TABLE 445-2 EXAMPLES OF GENES ASSOCIATED WITH EPILEPSY SYNDROMES[a]

Gene (Locus)	Function of Gene	Clinical Syndrome	Comments
CHRNA4 (20q13.2)	Nicotinic acetylcholine receptor subunit; mutations cause alterations in Ca^{2+} flux through the receptor; this may reduce amount of GABA release in presynaptic terminals	Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE); childhood onset; brief, nighttime seizures with prominent motor movements; often misdiagnosed as primary sleep disorder	Rare; first identified in a large Australian family; other families found to have mutations in *CHRNA2* or *CHRNB2*, and some families appear to have mutations at other loci
KCNQ2 (20q13.3)	Voltage-gated potassium channel subunits; mutation in pore regions may cause a 20–40% reduction of potassium currents, which will lead to impaired repolarization	Benign familial neonatal seizures (BFNS); autosomal dominant inheritance; onset in 1st week of life in infants who are otherwise normal; remission usually within weeks to months; long-term epilepsy in 10–15%	Rare; other families found to have mutations in *KCNQ3* or an inversion in chromosomal 5; sequence and functional homology to *KCNQ1*, mutations of which cause long QT syndrome and a cardiac-auditory syndrome
SCN1A (2q24.3)	α-Subunit of a voltage-gated sodium channel; numerous mutations affecting sodium currents that cause either gain or loss of function; network effects appear related to expression in excitatory or inhibitory cells	Generalized epilepsy with febrile seizures plus (GEFS+); autosomal dominant inheritance; presents with febrile seizures at median 1 year, which may persist >6 years, then variable seizure types not associated with fever; numerous other syndromes, including almost 80% of patients with Dravet's syndrome (severe myoclonic epilepsy of infancy) and some cases of Lennox-Gastaut syndrome	Incidence uncertain; GEFS+ identified in other families with mutations in other sodium channel subunits (*SCN2B* and *SCN2A*) and $GABA_A$ receptor subunit (*GABRG2* and *GABRA1*); significant phenotypic heterogeneity within same family, including members with febrile seizures only
LGI1 (10q24)	Leucine-rich glioma-inactivated 1 gene; previous evidence for role in glial tumor progression; recent studies suggest an influence in the postnatal development of glutamatergic circuits in the hippocampus	Autosomal dominant partial epilepsy with auditory features (ADPEAF); a form of idiopathic lateral temporal lobe epilepsy with auditory symptoms or aphasia as a major focal seizure manifestation; age of onset usually between 10 and 25 years	Mutations found in up to 50% of families containing two or more subjects with idiopathic localization-related epilepsy with ictal auditory symptoms, suggesting that at least one other gene may underlie this syndrome.
DEPDC5 (22q12.2)	Disheveled, Egl-10 and pleckstrin domain containing protein 5; exerts an inhibitory effect on mammalian target of rapamycin (mTOR)-mediated processes, such as cell growth and proliferation	Autosomal dominant familial focal epilepsy with variable foci (FFEVF); family members have seizures originating from different cortical regions; neuroimaging usually normal but may harbor subtle malformations; recent studies also suggest association with benign epilepsy with centrotemporal spikes	Study of families with limited number of affected members revealed mutations in approximately 12% of families; thus may be a relatively common cause of lesion-negative focal epilepsies with suspected genetic basis
CSTB (21q22.3)	Cystatin B, a noncaspase cysteine protease inhibitor; normal protein may block neuronal apoptosis by inhibiting caspases directly or indirectly (via cathepsins), or controlling proteolysis	Progressive myoclonus epilepsy (PME) (Unverricht-Lundborg disease); autosomal recessive inheritance; age of onset between 6 and 15 years, myoclonic seizures, ataxia, and progressive cognitive decline; brain shows neuronal degeneration	Overall rare, but relatively common in Finland and Western Mediterranean (>1 in 20,000); precise role of cystatin B in human disease unknown, although mice with null mutations of cystatin B have similar syndrome
EPM2A (6q24)	Laforin, a protein tyrosine phosphatase (PTP); involved in glycogen metabolism and may have antiapoptotic activity	Progressive myoclonus epilepsy (Lafora's disease); autosomal recessive inheritance; age of onset 6–19 years, death within 10 years; brain degeneration associated with polyglucosan intracellular inclusion bodies in numerous organs	Most common PME in Southern Europe, Middle East, Northern Africa, and Indian subcontinent; genetic heterogeneity; unknown whether seizure phenotype due to degeneration or direct effects of abnormal laforin expression
Doublecortin (Xq21-24)	*Doublecortin*, expressed primarily in frontal lobes; directly regulates microtubule polymerization and bundling	Classic lissencephaly associated with severe mental retardation and seizures in males; subcortical band heterotopia with more subtle findings in females (presumably due to random X-inactivation); X-linked dominant	Relatively rare but of uncertain incidence; recent increased ascertainment due to improved imaging techniques; relationship between migration defect and seizure phenotype unknown

[a]The first five syndromes listed in the table (ADNFLE, BFNC, GEFS+, ADPEAF, and FFEVF) are examples of idiopathic epilepsies associated with identified gene mutations. The last three syndromes are examples of the numerous Mendelian disorders in which seizures are one part of the phenotype.

Abbreviations: GABA, γ-aminobutyric acid; PME, progressive myoclonus epilepsy.

These observations emphasize the concept that the many causes of seizures and epilepsy result from a dynamic interplay between endogenous factors, epileptogenic factors, and precipitating factors. The potential role of each needs to be carefully considered when determining the appropriate management of a patient with seizures. For example, the identification of predisposing factors (e.g., family history of epilepsy) in a patient with febrile seizures may increase the necessity for closer follow-up and a more aggressive diagnostic evaluation. Finding an epileptogenic lesion may help in the estimation of seizure recurrence and duration of therapy. Finally, removal or modification of a precipitating factor may be an effective and safer method for preventing further seizures than the prophylactic use of anticonvulsant drugs.

CAUSES ACCORDING TO AGE

In practice, it is useful to consider the etiologies of seizures based on the age of the patient, because age is one of the most important factors determining both the incidence and the likely causes of seizures or epilepsy (Table 445-4). During the *neonatal period and early infancy*, potential causes include hypoxic-ischemic encephalopathy, trauma, CNS infection, congenital CNS abnormalities, and metabolic disorders. Babies born to mothers using neurotoxic drugs such as cocaine, heroin, or ethanol are susceptible to drug-withdrawal seizures in the first few days after delivery. Hypoglycemia and hypocalcemia, which can occur as secondary complications of perinatal injury, are also causes of seizures early after delivery. Seizures due to inborn errors of metabolism usually present once regular feeding begins, typically 2–3 days after birth. Pyridoxine (vitamin B_6) deficiency, an important cause of neonatal seizures, can be effectively treated with pyridoxine replacement. The idiopathic or inherited forms of benign neonatal convulsions are also seen during this time period.

The most common seizures arising in *late infancy and early childhood* are febrile seizures, which are seizures associated with fevers but without evidence of CNS infection or other defined causes. The overall prevalence