Key Words:** Photosensitivity—Phenotype—EEG—Genetics—Epilepsy.

GENETICS OF ELECTROENCEPHALOGRAPHIC TRAITS: HISTORY

From twin and family studies that have been conducted since the late 1930s, we know that most EEG parameters (theta, alpha, and beta frequencies, low voltage) are genetically determined. This has been proven by visual inspection as well as by power spectral analyses (1). Heritability also has been seen in event-related brain potentials, although to a lesser extent (for review, see 2).

Changes in the alpha waves by photic stimuli were detected in 1934 by Adrian and Matthews (3). In 1946 and 1949, Walter and co-workers showed (4,5) that 3–4% of the normal healthy population express such reactions, sometimes associated with nausea, vertigo, reduced consciousness, or even with slight limb jerks in the frequency of the light stimulus.

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Phenotype of the photoparoxysmal response

As is common in complex diseases, genetic dissection of PPR phenotype is hampered by difficulties in establishing accurate definitions and by changes in PPR expression in study subjects:

a. *The results of neurophysiologic assessments may vary considerably*, depending on the methods that are applied, such as different colors and patterns, instead of white flashing light and variation in length of stimulus (6). For example, the prevalence of PPR in patients with juvenile myoclonic epilepsy (JME) was recently found to be as high as 90 and not 40%, as usually quoted, if the photic stimulus exceeded 4 min (7). Therefore, standardized stimulation guidelines (technical equipment, eye-closure procedures) are needed to compare PPR study results, not only within families, but certainly also within larger studies and preferably between studies.
b. *The precise definition of a PPR and a generally accepted terminology for describing the PPR phenotype are required.* The questions of whether PPRs

are exclusively defined as a generalized reaction (of the parvocellular) or also as a focal, occipital reaction (of the magnocellular visual system) and whether (8) or not (9) the two reaction types are equally important for clinical and genetic classification must be addressed.

c. *Factors that influence the PPR phenotype are age* (maximal penetrance is between ages ~5 and 20 years) *and segregation pattern or family background* as observed in families with PPR-positive or PPR-negative mothers (10–12).
d. *PPR expression depends on vigilance*: the PPR is more pronounced in fatigued subjects after sleep deprivation (13).
e. *Multiple, successive examinations with varying time intervals show considerable variation in PPRs*, which indicates that a number of other unknown factors are in play.

These and other ambiguities cause difficulties in comparing PPR studies. Several investigations have focused only on visual-sensitive epilepsies but do not consider the EEG trait, which seems to be an important yet not exclusive factor for lowering the seizure threshold and which may segregate independent of the epilepsy (for review, see 14).

In general, because of these problems, the status of affected relatives of PPR-positive subjects is difficult to determine: only persons with a proven PPR can be considered affected, whereas individuals without the PPR in one or two properly performed examinations cannot be distinguished from unaffected persons or persons not predisposed; thus it is not known whether these persons are affected. Patients with generalized spike-and-waves in the resting EEG, independent of a light stimulus, must be carefully examined for photosensitivity to exclude the possibility of assigning a false-positive status. Thus, the expression of the PPR in sporadic cases as well as the PPR as a phenocopy (for example, due to brain lesions or intoxications) cannot be excluded by currently available means, but this situation seems to be rare.

Certain studies have shown an up to 2.5-fold higher prevalence of the PPR trait in girls (12). This may be caused by differences in hormonal changes, which also may be the cause of the age-related onset distribution. Alternatively, it could be the effect of a direct genetic or epigenetic pathogenesis related to the two X chromosomes (gynecotropism) or due to direct or indirect protective effects of the male sex chromosome. Moreover, the incidence of epileptic seizures is elevated in female relatives of the PPR carriers (mother's siblings compared with father's siblings) (15). The available data have not been analyzed to determine a possible role of genomic imprinting or PPR-influenced selective partner choice.

Genetics of PPR without epilepsy

Studies of the genetics of PPR without epilepsy or other disorders have been conducted mostly in families with one PPR-positive epileptic member. The mode of inheritance of PPR in nonepileptic relatives indicates an autosomal dominant trait indiscernible from PPR inheritance in epilepsy patients.

The prevalence of PPR in relatives of PPR-positive subjects is independent of the clinical (meaning epileptic) status of being affected. Waltz and Stephani (16) examined the records of families with one photosensitive parent and showed that the PPR in parents is a major determinant for the risk of PPR in offspring, compatible with an autosomal dominant transmission with age-dependent penetrance of the PPR.

Genetics of the PPR with epilepsy

PPRs are seen in idiopathic generalized, in idiopathic partial, in cryptogenic, and in symptomatic epilepsies.

IGE ("pure" epilepsies)

The rate of PPR-positive patients is highest in the following syndromes: myoclonic epilepsy in infancy and childhood, myoclonic astatic epilepsy (MAE), childhood absence epilepsies (CAE), epilepsy with myoclonic absences (EMA), facial myoclonia with absences (FMA), self-induced photosensitive epilepsy, juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), eyelid myoclonia with absences, and epilepsy with generalized tonic–clonic seizure (GTCS) on awakening. In these epilepsies, rates of photosensitive patients reach values up to 30% (17). Seizure equivalents such as an impairment of consciousness and pleasurable sensations also have been described as clinical signs of PPR.

Multifactorial inheritance is the rule in these epileptic syndromes. PPR is observed not only in the patients themselves but also in their first- and second-degree healthy relatives (8,16,18). PPRs can even be inherited through a family lineage not affected by epilepsy. This observation supports the oligogenic inheritance model of IGE and suggests that a gene causing PPR also increases the risk for IGE in combination with other genetic and environmental factors.

Idiopathic partial epilepsies

Children with neonatal seizures in their histories develop a PPR in 44% and focal sharp waves in 50% of cases. Comparable numbers were seen in patients with neonatal seizures classified as idiopathic, symptomatic, or unknown. Such percentages also were observed in patients who did or did not subsequently develop seizures, such as occurs in idiopathic partial epilepsies and febrile convulsions. Interestingly, no generalized epilepsies could be detected after neonatal seizures (19,20).

Symptomatic epilepsies

In these syndromes, the epilepsy is severe and is accompanied by other neurologic impairments: PPRs can be found in the progressive myoclonic epilepsy (PME), a heterogeneous group of rare, mostly autosomal recessive inherited disorders, including neuronal ceroid lipofuscinoses (mainly of the Jansky–Bielschowsky and the Kufs type), Unverricht–Lundborg disease, Lafora disease, myoclonic epilepsy with ragged red fibers (MERFF), and the sialidoses.

Two (at least) types of PPR?

Although the PPR appears to be a factor in the pathogenesis of epileptic seizure disorders in childhood, the actual trait may not necessarily cosegregate with the epilepsy but rather may affect the threshold for occurrence of seizures. In contrast, the high frequency of PPR in rare autosomal disorders such as Unverricht–Lundborg disease and certain types of ceroid lipofuscinosis suggests that PPR also may be a symptom of a neurodegenerative disease rather than one of causal interacting factors. It is tempting to consider pure or idiopathic PPR as an expression of an abnormal PPR pathway that may also predispose to epileptic seizures in patients who are already predisposed to epilepsy, and symptomatic PPRs as the result of a PPR pathway that by itself is normal but that is induced to function abnormally because of a specific neurodegenerative process.

MOLECULAR GENETICS

As yet, PPR cannot be assigned to a certain gene or multiple gene system. Epileptic syndromes associated with PPR are most commonly those with GTCSs, myoclonic seizures, and absences, seizure types within the IGEs.

In general, patients with IGEs with increased PPR expression are candidates for molecular genetic analyses of the PPR trait (16). However, in only a small percentage of patients, a mutation in one of the genes coding for ion channel subunits for sodium, chloride, potassium, or calcium and for subunits of the γ-aminobutyric acid $(GABA)_A$-receptor subunits was found within probands and family members with IGE and partial epilepsies (for review, see 21).

De novo mutations in the sodium channel gene SCN1A cause severe myoclonic epilepsy of infancy (22); this condition resembles or is identical to severe IGE of infancy with GTCSs, in which 90% express PPRs and in which the unaffected siblings, fathers, and mothers of the patients exhibit PPRs in 20, 19, and 10% of cases, respectively (20). The conflicting findings of de novo mutations, on the one hand, and inheritance of PPR in the families, on the other, await scientific study and clarification. One could hypothesize that the presence of a mutation in a gene causing PPRs also increases the severity of the clinical phenotype and thus increases the ascertainment rate. No studies have been performed as to whether the presence of the *SCN1A* mutation relates to the manifestation of PPR in SMEI patients. If the PPR occurs less frequently in the parents and siblings of SMEI patients without PPR as confirmed by DNA studies than in those of SMEI patients with PPR, this observation would clearly suggest a role for PPR genes in determining the phenotypic expression of SMEI.

Unfortunately, the most common types of IGE, CAE, and JME, in which PPRs are a common finding, could not be etiologically associated with a definite molecular genetic change in the vast majority of cases [for review, see Waltz and Stephani (16)]. Nevertheless, in single families and patients with CAE as well as other types of epilepsy, the epilepsy was found to be associated with $GABA_A$-receptor $\gamma 2$ subunit (*GABARG2*) or voltage-gated Ca^{2+}-channel subunit mutations (23–26). Additionally, it was shown recently that mutations in chloride channels are associated with idiopathic generalized epilepsies (27). This opens a wide range of candidate genes for further studies.

Sander et al. (28) reported 413 microsatellite polymorphisms in the genotyping in 617 IGE family members and found significant evidence for the IGE susceptibility locus on chromosome 3q26 and evidence suggesting that two IGE loci are located on chromosomes 14q23 and 2q36. On the basis of their data and those of others reporting chromosomal regions with linkage of different levels of significance on 6p, 6q, 14, and 15q, more than one genetic factor must be conferring susceptibility (28). Linkage studies have been published for IGEs proving or excluding linkage to other GABA-receptor subunits, ionotropic and metabotropic glutamate receptors, nicotinic acetylcholine receptors (subunits), μ-opioid receptor type 1, voltage-gated Na-, K-, and Ca-channel subunits, transporters for glutamate, dopamine, serotonin, monoamine oxidase type A, paired box 6, activity-regulated cytoskeleton-associated protein, signal transduction-associated, RNA binding 3, jerky homologue of humans on chromosome 8, and others (21). If a genetic link indeed exists between PPR and IGE, it may well be that the gene responsible for PPR resides in one of these regions.

Whether the two other known non-ionic channel gene mutations [LGI1 in autosomal dominant temporal lobe epilepsy (ADLTE) (29) and the Aristaless gene mutation in epilepsies with infantile spasms and mental retardation (30,31)] are related to PPR remains to be elucidated.

Further candidate genes for PPRs are those found to be affected in the PMEs Unverricht–Lundborg disease and Lafora disease. In neuropharmacologic studies, dopamine-receptor agonists compensate for PPR; therefore genes coding for central dopamine receptors also are candidates for analyses of the etiopathogenesis of PPR.

Animal studies on the genetics of PPR

The most prominently studied animal model for PPR is the baboon *Papio papio* from Senegal, in which

TABLE 1. *Rodent models of idiopathic epilepsy that could be used in genetic analyses of photosensitivity*

Name of the model	Mutated gene product (chromosomal localization)
Tottering mouse	Ca^{2+}-channel $\alpha 1$ subunit (chr. 8)
Lethargic mouse	Ca^{2+}-channel $\beta 4$ subunit (chr. 2)
Stargazer mouse	Ca^{2+}-channel $\gamma 2$ subunit, stargazin (chr. 15)
Mocha mouse	Adaptor-like protein complex (AP3; chr. 10)
Slow-wave-epilepsy mouse	Na/H exchanger (Nhe1, chr. 4)
Ducky mouse	Full-length functional $\alpha 2d2$ subunit of high-voltage activated Ca^{2+} channel (chr. 9)
Genetic absence epilepsy in rats, Strasbourg (GAERS)	Unknown
Wistar albino Glaxo rat, Rijswijk(WAG/Rij rat)	Unknown
High-voltage spike-and-wave spindles rat from Norway (HVS rat Fisher 344 and Brown)	Unknown
Cystatin B–deficient mouse	
Ion channels	
Kv1.1 mouse	Voltage-gated, delayed rectifying K^+ channel
GIRK2 mouse	G protein–gated, inward rectifying K^+ channel
Neurotransmitters	
NPY mouse	Neuropeptide Y
5HTC2c	Serotonin receptor
Receptors	
GluRB	Q/R site editing of glutamate-receptor subunit
GABR$\beta 3$	GABA receptor β subunit
IP_3	Inositol triphosphate receptor
Transporters	
Glyt-1	Glutamate transporter
Others	
GAD65	Glutamate decarboxylase isozyme
Gαo	G protein α subunit
PLC $\beta 1$	Phospholipase C β isozyme
Synapsin 1,2	Synaptic vesicle protein
Cam kinase Iia	Ca^{2+}/caldmodulin protein kinase
TNAP	Nonspecific alkaline phosphatase
OTX1	Homeodomain protein
CBP-B	Brain-specific DNA-binding protein
Bmi-1	Zn^{2+} finger motif protooncogene
P35	Cyclic-dependent kinase 5 activator
SV2A	Synaptic vesicle protein
AMT	Aspartate methyltransferase
NeuroD	BHLH transcription factor
CD	Cathepsin D

Chr, Chromosome (see references 21, 34).

intermittent photic stimuli (20–30 Hz) induce EEG discharges and clonic and myoclonic jerks in an otherwise healthy animal (32,33). Detailed analysis of the electroclinical manifestations observed in photosensitive humans and baboons shows differences concerning the localization of photically induced EEG changes (bifrontorolandic with secondary generalization in *Papio papio*). Accordingly, PPRs in *Papio papio* are also an idiopathic and thus genetic trait. No genetic mutation has been shown to be responsible for this feature, according to the published literature.

Several other animal models (mouse, rat, and dog) have been developed to study the genetics of IGE. These mutant models also could prove to be useful in future studies on the genetics of the PPR, although photosensitivity has not been looked for and published (see Table 1 from reviews 21 and 34). A strain of chicken, known as FEpi (for Fayoumi epileptic) and bearing an autosomal recessive mutation, exhibits a form of reflex epilepsy with EEG interictal paroxysmal manifestations and generalized seizures in response to either light or sound stimuli. In both types of responses, the seizure initiator and the convulsion generator seem to be localized in the brainstem, although reinforcement from telencephalic visual structures is required to trigger photogenic generalized convulsions (35,36). Nevertheless, differences between humans and animals must be considered: the mouse model of Unverricht–Lundborg disease, a PME in humans with marked photosensitivity, does not exhibit photosensitivity (37).

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