independent origins in each family and each apparently sporadic case we have analyzed, and that unlike the E200K mutation, the global distribution of the D178N mutation causing either FFI or CJD is determined by recurrent mutational events.

References

1. Brown P. Transmissible human spongiform encephalopathy (infectious cerebral amyloidosis): Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker Syndrome, and Kuru. In: Calne DB, ed. Neurodegenerative diseases. Philadelphia: WB Saunders, 1994:839–876.
2. Gambetti P, Petersen RB, Parchi P, et al. Inherited prion diseases. In: Prusiner SB, ed. Prion biology and diseases. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1999:509–583.
3. Medori R, Tritschler HJ, LeBlanc A, et al. Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. N Engl J Med 1992;326:444–449.
4. Goldfarb LG, Mitrova E, Brown P, et al. Mutation in codon 200 of scrapie amyloid protein gene in two clusters of Creutzfeldt-Jakob disease in Slovakia. Lancet 1990;336:514.
5. The EUROCJD Group. Genetic epidemiology of Creutzfeldt-Jakob disease in Europe. Rev Neurol (Paris) 2001;157: 633–637.
6. Windl O, Giese A, Schulz-Schaeffer W, et al. Molecular genetics of human prion diseases in Germany. Hum Genet 1999; 105:244–252.
7. Windl O, Dempster M, Estibeiro JP, et al. Genetic basis of Creutzfeldt-Jakob disease in the United Kingdom: a systematic analysis of predisposing mutations and allelic variation in the PRNP gene. Hum Genet 1996;98:259–264.
8. Goldfarb LG, Petersen RB, Tabaton M, et al. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism. Science 1992;258: 806–808.
9. Peoc'h K, Guerin C, Brandel J-P, et al. First report of polymorphisms in the prion-like protein gene (PRND): implications for human prion diseases. Neurosci Lett 2000;286: 144–148.
10. Long JC, Williams RC, Urbanek M. An E-M algorithm and testing strategy for multiple-locus haplotypes. Am J Hum Genet 1995;56:799–810.
11. Silburn P, Cervenakova L, Varghese P, et al. Fatal familial insomnia: a seventh family. Neurology 1996;47:1326–1328.
12. Lee HS, Sambuughin N, Cervenáková L, et al. Ancestral origins and worldwide distribution of the *PRNP* 200K mutation causing familial Creutzfeldt-Jakob disease. Am J Hum Genet 1999; 64:1063–1070.
13. Ikehata H, Takatsu M, Saito Y, Ono T. Distribution of spontaneous CpG-associated G:C → A:T mutations in the *lac*Z gene of Muta mice: effects of CpG methylation, the sequence context of CpG sites, and severity of mutations on the activity of the *lac*Z gene product. Environ Mol Mutagen 2000;36: 301–311.
14. Scott MR, Safar J, Telling G, et al. Identification of a prion protein epitope modulating transmission of bovine spongiform encephalopathy prions to transgenic mice. Proc Natl Acad Sci USA 1997;94:14279–14284.

Exclusion Mapping of the Genetic Predisposition for Cervical Artery Dissections by Linkage Analysis

Caspar Grond-Ginsbach, PhD,[1] Bernhard Klima, MD,[1] Ralf Weber, MD,[1] Johannes Striegel, MD,[1] Christine Fischer, MS,[2] Werner Hacke, MD,[1] Tobias Brandt, MD,[1] and Ingrid Hausser, MD[3]

Skin biopsies from a patient with a dissection of the left internal carotid artery and from four of his children were analyzed by electron microscopy. The index patient and three children showed mild but regular electron microscopic connective tissue aberrations. They were considered as carriers of an unknown autosomal dominant mutation. Thirty-four candidate genes involved in the biosynthesis of the extracellular matrix were excluded by genetic linkage analysis as possible sites of a disease-causing mutation in this family (logarithm of odds [LOD]-score less than −2.0).

Ann Neurol 2002;52:359–364

Spontaneous cervical artery dissections (sCADs) are increasingly recognized as a cause of stroke in young and middle-aged patients. Their cause is still poorly understood but is likely to be multifactorial, and the involvement of a primary arteriopathy is hypothesized.[1] Several genetic factors are known to increase the risk for sCAD: in particular, complex connective tissue syndromes such as Ehlers–Danlos syndrome or osteogenesis imperfecta appear to predispose for angiopathic processes.[2,3] However, most sCAD patients do not present symptoms of an underlying systemic disorder.[4] In two prospective studies, we systematically searched for electron microscopic aberrations of dermal connective tissue and detected mild but regular aberrations in the collagen or elastic fibers or both in the reticular dermis of most of the patients.[5,6] Similar connective tissue alterations were not found either in a large series

From the [1]Department of Neurology, [2]Institute of Human Genetics, and [3]Department of Dermatology, University of Heidelberg, Heidelberg, Germany.

Received Aug 10, 2001, and in revised form Jan 30, 2002. Accepted for publication Apr 3, 2002.

Address correspondence to Dr Grond-Ginsbach, Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany.
E-mail: caspar grond-ginsbach@med.uni-heidelberg.de

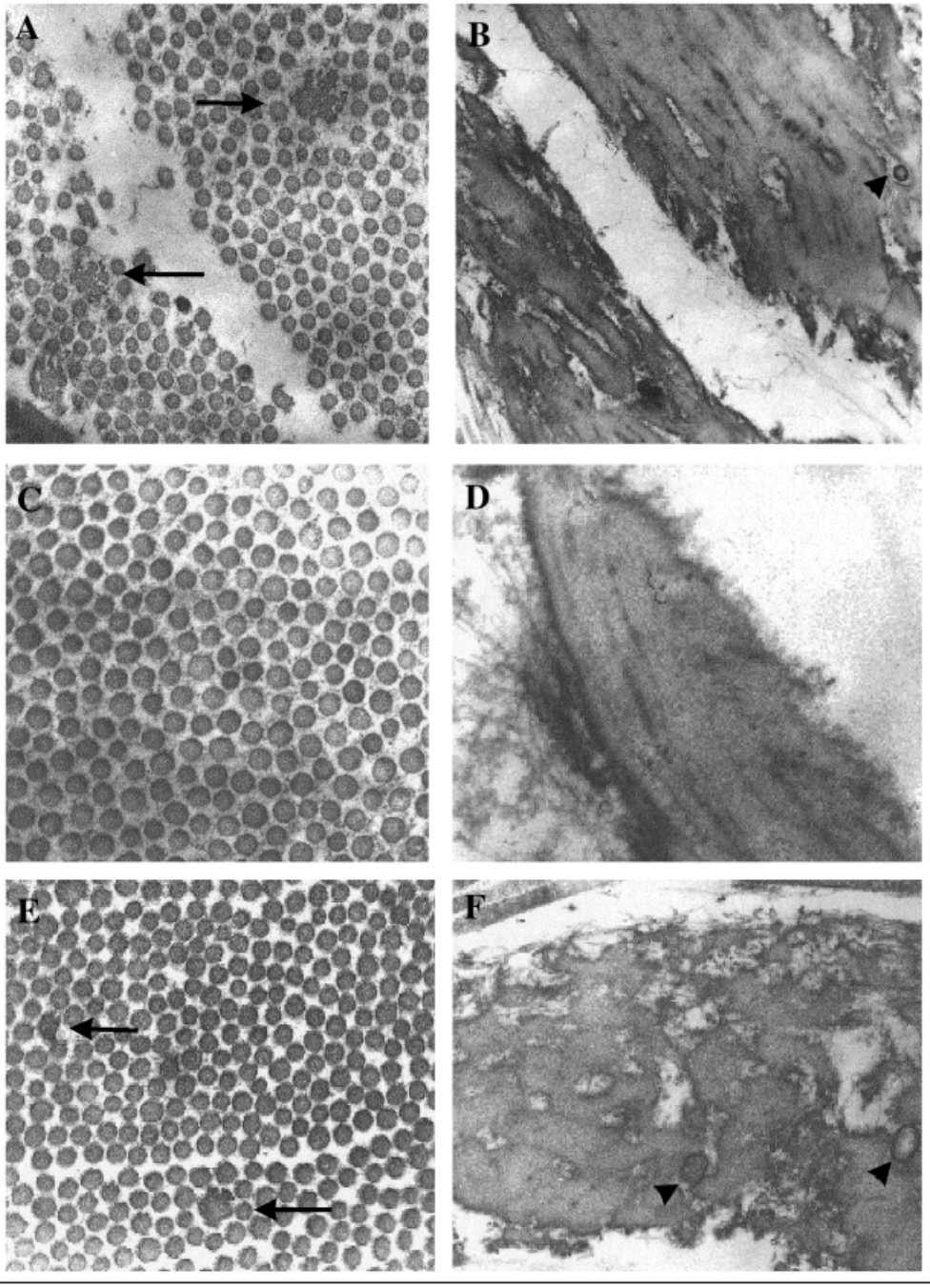

Fig 1. Electron micrographs from ultrathin sections of the reticular dermis. All sections were stained with uranyl acetate and lead citrate. (A, B) Index patient with sCAD ("1" in Fig 2) showing ultrastructural aberrations of collagen and elastic fibers. (A) Collagen bundle containing fibrils with enlarged cross-sections and "flower-like" serrated contours (arrows)*, so-called composite fibrils. (B) Discontinuous amorphous elastin component resulting in a fragmented, porous or "moth-eaten" aspect of the elastic fiber outline. Note focal electron dense inclusions representing minicalcifications* (arrowhead)*. (C, D) normal ultrastructure of dermal collagen and elastic fiber in the reticular dermis of the daughter of the first marriage ("5" in Fig 2). (C) Collagen bundle within the reticular dermis: closely packed collagen fibrils with uniform diameters and circular cross-sections with even contours. (E) Mature elastic fiber: the amorphous elastin core almost completely covers the microfibrillar network that appears only at the periphery of the fiber. (E, F) Ultrastructural aberrations within the dermal connective tissue of the healthy children of the index patient with an ultrastructural phenotype. (E) Collagen bundle with aberrant fibrils* (arrows) *from the son of the second marriage ("6" in Fig 2). (F) Elastic fiber with porous, discontinuous aspect and with focal electron-dense inclusions* (arrowheads) *from the daughter of the second marriage ("7" in Fig 2).*

of diagnostic biopsies or in age and gender-matched patients with stroke from another cause. The dermal connective tissue aberrations in sCAD patients might indicate a systemic disorder also responsible for structural defects of the arterial walls.

The first question of this study was whether the connective tissue alterations found in sCAD patients are inherited. We investigated skin biopsies from four healthy children of an sCAD patient by electron microscopy and searched for regular and reproducible morphological alterations.

Our second question was whether the connective tissue phenotype in this family might be linked to a possible candidate gene for sCAD. DNA from all family members was studied by linkage analysis with microsatellite markers for genes that are involved in the synthesis of extracellular matrix components. We tested 43 candidate genes that were flanked by one or two microsatellite markers. A multipoint linkage analysis was performed for loci flanked with two markers, a two-point analysis for loci with a single marker. Two further candidate genes were not analyzed molecularly, as they are known to be X-chromosomal.

The maximum theoretical logarithm of odds (LOD) score was calculated and found to be 0.9 in the small family analyzed in this study. For the detection of linkage, the statistical power is not high enough in this family,[7] but exclusion mapping is possible.

Subjects and Methods

After informed consent and with permission from the local ethics committee, knife skin biopsy specimens extending to the subcutaneous fat tissue were taken from the outer aspect of the upper arm close to the elbow and processed as already described.[5,8] The skin specimens were investigated by light and electron microscopy. The morphology of the connective tissue components, especially collagen fibrils and elastic fibers, was compared with that of a control group of 10 patients (age younger than 50 years) with acute cerebral ischemia of other causes and without known connective tissue disorder. The observation also were compared with numerous skin biopsies of our electron microscopic laboratory. For morphological evaluation, we focused on the reticular dermal region, where in normal individuals collagen and elastic material are very regular and mostly independent of exogenous influences. Clinical, neuroradiological, and electron microscopic dermal connective tissue findings of the index patient were described in detail elsewhere.[5]

EDTA blood was sampled from the index patient, from his four children, and from his second spouse. DNA was isolated after sodium dodecyl sulfate proteinase-K digestion and phenol-chlorophorm extraction after standard procedures. Locus-specific microsatellite markers were analyzed with the PE Biosystems (Weiterstadt, Germany) linkage mapping sets or with primers from Genethon (Paris, France),[9] evaluated with the GeneScan software at the automatic genetic analyzer ABI Prism 310. We identified the map position of possible candidate genes with http://www.dkfz-heidelberg.de/GeneCards/ and searched for flanking markers and their positions with http://cedar.genetics.soton.ac.uk/public_html/summaryml.html (Genetic Epidemiology Research Group, University of Southampton, UK). LOD scores were calculated with the Genehunter Linkage Analysis Program (version 2.0).[10]

Results

The index patient suffered from a dissection of the left internal carotid artery at the age of 48 years. The dissection was confirmed by magnetic resonance imaging. Symptoms of known heritable connective tissue disorders were found neither in the patient, nor in his children.

By light microscopy, the overall architecture of the dermal connective tissue was normal in the patient and all children. However, particularly regular and well pronounced collagen abnormalities were found in an ultrastructural evaluation of the biopsy of the index patient. Regularly, collagen bundles within the reticular dermis contained a few aberrant collagen fibrils with enlarged diameters and serrated, flower-like contours of cross-sections (Fig 1A). The findings were so clear that they resembled those found in Ehlers–Danlos syndrome type III. Elastic fibers presented pronounced fragmentation and a porous, "moth-eaten" aspect of the fiber with frequent focal electron dense deposits presenting minicalcifications (see Fig 1B).

Three children (Fig 2: Subjects 4, 6, 7) showed similar collagen fibril aberrations within the reticular dermis (see Fig 1E). Elastic fiber abnormalities were also obvious (see Fig 1F). In the dermal connective tissue of one child (see Fig 2: Subject 5), we did not find regular aberrations (see Fig 1C and D).

The candidate genes and the analyzed microsatellite markers are shown in the Table 1. Negative LOD scores were found for most loci, indicating that the ultrastructural connective tissue phenotype did not cosegregate with an allele of the locus-specific genetic

Fig 2. (Circles) Females: (Squares) Males: (Arrow) Index patient with sCAD and with ultrastructural connective tissue abnormalities; (Open symbols). Healthy subjects without ultrastructural connective tissue abnormalities. (Filled symbols) 4,6,7: Healthy subjects without ultrastructural connective tissue abnormalities.

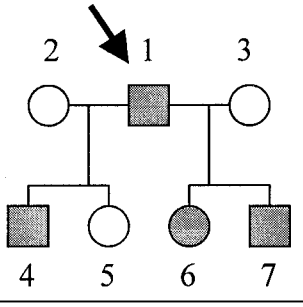

Table. Exclusion Mapping of Genes Encoding Matrix Components That Were Suspected to Be Involved in the Morphologic Aberrations of the Dermal Connective Tissue Observed in Patients with sCAD

Matrix Component	Gene	Flanking Microsatellites (with distances in cM from marker to candidate gene)		LOD at Candidate Gene
Type I collagen, α1 chain	*COL1A1*	D17S1868 (4.49)	D17S787 (3.04)	<−2.1
Type I collagen, α2 chain	*COL1A2*	D7S657 (2.26)	D7S2431 (1.95)	<−2.4
Type III collagen, α1 chain	*COL3A1*	D2S364 (2.70)	D2S118 (2.08)	<−3.4
Type V collagen, α1 chain	*COL5A1*	D9S164 (0.48)	D9S1793 (0.54)	<−3.7
Type V collagen, α2 chain	*COL5A2*	D2S364 (2.70)	D2S118 (2.08)	<−3.4
Type V collagen, α3 chain	*COL5A3*	D19S884 5.79)	D19S865 (0.88)	<−2.2
Type XII collagen, α1 chain	*COL12A1*	D6S460 (1.11)	D6S1609 (0.19)	<−3.7
Type XIV collagen, α1 chain	*COL14A1*	D8S1784 (0.12)		<−4.7[a]
Type XVI collagen, α1 chain	*COL16A1*	D1S513 (0.10)		+ 0.9[a]
C-propeptide proteinase	*BMP1*	D8S258 (2.52)	D8S1786 (1.81)	<−2.4
Fibrillin I	*FBN1*	D15S994 (4.29)	D15S978 (1.29)	<−4.4
Fibrillin II	*FBN2*	D5S471 (3.80)	D5S2115 (4.10)	<−1.8
Tropoelastin	*ELN*	D7S672 (5.77)	D7S669 (1.93)	<−2.1
Microfibril-associated protein 1	*MFAP1*	D15S1012 (3.55)	D15S994 (1.77)	<−4.0
Microfibril-associated protein 2	*MFAP2*	D1S2697 (2.43)	D1S507 (1.59)	<−2.0[a]
Microfibril-associated protein 3	*MFAP3*	D5S410 (0.44)		<−1.5[a]
Microfibril-associated protein 4	*MFAP4*	D17S1857 (0.43)	D17S798 (7.14)	<−3.7
Lysyl hydroxylase	*PLOD*	D1S513 (0.27)		+0.9[a]
Lysyl oxydase	*LOX*	D5S471 (0.01)	DS52115 (7.89)	<−3.0
Matrix metalloproteinase 1	*MMP1*[b]	D11S898	D11S4090	<−2.1
Matrix metalloproteinase 2	*MMP2*	D16S3140 (1.40)	D16S3057 (1.01)	<−6.2
Matrix metalloproteinase 3	*MMP3*[b]	D11S898	D11S4090	<−2.1
Matrix metalloproteinase 7	*MMP7*[b]	D11S898	D11S4090	<−2.1
Matrix metalloproteinase 8	*MMP8*[b]	D11S898	D11S4090	<−2.1
Matrix metalloproteinase 9	*MMP9*	CA-repeat in promoter		−∞
Matrix metalloproteinase 10	*MMP10*[b]	D11S898	D11S4090	<−2.1
Matrix metalloproteinase 12	*MMP12*[b]	D11S898	D11S4090	<−2.1
Matrix metalloproteinase 13	*MMP13*[b]	D11S898	D11S4090	<−2.1
Tissue inhibitor 1 of MMP	*TIMP1*	X-linked		
Tissue inhibitor 2 of MMP	*TIMP2*	D17S784 (1.95)		<−1.5[a]
Tissue inhibitor 3 of MMP	*TIMP3*	D22S280 (0.02)		<−3.0[a]
Tissue inhibitor 4 of MMP	*TIMP4*	D3S2338 (1.05)		+ 0.9[a]
Biglycan	*BGN*	X-linked		
Versican	*CSPG2*	D5S2029 (0.32)	D5S428 (3.66)	<−2.8
Decorin	*DCN*	D12S1345 (0.40)		<−1.5[a]
Fibronectin 1	*FN1*	D2S2361 (0.96)	D2S2382 (1.69)	<−3.0
Tenascin XA	*TNXA*	D6S1666 (2.69)	D6S1610 (4.16)	<−2.1
PXE disease gene	*MRP6*	D16S3069 (2.84)	D16S3060 (4.00)	<−4.5
Polycystic kidney disease 1	*PKD1*	D16S3075 (0.18)		<−3.0[a]
Polycystic kidney disease 2	*PKD2*	D4S2460 (1.53)		<−2.4[a]
Thrombospondin 1	*THBS1*	D15S1012 (4.66)	D15S994 (0.66)	<−4.3
Thrombospondin 2	*THBS2*	D6S281 (1.95)		<−2.3[a]
Matrix gla protein	*MGP*	D12S364 (0.58)		<−1.5[a]
Fibulin1	*FBLN1*	D22S1141 (0.46)		<−2.8[a]
Fibulin2	*FBLN2*	D3S1259 (1.30)		+0.9[a]

Each candidate locus was flanked by one or two informative microsatellite markers. A LOD score profile was calculated in the family around the markers in a two-point or a three-point analysis by mathematically moving an imaginary trait locus along an axis with units in recombination frequency. For the positions of the candidate genes and the markers, we followed the genetics maps of the Genetic Epidemiology Research Group, University of Southampton, UK (http://cedar.genetics.soton.ac.uk/public_html/summaryml.html).

[a]Two-point analysis; all others were calculated in a three-point analysis.
[b]The genes encoding MMP1, -3, -7, -8, -10, -12 and -13 are all located between the same microsatellite markers. The highest LOD score between these markers was −2.1.

sCAD = spontaneous cervical artery dissection; LOD = logarithm of odds.

marker. Moreover, the genes for TIMP1 and biglycan were excluded because their X-chromosomal localization was incompatible with the observed pattern of inheritance of the ultrastructural phenotype. LOD scores were positive for four genes: *PLOD*, *FBLN2*, *COL16A1*, and *TIMP4*.

Discussion

sCAD is known to be associated with connective tissue abnormalities in most patients without other symptoms of a connective tissue disease.[5,6] An extracellular matrix defect, as found in Ehlers–Danlos syndrome or other rare inherited disorders,[8,11] therefore also might predispose for sCAD in most apparently nonsyndromic patients. The electron microscopic observations in this study showed a further analogy between the predisposition for sCAD and other matrix disorders. The connective tissue abnormalities in sCAD patients are familial, and their mode of inheritance is compatible with the presence of a single causative autosomal dominant mutation with complete penetrance. Hence, the predisposition to sCAD was considered as a monogenic Mendelian disorder.

The electron microscopic phenotype does not give a direct hint to the underlying molecular defect, because the normal biosynthesis of collagen fibrils and elastic fibers is far from completely understood. A variety of candidate genes might be discussed. Several genes encoding fibrillar and interstitial collagens, as well as enzymes involved in collagen fibril organization and components of the elastic fiber, are known to bear mutations in some heritable connective tissue disorders.[11] Few genes have been analyzed so far in sCAD patients without signs of a known connective tissue disorder. Disease-causing mutations were not yet found.[12–15]

In this study, we use the electron microscopic alterations in skin biopsies as a well-defined phenotype to identify carriers of an unknown autosomal dominant mutation. We tested various genes that code for components of the extracellular matrix. COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, COL5A3, LOX, PLOD, and some genes encoding small proteoglycans are involved in the morphogenesis of type I collagen fibrils.[16,17] FBN1, FBN2, ELN, MFAP1, MFAP2, MFAP3, and MFAP4 contribute to the biosynthesis of elastic fibers.[18] Metalloproteinases and their inhibitors influence the structure of the matrix.[19]

For three loci that harbor four candidate genes (*PLOD*, *FBLN2*, *COL16A1*, and *TIMP*), we observed a perfect cosegregation of the hypothetical disease locus and the analyzed microsatellite markers. Theoretically, sCAD might be caused by a mutation in one of these genes. However, in a "genome-wide" scan a LOD score of greater than 3 traditionally is accepted as sufficient to reject the hypothesis of free recombination between the trait locus and the marker locus and permits the identification of a disease locus. The LOD score for the three loci with positive LOD scores in this study is only 0.9, which is not enough to demonstrate linkage. We therefore did not analyze further the *PLOD*, *FBLN2*, *COL16A1*, and *TIMP4* genes in this family and will look for larger families for further genetic investigation of the underlying matrix defect in patients with sCAD.

Most of these genes were excluded as candidate genes with LOD scores less than −2.0. This LOD value traditionally is accepted as the threshold for exclusion in genome-wide analyses. The exclusion of these candidate genes is valuable only for this family. Because sCAD is possibly an heterogeneous disease, several other families must be tested in the same way before candidate genes can be excluded in general. The exclusion of the candidate genes in this family is definitive under a model assuming a monogenic trait with complete penetrance and no phenocopies. Even if this exclusion is still restricted to a single family, it suggests that the predisposition for sCAD might not be caused by a mutation in a "classic" candidate gene. This suggestion is a further argument for genome-wide searches for candidate genes. Future genetic linkage analyses on larger families are now possible, because the electron microscopic analysis of skin biopsies permits the reliable identification the phenotype of interest.

This work was supported by grants from the Graduiertenkolleg "Cellular and Molecular Neurobiology" (R.W.) and the Deutsche Forschungsgemeinschaft (D.F.G.) (Br 1858 1-1, 1997–1999), (C.G.G., T.B., I.C.H.) the National Stroke Network program of the German Federal Ministry of Science and Education (B.M.F.T.) (C.G.G., T.B., I.C.H.) and the medical faculty of the University Heidelberg (C.G.G., B.K., J.S.).

We thank the index patient and his family for their cooperation. We are indebted to Dr E. Orberk for assisting in taking skin biopsies. R. Ayubi, A. Gyufko, I. Werner and P. Pflanz are thanked for expert technical and phototechnical assistance, J. Piotrowski for secretarial assistance.

References

1. Schievink W. Spontaneous dissection of the carotid and vertebral arteries. N Engl J Med 2001;344:898–906.
2. Schievink WI, Michels VV, Piepgras DG. Neurovascular manifestations of heritable connective tissue disorders. A review. Stroke 1994;25:889–903.
3. Beighton P, De Paepe A, Steinmann B, et al. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Genet 1998;77:31–37.
4. Schievink WI, Wijdicks EFM, Michels VV, et al. Heritable connective tissue disorders in cervical artery dissections: a prospective study. Neurology 1998;50:1166–1169.
5. Brandt T, Hausser I, Orberk E, et al. Ultrastructural connective tissue abnormalities in patients with spontaneous cervicocerebral dissections. Ann Neurol 1998;44:281–285.

6. Brandt T, Orberk E, Weber R, et al. Pathogenesis of cervical artery dissections: association with connective tissue abnormalities. Neurology 2001;57:24–30.
7. Ott J. Analysis of human genetic linkage. 3rd ed. Baltimore and London: John Hopkins University Press, 1999.
8. Hausser I, Anton-Lamprecht I. Differential ultrastructural aberrations of collagen fibrils in Ehlers-Danlos syndrome types I-IV as a means for diagnostics and classification. Hum Genet 1994; 93:394–407.
9. Gyapay G, Morissette J, Vignal A, et al. The 1993–94 Genethon human genetic linkage map. Nat Genet 1994;7:246–339.
10. Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES. Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 1996;58:1347–1363.
11. Uitto J. Heritable connective tissue disorders. Adv Exp Med Biol 1999;455:15–21.
12. Kuivaniemi H, Prockop DJ, Wu Y, et al. Exclusion of mutations in the gene for type III collagen (COL3A1) as a common cause of intracranial aneurysms or cervical artery dissections: results from sequence analysis of the coding sequences of type III collagen from 55 unrelated patients. Neurology 1993;43: 2652–2658.
13. van den Berg JS, Limburg M, Kappelle LJ, et al. The role of type III collagen in spontaneous cervical artery dissections. Ann Neurol 1998;43:494–498.
14. Grond-Ginsbach C, Weber R, Haas J, et al. Mutations in the COL5A1 coding sequence are not common in patients with cervical artery dissections. Stroke1999;30:1887–1890.
15. Grond-Ginsbach C, Thomas-Feles C, Werner I, et al. Mutations in the tropoelastin gene (ELN) were not found in patients with spontaneous cervical artery dissections. Stroke 2000;31: 1935–1938.
16. Myllyharju J, Kivirikko KI. Collagens and collagen-related diseases. Ann Med 2001;33:7–21.
17. Kessler E, Takahara K, Biniaminov L, et al. Bone morphogenetic protein-1: the type I procollagen C-proteinase. Science 1996;271:360–362.
18. Brown-Augsburger P, Broekelmann T, Rosenbloom J, Mecham RP. Functional domains on elastin and microfibril-associated glycoprotein involved in elastic fibre assembly. Biochem J 1996; 318:149–155.
19. Brew K, Dinakarpandian D, Nagase H. Tissue inhibitors of metalloproteinases: evolution, structure and function. Biochim Biophys Acta 2000;1477:267–283.

LGI1 Is Mutated in Familial Temporal Lobe Epilepsy Characterized by Aphasic Seizures

Wenli Gu, PhD,[1] Eylert Brodtkorb, MD, PhD,[2] and Ortrud K. Steinlein, MD[3]

Autosomal dominant lateral temporal lobe epilepsy previously has been linked to chromosome 10q22-q24, and recently mutations in the *LGI1* gene (Leucine-rich gene, Glioma Inactivated) have been found in some autosomal dominant lateral temporal lobe epilepsy families. We have now identified a missense mutation affecting a conserved cysteine residue in the extracellular region of the LGI1 protein. The C46R mutation is associated with autosomal dominant lateral temporal lobe epilepsy in a large Norwegian family showing unusual clinical features like short-lasting sensory aphasia and auditory symptoms.

Ann Neurol 2002;52:364–367

Sporadic and familial temporal lobe epilepsies can be divided into two main categories according to the seizure semiology, one with medial temporal lobe symptoms[1] and one with lateral symptoms.[2,3] The clinical expression of medial temporal lobe epilepsy includes autonomic auras, perceptual changes, and psychic and dysmnestic symptoms, usually evolving to complex partial seizures and/or secondary generalization.[1] The symptoms of sporadic and familial lateral temporal lobe epilepsy usually consist of simple partial seizures with mainly acoustic and sometimes even visual hallucinations.[2–7]

Familial lateral temporal lobe epilepsy (ADLTE; alias epilepsy, partial (EPT, Online Medelian Inheritance in Man [OMIM] 600512) previously has been linked to chromosome 10q22-q24,[2] and recently mutations in the *LGI1* gene (Leucine-rich gene, Glioma Inactivated) have been identified in some ADLTE families.[8] The *LGI1* gene codes for a putative

From the [1]Institute of Human Genetics, University Hospital Bonn, Bonn, Germany; and [2]Department of Neurology, Trondheim University Hospital, Trondheim, Norway.

Received Feb 15, 2002, and in revised form Apr 5. Accepted for publication Apr 6, 2002.

Published online Jul 14, 2002, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.10280

Address correspondence to Dr Steinlein, Institute of Human Genetics University Hospital Bonn, Wilhelmstrasse 31, 53111 Bonn, Germany. E-mail: ortrud.steinlein@ukb.uni-bonn.de

