Genetics of Epilepsy

Epilepsi Genetiği

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In about forty percent of patients with epilepsy a genetic contribution to aetiology has been estimated to be present. There may be a direct or indirect genetic control on neurons so there are various approaches for the classification. Categorization according to the mechanisms of inheritance identifies three groups of genetic epilepsies: mendelian disorders, non-mendelian or complex diseases, and chromosomal disorders. A second distinction is to identify the epilepsies in which recurrent seizures are one component of a multi-faceted neurological phenotype, and those in which recurrent seizures occur in otherwise neurologically intact individuals. In this article a selection of individual epilepsies are considered to illustrate current progress in gene mapping and cloning.

Anahtar Sözcükler: Epilepsy, genetics, neurogenetics, brain, genes.

Epilepsili hastaların yaklaşık yüzde kırkının etyolojisinde genetik katkıdan söz edilebilir. Nöronlardaki genetik kontrol dolaylı veya dolaysız olabileceğinden sınıflandırmaya yönelik çeşitli girişimler bulunmaktadır. Kalıtım mekanizmaları göz önüne alınarak gerçekleştirilen sınıflamada üç ana grup bulunmaktadır: Mendelyan hastalıklar, mendelyan olmayan veya kompleks hastalıklar, ve kromozomal hastalıklar. Bir başka ayrım ise, tekrarlayan nöbetlerin çeşitli semptomları olan nörolojik hastalığın bir parçası olarak ortaya çıktığı epilepsiler ile tekrarlayan nöbetlerin nörolojik ve kognitif olarak tamamen normal kişilerde ortaya çıktığı epilepsileri belirlemeye yöneliktir. Bu yazıda, gen haritalandırması ve klonlamasında günümüzdeki gelişmeleri yansıtma düşüncesiyle bazı epilepsiler üzerinde durulmuştur.

Key Words: Epilepsi, genetik, nörogenetik, beyin, gen.

A genetic contribution to aetiology has been estimated to be present in about forty per-cent of patients with epilepsy. The genetic control of neuronal synchrony may be direct or indirect, and the various approaches to the classification of genetic epilepsies reflect this.

It is useful to categorise genetic epilepsies according to the mechanisms of inheritance involved. This identifies three major groups: mendelian disorders in which a single major locus can account for segregation of the disease trait; non-mendelian or "complex" diseases in which the pattern of familial clustering can be accounted for by the interaction of several loci together with environmental factors, or by the maternal inheritance pattern of mitochondrial DNA; chromosomal disorders in which a gross cytogenetic abnormality is present. A second useful distinction is between those epilepsies in which recurrent seizures are one component of a multi-faceted neurological phenotype, and those in which recurrent seizures occur in individuals who are otherwise neurologically and cognitively intact and who have no detectable anatomical or metabolic abnormality.

There are over one-hundred and sixty mendelian diseases which include epilepsy as part of the phenotype. Many of these are associated with obvious structural lesions -tuberous sclerosis for example- or generalised metabolic changes which can be assumed to generate neuronal hyperexcitability. A small number are "pure" epilepsy syndromes, and these may be either generalised epilepsies (eg. Benign familial neonatal convulsions) or partial epilepsies (eg. Autosomal dominant nocturnal frontal lobe epilepsy). Although numerous, the mendelian epilepsies are individually rare, and probably account for no more than one per-cent of patients.

The common familial epilepsies tend to display "complex" inheritance. They include well-characterised entities such as juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE) and benign childhood epilepsy with centrotemporal spikes (BCECTS). Several gross chromosomal aberrations are associated with epilepsy, including Down Syndrome and Trisomy 12p.

The molecular basis of the genetic epilepsies has until recently been entirely obscure. It is likely of

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course that this is heterogeneous, as seizures may be the end-point of myriad molecular aberrations which ultimately disturb neuronal synchrony. The methods now exist for elucidating the molecular genetics of the epilepsies and the recent demonstration of a mutation in the gene encoding the α4 subunit of the neuronal nicotinic acetylcholine receptor in a family segregating autosomal dominant nocturnal frontal lobe epilepsy is an encouraging step in that direction.

A selection of individual epilepsies are considered to illustrate current progress in gene mapping and cloning.

Mendelian Epilepsies

Epilepsy forms part of the phenotype of a number of Mendelian diseases including tuberous sclerosis (TSc), fragile X syndrome (FRAX), neurofibromatosis (NFI) and an array of metabolic disorders, all of which are individually rare. In these diseases seizures are symptomatic of underlying neurological involvement and may be accompanied by other neurological signs such as mental retardation or developmental regression. There are a few primary epilepsies which are inherited in a Mendelian fashion. They are rare and together account for only a small fraction of all epilepsies. However, they form an important group because recognition of the characteristic features and presence of a family history will enable the correct diagnosis to be made.

A description is given of recent work on three autosomal dominant conditions: Benign familial neonatal convulsions (EBN1, EBN2), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and partial epilepsy with auditory symptoms and three autosomal recessive progressive myoclonic epilepsies: the neuronal ceroid lipofuscinoses (CLN1, CLN3), Unverricht-Lundborg disease (EPM1) and Lafora body disease.

"Primary" Mendelian Epilepsies

Benign Familial Neonatal Convulsions

Benign familial neonatal convulsions (BFNC) is a rare form of idiopathic primary epilepsy which is inherited in an autosomal dominant fashion. It is characterized by the onset of seizures in the first few days of life with remission occurring commonly by six weeks. The seizures are usually brief and generalised with tonic and clonic phases. However, they may be accompanied by motor automatisms, ocular manifestations and apnoea. Subsequent neurodevelopment is normal although about ten per cent of individuals will continue to have epilepsy in adult life.

A gene for BFNC was localized by linkage analysis to the long arm of chromosome 20 in a single three generation family in 1989[1] and the locus designated EBN1. A maximum two point lod score of 3.12 at q = 0.003 was obtained at the telomeric marker D2OS20 (RMR6). In this family no recombination was detected between either of the markers D2OS19 (CMM6) or D2OS20 and the trait. The results were subsequently confirmed in six French pedigrees.[2] However, an additional study of two North American families suggested the presence of both clinical and genetic heterogeneity.[3] In a family of North European origin four out of fifteen individuals experienced seizures persisting beyond twelve months and one continued to have epilepsy into adolescence. The results of linkage analysis were suggestive of linkage between the BFNC trait and chromosome 20 markers. In the other family of Mexican-American extraction (family 1) seizures had ceased in all family members by the age of two months and none went on to develop epilepsy later. Linkage to D2OS20 and D2OS19 was excluded in this family. Subsequently, a lod score of 4.43 was obtained in family one between the disease trait and the markers D8S284 and D8S256 suggesting that a second locus (EBN2) exists on chromosome 8q.[4] Further evidence for a locus on chromosome 8q has been obtained in a German family.[5]

The region to which EBN1 maps contains the gene encoding the α4 subunit of the nicotinic acetylcholine receptor CHRNA4. A mutation has been found in CHRNA4 in a family with autosomal dominant frontal lobe epilepsy.[6] It therefore represents a likely candidate gene for BFNC, although, to date no mutations have been found in CHRNA4 in families with BFNC.

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

Very recently six families from Australia, UK and Canada with an autosomal dominantly inherited form of partial epilepsy were described.[7,8] Seizures occurred during sleep and had frequently been misdiagnosed as nightmares, night terrors, hysteria, sleep paralysis and paroxysmal nocturnal dystonia. The familial nature of the condition had therefore gone unrecognised. Seizures begin predominantly in childhood and persist into adulthood. They occur in clusters of between four and eleven episodes a night usually soon after falling asleep or before waking. Several individuals report an aura which may be sensory, somatosensory or psychic. The majority of subjects are aware throughout the seizure although many develop secondarily generalised seizures at some time. Affected individuals are neurologically and intellectually normal. The interictal

EEG is usually normal although the ictal EEG may show sharp and slow wave activity in the anterior quadrants bilaterally.

Segregation analysis performed in the five families described supported autosomal dominant inheritance with 69% penetrance and variable expression. Linkage studies performed in a single large Australian pedigree assigned the gene to chromosome 20q13.2, the same region to which EBN1 maps.[9] However, the remaining families do not appear to be linked to chromosome 20q indicating the presence of genetic heterogeneity. This region of chromosome 20q contains a candidate gene, CHRNA4, which encodes the α4 subunit of the nicotinic acetylcholine receptor. A missense mutation that replaces a serine with phenylalanine at codon 248 has recently been demonstrated in CHRNA4 in the chromosome 20-linked family.[6] This highly conserved amino acid lies in the second transmembrane domain and it is likely that mutation at this site would cause disease. Moreover, the mutation has been demonstrated in 21 affected family members and four obligate carriers but not in 333 healthy controls. It therefore appears that mutation in CHRNA4 is the first genetic defect known to result in epilepsy.

Partial Epilepsy with Auditory Symptoms

During the ascertainment of patients as part of a large study of the genetic contribution to epilepsy a family in which eleven individuals over three generations had idiopathic partial epilepsy was identified.[10] Ten of the affected family members had either simple partial or complex partial seizures with secondarily generalized tonic-clonic seizures. Six individuals also reported auditory disturbance such as a hum or a ringing which grew gradually louder as part of the seizure. The age of onset was between eight and nineteen years. The interictal EEG was normal in all cases and neurological examination was also normal in those that were examined. Three members of the family had symptomatic epilepsy and a further three had acute symptomatic seizures. In two, epilepsy was suspected but insufficient information was available for a definitive diagnosis to be made. All these individuals were classified as unknown for the purposes of linkage analysis. Linkage analysis was performed assuming autosomal dominant inheritance with a penetrance of 71% in those over the age of twenty. A maximum two point lod score of 3.99 was obtained at $\theta = 0$ with the marker D1OS192. All living affected individuals shared a haplotype for seven markers spanning 10cM of chromosome 10q placing the gene somewhere between the markers D10S185 and D10S566. This locus could represent a susceptibility gene for a very specific type of epilepsy in which auditory features form part of the phenotype as in this family. Alternatively, allelic heterogeneity at the same locus may predispose to other forms of epilepsy.

Mendelian Disorders in which Epilepsy Forms Part of the Phenotype

Unverricht - Lundborg Disease - Baltic Myoclonus

Progressive myoclonic epilepsy of the Unverricht-Lundborg type (locus symbol, EPM1) is an autosomal recessive disorder which is enriched in the Finnish population with an incidence of 1 in 20,000 births. Stimulus sensitive myoclonus begins between the age of about 6 and 15 years and with time, mild mental retardation, dysarthria and ataxia develop. Non-specific histological changes are found in the brain; Lafora bodies or autofluorescent lipopigment are not found. Present evidence suggests that ULD, Baltic myoclonus,[11] and so-called Mediterranean myoclonus[12] are genetically homogeneous. The combination of a high degree of consanguinity and a risk rate for siblings of 1 in 4 demonstrate that inheritance is autosomal recessive.[13]

ULD was mapped to the long arm of chromosome 21 in a group of 11 nuclear pedigrees from Finland. A genome search was undertaken and linkage found after testing 64 marker loci.[14] A maximum multipoint lod score of 10.08 was obtained with three loci in 2lq22.3. The localisation has been further refined[15] and refined most recently using the technique of linkage disequilibrium mapping to a region of about 0.3 cM. Linkage studies in non-Finnish families have demonstrated genetic (locus) homogeneity within this phenotype.

The EPM1 gene was recently isolated and shown to be the gene encoding Cystatin B.[16]

Neuronal Ceroid Lipofuscinoses

The neuronal ceroid lipofuscinoses (NCL) are a group of inherited neurodegenerative disorders characterised by the accumulation of the autofluorescent lipopigments ceroid and lipofusein in neurones and other cell types.[17] At least five subtypes are recognised on the basis of age of onset, clinico-pathological features and chromosomal location. The childhood onset varieties are inherited in an autosomal recessive fashion and include the following : infantile NCL (CLN1; Haltia-Santavuori disease, MIM 256730), classical late-infantile NCL (CLN2; Jansky-Bielschowsky disease, MIM 204500), Finnish variant late-infantile NCL (CLN5; MIM 256731) and juvenile NCL (CLN3; Batten or Spielmeyer-Vogt-Sjogren disease, MIM 304200). Until recently the underlying biochemical defects in this group of disorders has been entirely unknown.

Infantile NCL is a Finnish disease with an incidence of 1 in 20,000 in that population, although

occasional patients are found in other populations. Onset occurs in the first two years of life with seizures, visual failure, choreoathetosis and ataxia. The ultrastructural hallmark is so-called granular osmiophilic deposits (GRODS). Initial linkage to a locus on chromosome 1p, D1S57, was established using 26 Finnish families.[18]

The map localisation was subsequently refined[19] and the CLN1 gene was successfully cloned in 1995.[20] The gene encodes palmitoyl protein thioesterase. Prenatal diagnosis has been carried out using linked DNA markers.

Juvenile onset NCL has an incidence of up to 1 in 25,000 births, with an increased prevalence in the Northern European population. Onset usually begins with visual failure between the age of 5 and 10 years followed by seizures and relentless mental deterioration. The lymphocytes are vacuolated on light microscopy, and so-called "finger-print" profiles are the characteristic ultrastructural feature.

The gene locus for Batten disease, CLN3, was assigned to chromosome 16 by demonstration of linkage to the haptoglobin locus.[21] Localisation was subsequently refined to the region 16pl2 by analysis of additional families and marker loci.[22-25] Strong linkage disequilibrium was identified with four microsatellite loci in the disease gene region: D16S288, D16S299, D16S298 and SPN. Haplotype analysis indicated a strong founder effect with the majority of CLN3 chromosomes having a common origin.[24]

The CLN3 gene was recently cloned. Linkage disequilibrium mapping in the Finnish population suggested that CLN3 was very close to the locus D16S298.[26] Exon amplification of a cosmid containing D16S298 yielded a candidate gene which was disrupted by a 1kb deletion in all patients carrying the disease chromosome with the common "56" haplotype. Two separate deletions and a point mutation altering a splice site in three unrelated families confirmed that this candidate was CLN3. CLN3 encodes a 438 amino acid protein of unknown function.[27]

Lafora Disease

Progressive myoclonus epilepsy with polyglucosan intracellular inclusion bodies was first described in 1911 by Lafora and has become known as Lafora disease.[28,29] It is an autosomal recessive disease characterised by the presence of periodic acid-Schiff-positive cytoplasmic inclusion bodies, known as Lafora bodies, in neurones, heart, liver and muscle. The biochemical defect is unknown. During adolescence, affected individuals develop a seizure disorder which may include generalised tonic-clonic seizures, absences, drop attacks or focal occipital seizures. Soon after presentation, subjects develop asymmetric myoclonic jerks. Dementia rapidly follows accompanied by apraxia and visual loss. The EEG shows high voltage bilateral synchronous, spike-wave and polyspike-wave complexes. Diagnosis is based on the presence of Lafora bodies in the eccrine sweat duct cells, most readily detected on axillary skin biopsy.

In 1991 a gene for progressive myoclonus epilepsy of the Unverricht-Lundborg type (ULD) was localised to chromosome 21q22.[14] Subsequent linkage studies demonstrated that Lafora disease was not allelic to ULD.[15] More recently, linkage analysis performed in nine families with Lafora disease produced a maximum two point lod score of 10.54 at $\theta=0$ at the marker D6S311, localising the gene to 6q23-25. Homozygosity mapping in four consanguineous families revealed a region of homozygosity extending over a 17cM interval from D6S292 and D6S420.[30] Candidate genes for Lafora disease would include enzymes that play a role in carbohydrate metabolism. To date, no genes encoding enzymes involved in the synthesis or degradation of polysaccharides have been mapped to 6q23-25. The disease gene will be amenable to positional cloning techniques although further families will be required to narrow down the region to which the Lafora disease gene maps.

Non-Mendelian Epilepsies

Juvenile Myoclonic Epilepsy

Juvenile myoclonic epilepsy (JME) is a common form of idiopathic generalised epilepsy representing five to ten per cent of epilepsy as a whole. Individuals most commonly present between the ages of eight and twenty-six with early morning myoclonus, symmetrical shock-like jerks predominantly of the upper limbs, precipitated by fatigue, alcohol and menstruation. Over ninety per cent also have generalized tonic-clonic seizures and thirty per cent have absence seizures. The EEG characteristically shows bilateral symmetrical 4-6Hz polyspike and wave although it may be normal. JME is usually readily treated with sodium valproate.

A genetic contribution to JME has long been established although the mode of inheritance is unclear. Autosomal dominant,[31] autosomal recessive,[32] two locus,[33] and multifactorial models[34] have been proposed.

Four studies from two groups have provided evidence for the existence of a locus predisposing to JME on chromosome 6p and the locus has been designated EJM1. In 1988 Greenberg and colleagues performed linkage analysis in twenty-four families in which the proband had JME using the classical markers HLA and properdin factor B (BF).[35] Eleven families were informative, eight for BF and three for HLA. Asymptomatic relatives with an abnormal EEG were classified as affected. The maximum lod score of 3.04 was obtained when HLA and BF were

considered together and under the assumption of autosomal recessive inheritance with full penetrance. When asymptomatic relatives with abnormal EEGs were considered unaffected the lod score fell to -3.6. By increasing the family resource, the same group later obtained a maximum lod score of 3.78 ($\theta_{m=f}$=0.01) with HLA assuming autosomal dominant inheritance and classifying asymptomatic relatives with abnormal EEGs as affected.[33] They suggested that EJM1 lay close to, but not within, the HLA region. In 1991, a study in a separately ascertained group of thirty-three German families using HLA serological markers provided further evidence for the existence of a locus on chromosome 6p.[36] A further study of a subset of twenty of these families with one additional family using HLA-DQ RFLP markers, provided a maximum lod score of 4.1 under the assumption of dominant inheritance with 90% penetrance.[37] More recently, a study in a single large pedigree of Belize origin using microsatellite markers on chromosome 6p obtained a maximum lod score of 3.67 ($\theta_{m=f}$=0) between the centromeric marker D6S257 and a trait defined as the presence of clinical JME or an EEG showing diffuse 3.5-6 Hz multispike and slow wave complexes.[38]

Two studies from a single group have failed to find evidence for the existence of a locus on chromosome 6p. Linkage analysis was carried out in a third set of twenty-five families including a patient with JME and at least one first degree relative with JME or a related IGE. Pairwise and multipoint linkage analysis was performed using eight loci spanning the HLA region on chromosome 6p and assuming autosomal dominant and autosomal recessive inheritance with age-dependent high and low penetrance.[39] No significant evidence in favour of linkage was obtained. However, due to a lack of suitable markers, the centromeric region of chromosome 6p was not adequately covered. In a more recent study, linkage analysis was performed in nineteen families in which the proband and at least one first degree relative had JME using micro satellite markers spanning a 61cM region on chromosome 6p and centromeric 6q.[40] Again, no significant evidence in favour of linkage was obtained under any of the models tested. These results suggest that genetic heterogeneity may exist within this epilepsy phenotype. All the studies to date have relied on small groups of families, incapable on their own of demonstrating the presence of heterogeneity. Further work is needed using a large family resource in order to determine whether heterogeneity does exist.

Mitochondrial Disorders

The mitochondrial genome (mtDNA) is a circular DNA molecule, 16,569 bp long, present in up to 10 copies per mitochondrion, and therefore, in up to several hundred copies per cell. Mitochondrial DNA encodes two ribosomal RNAs, twenty-two transfer RNAs and thirteen messenger RNAs encoding components of the inner mitochondrial membrane respiratory chain. The entire mitochondrial genotype of an individual is inherited from the mother.

Human diseases due to mutations of mtDNA include myopathies, encephalopathies, cardiomyopathies and various multi-system disorders. Two diseases with CNS involvement have been described, which in part presented as epilepsy and were caused by point mutations in mitochondrial transfer RNA genes. These are so-called myoclonic epilepsy with ragged-red fibres (MERRF) and mitochondrial encephalomyopathy, lactic-acidosis and stroke-like episodes (MELAS).

MERRF is characterised by epilepsy, intention myoclonus, muscle weakness, progressive ataxia and deafness. An A to G transition mutation at nucleotide pair 8344 in the pseudouridyl loop of the $tRNA^{lys}$ gene was first described in three unrelated MERRF families.[41] This mutation has now been described in most MERRF families. The patients are heteroplasmic -both normal and mutated mtDNA populations are found. Variability of the clinical phenotype appears to depend on the amount and tissue distribution of mutant mtDNA in each individual.

An A to G transition at nucleotide 3243 was reported in 26 out of 31 unrelated Japanese patients with MELAS. This mutation affects a nucleotide position in the dihydrouridine loop of the transfer RNA for leucine. Again, heteroplasmy was present with 50-92% of mutant mtDNA present.[42] Maternal transmission was documented in one family.

These observations confirm that seizures can be caused by deficiencies in mitochondrial energy production and raise the interesting question of whether mutations in mtDNA could contribute to the unexplained but well-documented maternal influence on the transmission of epilepsy.

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