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Report

eIF2B-Related Disorders: Antenatal Onset and Involvement of Multiple Organs

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Leukoencephalopathy with vanishing white matter, also called "childhood ataxia with central nervous system hypomyelination," is the first human disease related to mutations in any of the five genes encoding subunits of eukaryotic initiation factor eIF2B or any translation factor at all. eIF2B is essential in all cells of the body for protein synthesis and the regulation of this protein synthesis under different stress conditions. It is surprising that mutations in the eIF2B genes have been reported to lead to abnormalities of the white matter of the brain only, although it has been shown recently that ovarian failure may accompany the leukoencephalopathy. Another surprising observation is that the onset of the disease varies from early childhood to adulthood, with the exception of Cree leukoencephalopathy, a disease related to a particular mutation in one of the eIF2B genes, which invariably has its onset within the first year of life. We analyzed the eIF2B genes of nine patients with an antenatal- or early-infantile–onset encephalopathy and an early demise and found mutations in eight of the patients. In addition to signs of a serious encephalopathy, we found oligohydramnios, intrauterine growth retardation, cataracts, pancreatitis, hepatosplenomegaly, hypoplasia of the kidneys, and ovarian dysgenesis. Until now, no evidence had been found for a genotype-phenotype correlation, but the consistently severe phenotype in affected siblings among our patients and in Cree encephalopathy patients suggests an influence of the genotype on the phenotype.

Translation of mRNA into polypeptides is one of the major energy-consuming processes in the cell and is therefore, not surprisingly, a tightly regulated process (Proud 2002). The initiation phase, in which ribosomes are assembled on mRNA, is controlled via several different signaling pathways (Kleijn et al. 1998). Multiple eukaryotic initiation factors (eIFs) are involved in translation initiation, and, among them, the guanine-nucleotide-exchange factor eIF2B plays a key regulatory role (Proud 2001). A crucial step in translation initiation is the delivery by eIF2 of the initiator methionyl-transfer RNA (Met-tRNA$_i$) to the small ribosomal subunit. Upon recognition of the start codon, the eIF2-bound guanosine triphosphate (GTP) is hydrolyzed, and eIF2 is released in its inactive guanosine diphosphate (GDP)–bound form. To bind another Met-tRNA$_i$, active eIF2 must be regenerated by the exchange of GDP for GTP. This step is catalyzed by eIF2B. The exchange of GDP for GTP by eIF2B is required for each round of translation initiation, and regulation of this step can control global rates of protein synthesis under diverse conditions (Hinnebusch 2000).

Protein synthesis is markedly inhibited under a variety of stress conditions and in the recovery phase that fol-

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lows. This response is part of a protective mechanism of cells that is elicited by various stimuli, including physical, chemical, oxidative, and thermal trauma, called the "cellular stress response" or "heat shock response" (Welch 1992). Stress may lead to the misfolding and denaturation of proteins, contributing to cell dysfunction and death. The inhibition of normal RNA translation during stress is thought to enhance cell survival by limiting the accumulation of denatured proteins and saving cellular energy.

Inhibition of mRNA translation can be achieved through the modification of several initiation factors (Schneider 2000). Most stress conditions, including heat stress (Duncan and Hershey 1989; Scheper et al. 1997), lead to activation of specific kinases that phosphorylate eIF2 on its α-subunit. In this phosphorylated form, eIF2 is a competitive inhibitor of eIF2B, preventing the recycling of eIF2 (Hershey and Merrick 2000). The concentration of eIF2 usually exceeds that of eIF2B (Oldfield et al. 1994). Therefore, even modest levels of eIF2α phosphorylation can potentially lead to a complete inhibition of translation initiation and protein synthesis (Rowlands et al. 1988; Oldfield et al. 1994). In certain cell types, inactivation of eIF2B at 40–41°C, in the febrile range for humans, can be achieved without changes in eIF2α phosphorylation (Scheper et al. 1997). eIF2B activity can also be regulated through other pathways, such as phosphorylation at different sites, which can enhance or suppress eIF2B activity (Proud 2002). Whether these pathways are involved in the regulation of eIF2B activity under stress conditions is unclear.

eIF2B is a protein complex, composed of five nonidentical subunits (α–ε), encoded by five different genes, *EIF2B1–EIF2B5*, located on different chromosomes (12q24.3, 14q24, 1p34.1, 2p23.3, and 3q27, respectively). The essential role of eIF2B, both in normal protein production and in its regulation under different conditions, including elevated temperature, is reflected by the evolutionary conservation of the complex (Hershey and Merrick 2000) and the nonviability of yeast null mutants for each of the subunits except eIF2Bα (Hinnebusch 2000). Considering the indispensability of eIF2B for normal cell function, it was expected that human cells bearing two inactivating mutations in one of the eIF2B subunits would not be viable.

We were surprised to find that vanishing white matter (VWM [MIM 603896]) (van der Knaap et al. 1997), also called "childhood ataxia with central nervous system hypomyelination" (CACH) (Schiffmann et al. 1994), is caused by mutations in any of the five eIF2B genes (Leegwater et al. 1999, 2001; van der Knaap et al. 2002). VWM/CACH is one of the novel leukoencephalopathies described in the 1990s (Hanefeld et al. 1993; Schiffmann et al. 1994; van der Knaap et al. 1997). It is one of the most prevalent inherited childhood white matter disorders (van der Knaap et al. 1999). The disease is characterized by progressive neurological deterioration with cerebellar ataxia, spasticity, and relatively mild mental decline. The disease is chronic progressive with episodes of major and rapid deterioration following minor head trauma and especially febrile infections. These episodes may end in unexplained coma. Death usually follows an episode of coma. If a patient survives the coma, partial recovery occurs. Magnetic resonance imaging (MRI) of the brain shows extensive cerebral white matter changes from the presymptomatic stage onwards and, over time, evidence of disappearance of the affected white matter, which is replaced by fluid (van der Knaap et al. 1997, 1998). This was confirmed by multiple autopsies, which showed rarefaction and cystic degeneration of the cerebral white matter (van der Knaap et al. 1997, 1998; Rodriguez et al. 1999; Wong et al. 2000; Brück et al. 2001). MRI shows that VWM/CACH, in contrast to other cystic leukoencephalopathies, exhibits radiating stripes of preserved tissue strands within the rarefied and cystic white matter, giving the images a highly characteristic appearance (van der Knaap et al. 1997, 1998).

In patients with VWM/CACH, serious deteriorations often follow febrile infections, which could correlate with the heat sensitivity of eIF2B. It is surprising that the disease has been reported to exclusively affect the white matter of the brain, even though eIF2B is present and essential for protein synthesis and its regulation in all cells of the body. Not only are other organs spared but, within the brain, the cerebral cortex is usually spared as well (van der Knaap et al. 1997, 1998; Rodriguez et al. 1999; Wong et al. 2000; Brück et al. 2001). Another surprising observation was that most patients have a normal initial development and a childhood onset of clinical symptomatology (Hanefeld et al. 1993; Schiffmann et al. 1994; van der Knaap et al. 1997). Adolescent and adult onsets also have been described (van der Knaap et al. 1998). Apparently, it is possible to be homozygous or compound heterozygous for mutations in any of the eIF2B genes and have normal neurological function for a period of a few to many years.

Since a DNA-based diagnosis of VWM/CACH is now available, patients with atypical clinical and MRI findings can be analyzed for mutations in *EIF2B1–EIF2B5*. Until now, we had mainly found missense mutations in typical patients with VWM/CACH (Leegwater et al. 2001; van der Knaap et al. 2002). Major mutations, which prevent the expression of full-length eIF2B subunits, were only observed in the compound-heterozygous state with a missense mutation as second mutation (Leegwater et al. 2001; van der Knaap et al. 2002). Several atypical cases of patients with VWM/CACH or related disorders suggested that other or more serious mutations might lead to an earlier onset of the disease and

possibly to involvement of other organs. (1) Two sibling patients with VWM/CACH were described with an unusually early onset at 11 and 10 mo and death at 18 and 13 mo (Fogli et al. 2002*a*). (2) Cree leukoencephalopathy was found to be a variant of VWM/CACH (Fogli et al. 2002*b*). The onset of Cree encephalopathy is between 3 and 9 mo, and death occurs before the age of 2 years (Black et al. 1988). (3) In 1997, one patient was described who had VWM/CACH and ovarian dysgenesis at autopsy (van der Knaap et al. 1997). The cooccurrence of mutations in the eIF2B genes with a combination of a leukoencephalopathy and ovarian failure was recently confirmed in a much larger series of patients, providing the first evidence that mutations in eIF2B genes can lead to involvement of organs other than the brain (Fogli et al. 2003).

Considering the cases above, we reasoned that mutations in the eIF2B genes might lead to an earlier onset of the disease and possibly to involvement of other organs. Following these hypotheses, we decided to perform DNA analysis in nine patients with an early-onset leukoencephalopathy and, in some of them, involvement of other organs.

Patients 1, 2, and 3 are sisters. The parents are healthy and unrelated. The mother had two miscarriages, at 9 and 10 wk into pregnancy. There are two healthy children. In patient 1, decreased movements and oligohydramnios were noted late in gestation. After birth at 38 wk of gestation, she had some initial difficulties with hypotonia and a low body temperature. Blood sugars were just below normal. She had congenital dislocation of the hips. She was an irritable baby. From the age of 3 mo, she deteriorated, with intractable seizures, feeding difficulties, hypotonia, apathy, and finally coma and respiratory failure. On physical examination, she had hepatosplenomegaly, oil-droplet cataracts, hypotonia, and brisk reflexes. A liver biopsy revealed nonspecific abnormalities, with markedly increased smooth endoplasmic reticulum, decreased glycogen stores, and reactive Kupffer cells, but otherwise intact architecture. Patient 1 died at the age of 8 mo. Her affected sisters had a similar clinical picture and died at 4.5 and 5 mo.

Patients 4 and 5 are the only son and daughter of healthy, consanguineous parents. Both patients had serious fetal growth retardation, oligohydramnios, and microcephaly at term birth. The clinical course after birth was rapidly downhill, with feeding difficulties, vomiting, apathy, axial hypotonia, hypertonia and hyperreflexia of the extremities, seizures, and finally apneic events. Abdominal ultrasounds revealed hypoplastic kidneys. The patients died at 3.5 and 4 mo, respectively.

Patient 6 is the daughter of healthy, unrelated parents. There are two healthy siblings. She was described in detail in the work of Boltshauser et al. (2002). Growth retardation and oligohydramnios were noted at 31 wk gestational age. Born at 38 wk of gestation, she had microcephaly, bilateral cataracts, and mild contractures. The clinical course was dominated by impaired swallowing, failure to thrive, myoclonic convulsions, and absence of any psychomotor development. Aspiration pneumonia led to death at 10 mo. An autopsy revealed, apart from the aspiration pneumonia, mild pancreatitis and dysgenesis of the ovaries.

Patient 7 is a boy with healthy, unrelated parents. He has two healthy siblings. He was born at term. At age 5 mo, developmental delay and hypotonia became apparent shortly after a vaccination and an upper respiratory tract infection. The hypotonia gradually changed into hypertonia with hyperreflexia. He became progressively lethargic and finally lapsed into coma. He died at age 7 mo because of respiratory insufficiency.

Patient 8 is the son of healthy, consanguineous parents. His sister died of a similar disease at 13 mo. He has three healthy siblings. He was born at term. At age 6 mo, he developed axial hypotonia and lost head control. Following a mild febrile illness, he became comatose, with episodes of irregular breathing. He died at age 9 mo.

Patient 9 is a boy, the only child of healthy, unrelated parents. He was born at term. At the age of 4.5 mo, he presented symptoms of chronic and episodic neurological deterioration. The episodes of rapid deterioration were provoked by infections. His clinical picture was dominated by hypotonia and cerebellar ataxia without spasticity. Following a viral infection with fever, he lapsed into coma and died at age 25 mo.

In summary, only in patients 7, 8, and 9 was the clinical picture that of typical VWM/CACH, with an episodic course and exclusive involvement of the brain, although with an earlier onset than usual.

In all patients, extensive routine and metabolic investigations were performed, which were unrevealing. MRIs of the brain were obtained at the following ages: 3, 4, and 5 mo in patient 1; 2 d in patient 2; 3 mo in patients 3 and 4; 1 and 4 mo in patient 5; 6 d and 5 mo in patient 6; 6 mo in patient 7; 9 mo in patient 8; and 17 and 24 mo in patient 9. All cerebral and cerebellar white matter structures had a high signal intensity on T_2-weighted images and a low signal intensity on T_1-weighted images, as would be normal for unmyelinated white matter (Barkovich et al. 1988; van der Knaap et al. 1990). However, in all patients except patients 2, 3, and 6 (first MRIs), the cerebral white matter had a higher T_2 signal intensity than normal for unmyelinated white matter (fig. 1). The white matter signal intensity became more abnormal on follow-up (fig. 2). Some cerebral white matter structures should be myelinated at birth, but there was no evidence of this in our patients, indicating a defect in myelination (fig. 1). In addition, the gyri were slightly broader than normal in all patients

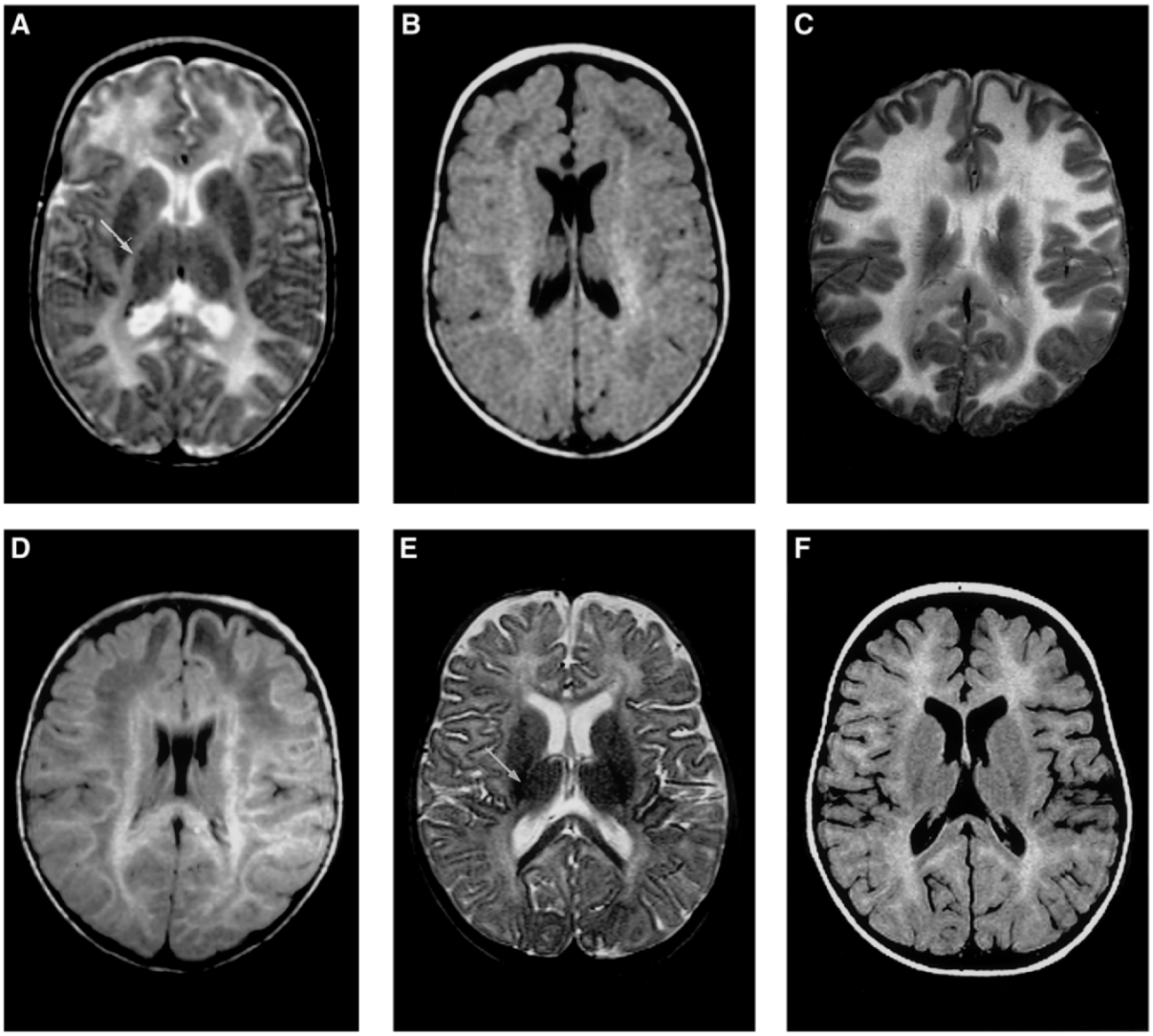

Figure 1 Illustration of the variation in white matter abnormalities in patients with VWM/CACH. For this purpose, T_2-weighted and FLAIR images of patient 3 at 3 mo (*A* and *B*, respectively) and patient 7 at 6 mo (*C* and *D*, respectively) are shown, as well as T_2-weighted and FLAIR images of a normal infant at 4 mo (*E* and *F*, respectively). In patient 3, the transverse T_2-weighted image (*A*) is normal for the age, except that the progress of myelination is insufficient. The myelin deposition should cause the internal capsule to have a low signal intensity (*arrow* in *E*), but it still has a high signal intensity throughout (*arrow* in *A*). The FLAIR image is shown at a slightly higher level, where areas of low signal intensity are seen within the cerebral white matter, indicative of rarefaction (*B*). Such areas are not seen on the FLAIR image of the normal infant (*F*). In patient 7, the cerebral white matter has too high a signal intensity on the T_2-weighted image (*C*), higher than normal for unmyelinated white matter (*E*). The gyri are mildly broadened. The FLAIR image shows that a large part of the white matter has a lower signal intensity, consistent with rarefaction (*D*). A subtle stripe-like pattern is visible within the rarefied white matter (*D*).

except patient 3, indicating delayed gyral development or slight white matter swelling. Proton density images and/or fluid-attenuated inversion recovery (FLAIR) images were obtained in patients 1, 2, 3, 7, 8, and 9. With the exception of patient 2 at age 2 d, these showed a lower signal intensity in parts of the cerebral white matter, although not as low as cerebrospinal fluid, indicative of white matter rarefaction but not (yet) cystic degeneration (fig. 1). Only in patients 7 and 8 did the abnormal white matter have the stripe-like pattern on axial FLAIR or sagittal T_1-weighted images (fig. 1) so typical of VWM/CACH, and only in these two patients did the MRI display the classic appearance of VWM/CACH (van der Knaap et al. 1997, 1998). In patients 1, 2, 3, and 9, the white matter rarefaction could suggest a diagnosis of VWM/CACH, but the typical stripes were

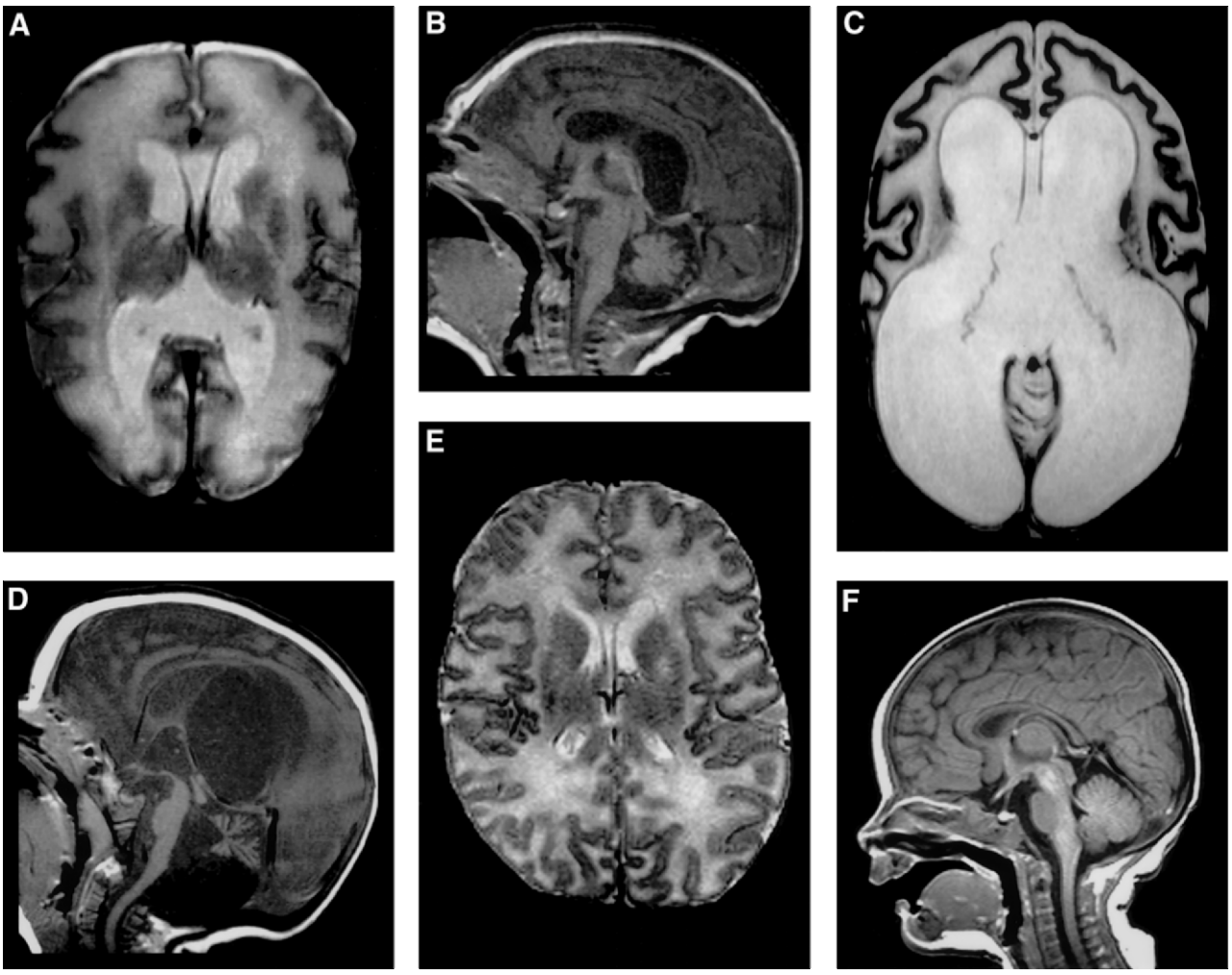

Figure 2 Illustration of the degree of white matter volume loss. Transverse T_2-weighted and sagittal T_1-weighted images of patient 6, obtained at 6 d (*A* and *B*, respectively) and 5 mo (*C* and *D*, respectively), and transverse T_2-weighted and sagittal T_1-weighted images of a normal-term neonate (*E* and *F*, respectively) are shown. The first MRI in patient 6, obtained at 6 d, shows broadening of gyri (*A*) as compared to the width of gyri in a normal neonate (*E*). The cerebral white matter has a normal signal intensity for unmyelinated white matter on the T_2-weighted image (compare *A* and *E*). The lateral ventricles are mildly dilated. The cerebellar vermis is on the small side (compare *B* and *F*). The T_2-weighted image at 5 mo shows that an impressive atrophy of the cerebral white matter has occurred with enormous dilatation of the lateral ventricles (*C*). What remains of the white matter now has too high a signal intensity, even for unmyelinated white matter. The sagittal image shows marked atrophy of the cerebellum (*D*). Also the pons is flatter than normal. These images are reproduced from the work of Boltshauser et al. (2002) with permission.

lacking. In patients 5 and 6, the lateral ventricles became highly dilated because of pronounced white matter atrophy (fig. 2), which is not a feature of typical VWM/CACH (van der Knaap et al. 1997, 1998). They also had striking atrophy of the cerebellum. In patient 9, the splenium of the corpus callosum was abnormal and highly swollen, which has not been reported before in patients with VWM/CACH. The globus pallidus and thalamus showed an abnormal signal intensity, which is also unusual in individuals with VWM/CACH.

We performed mutational analysis of *EIF2B1–EIF2B5* in all nine patients. The exons and flanking intron DNA of the genes under investigation were amplified by PCR, as described elsewhere (Leegwater et al. 1999, 2001), with oligonucleotide primers whose sequences are available on the VU University Medical Center Web site. The DNA fragments were subsequently analyzed by DNA sequencing with BigDye Terminators on an ABI PRISM 310 Genetic Analyzer (Applied Biosystems) as recommended by the manufacturer.

We found mutations in individual eIF2B genes in patients 1–8 (table 1). None of the mutations were found in 210 control chromosomes of individuals of northern European descent, making it unlikely that they represent polymorphisms. In agreement with this, these mutations are not reported in the SNP databases of NCBI and

Table 1

Genotypic and Phenotypic Data for Eight Patients with eIF2B Gene Mutations

Patient	Gene	Subunit	Mutation Position	Protein Undergoing Mutation	State	Parent Carrying Allele	Organs Involved/ Phenotype
1–3	*EIF2B2*	eIF2Bβ	599G→T	G200V	Heterozygous	Father	Brain, lens, liver
			871C→T	P291S	Heterozygous	Mother	
4, 5	*EIF2B4*	eIF2Bδ	1447C→T	R483W	Homozygous	Father, mother	Brain, kidney, body growth
6	*EIF2B4*	eIF2Bδ	1172C→A	A391D	Homozygous	Father, mother	Brain, lens, pancreas, ovaries, body growth
7	*EIF2B5*	eIF2Bε	1289T→C	V430A	Heterozygous	Father	Brain
			1340C→T	S447L	Heterozygous	Mother	
8	*EIF2B5*	EIF2Bε	1484A→G	Y495C	Homozygous	Father, mother	Brain

Celera. The two healthy siblings of patient 7 and the three healthy siblings of patient 8 were investigated as well. Three were found to be heterozygous for one mutation; two did not carry any mutation in *EIF2B5*. All parents were investigated, and each of them was found to carry one mutation. Only in patient 9 were we unable to identify a mutation in one of the five genes. Although his clinical picture was very suggestive of VWM, his MRIs showed some features that are atypical for patients with VWM/CACH.

Formerly, no evidence was found for a genotype-phenotype correlation, but the consistently severe phenotype in affected siblings among our patients and in Cree encephalopathy patients suggests an influence of the genotype on the phenotype.

All mutations observed in patients 1–8 are novel except for the Val430Ala mutation in eIF2Bε (Leegwater et al. 1999) in patient 7. Most mutations involve highly conserved amino acids (for two examples, see fig. 3). The α-, β-, and δ-subunits of eIF2B display mutual sequence similarity. Alanine at position 391 (Ala391) in eIF2Bδ and Gly200 in eIF2Bβ (fig. 3*a*) are not only generally conserved in different species but also in the homologous sequences of the other two subunits, suggesting they are key residues. Arg483 in eIF2Bδ is conserved in mammals only. However, the mutation to tryptophan (a basic residue replaced by a bulky aromatic amino acid) is likely to result in a substantial alteration in the three-dimensional structure of the protein. Valine at position 430 and serine at position 447 of eIF2Bε are conserved in mammals, and nonmammalian species have a hydrophobic and hydroxy amino acid here, respectively. The changes of Val430Ala (from a branched-chain amino acid to a much smaller and less hydrophobic residue) and Ser447Leu (from a small and polar amino acid to a branched-chain hydrophobic residue) may both lead to major alterations in the conformation of the protein. Pro291 in eIF2Bβ and Tyr495 in eIF2Bε are conserved in all mammals and several nonmammalian species (fig. 3*b*). Again the changes from the imino acid proline to the small polar residue serine (in Pro291Ser) and from tyrosine with an aromatic side chain to the small sulphur-containing cysteine (in Tyr495Cys) are likely to affect the (local) structure of the subunit. Thus, our patients are homozygous or compound-heterozygous for mutations that are likely to affect markedly the structure of eIF2B and therefore its function, contributing to the severe phenotype.

The Arg195His mutation in eIF2Bε is found in Cree leukoencephalopathy (Fogli et al. 2002*b*). Arg195 is conserved in mammals and the change from an aliphatic side-chain containing a positively charged guanidino group to a heterocyclic imidazole group is likely to affect the conformation of this subunit as well. In contrast, the drastic effect of the Val309Leu mutation in two severely affected sibling patients (Fogli et al. 2002*a*) is unclear. Both valine and leucine are branched-chain aliphatic amino acids; branched-chain residues are conserved at the position corresponding to Val309 in all ε-subunit sequences and at the corresponding position in the related sequence of eIF2Bγ. Most strikingly, leucine is present at this position in *Caenorhabditis elegans* eIF2Bε and in rat and yeast eIF2Bγ.

Some of the earlier-published mutations—for instance, the mutation that causes the alteration Glu213Gly in eIF2Bβ (Leegwater et al. 1999)—also involve well-conserved residues, whereas the clinical picture is that of classic VWM/CACH. It is important to realize that, of course, not only the nature of the changes caused by the mutations in both alleles or the conservation of the residues involved but also the position of the changes within the protein will determine the effect of the mutations on the activity of the eIF2B complex. However, too little is known presently about the various functional domains in the eIF2B subunits to allow correlation of the position of the mutations with the severity of the disease. None of the amino acid changes mentioned in table 1 occurs in the catalytic domain of the ε-subunit or affects known phosphorylation sites.

Our findings demonstrate that patients with VWM/

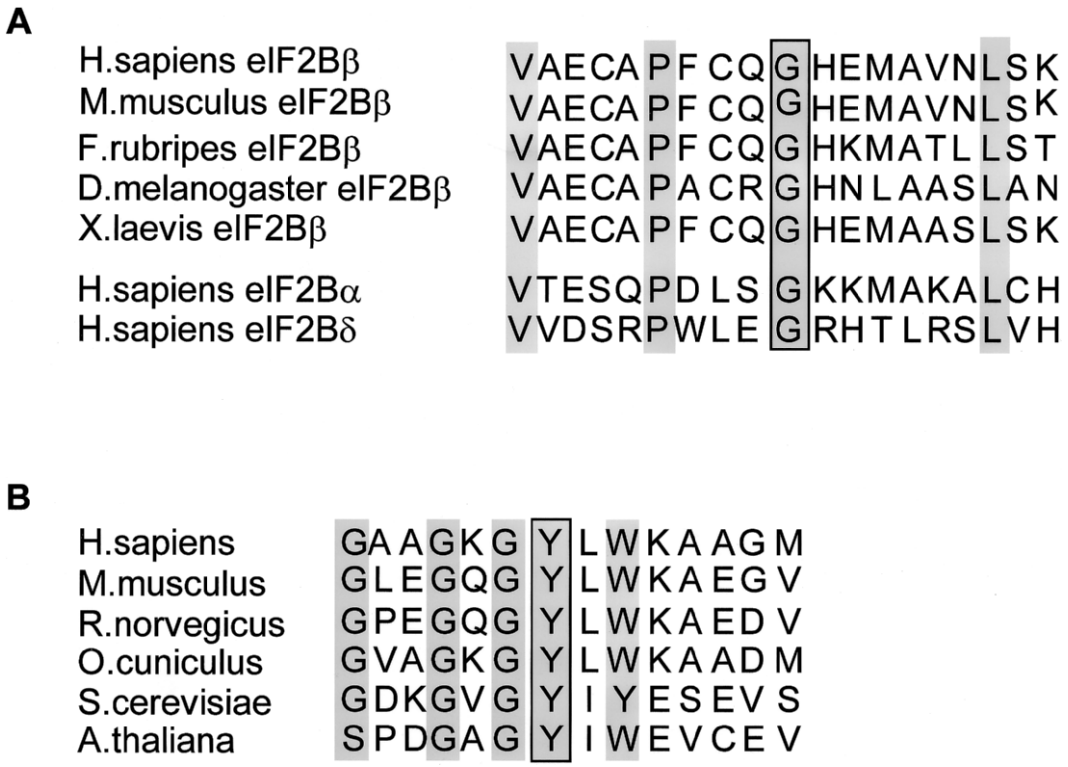

Figure 3 Examples of conserved residues in eIF2B involved in severe forms of VWM. *A*, Alignment of the sequence containing Gly200 (*box*) of human eIF2Bβ with corresponding sequences of eIF2Bβ of the indicated species and with the corresponding sequences of human eIF2Bα and eIF2Bδ. Residues conserved among all three human subunits and eIF2Bβ of all species are indicated in gray. *B*, Alignment of the region surrounding Tyr495 in human eIF2Bε with the corresponding sequences of eIF2Bε in other species. The conserved tyrosine is indicated by the box; residues that are conserved in at least five species are indicated in gray.

CACH can have a very early, even antenatal, onset with decreased fetal movements, retardation of intrauterine growth, and oligohydramnios, and at birth microcephaly and contractures. More importantly, it is clear for the first time that patients with mutations in eIF2B genes can suffer from a multisystem disorder with growth retardation, dysgenesis of the ovaries, pancreatic abnormalities, hypoplastic kidneys, hepatosplenomegaly, or cataracts, in addition to the leukoencephalopathy. It is unlikely that an unrelated disease caused these additional abnormalities. Most importantly, affected siblings showed involvement of the same organs, whereas siblings carrying no mutations or only one mutation did not show signs of any disease.

Whereas mutations in eIF2B subunit genes that cause VWM/CACH probably lead to decreased eIF2B activity, a persistent high activity of eIF2B underlies Wolcott-Rallison syndrome (MIM 226980). This is an exceedingly rare autosomal recessive multisystem disorder characterized by intrauterine growth retardation, early infantile permanent diabetes mellitus, multiple epiphyseal dysplasia, renal impairment, central hypothyroidism, developmental delay, and recurrent episodes of hepatic dysfunction, ascribed to "hepatitis" (Bin-Abbas et al. 2002). The disease is caused by mutations in *EIF2AK3* (Delépine et al. 2000), also called *PEK* or *PERK*, the gene encoding the enzyme eukaryotic translation initiation factor 2α kinase 3, also called pancreatic eIF2α kinase (PEK) or PKR-like ER kinase (PERK). PERK is an endoplasmic-reticulum-resident, transmembrane protein. It couples stress signals that are initiated by protein malfolding in the lumen of the endoplasmic reticulum with phosphorylation of eIF2α, which inhibits the activity of eIF2B, resulting in decreased protein synthesis (Harding et al. 1999, 2000). In patients with Wolcott-Rallison syndrome, the mutations, where tested, led to a loss of function of PERK. This presumably results in persistent high eIF2B activity and consequent inability to switch off protein synthesis in response to endoplasmic reticulum stress. There are evident clinical differences between VWM/CACH and Wolcott-Rallison syndrome, but the two disorders share the inability to regulate protein synthesis adequately under different stress conditions.

Although the patients presented here were different from typical patients with VWM/CACH, they still had

a leukoencephalopathy. The next, most intriguing question is whether it is possible that patients with selective involvement of other organs without an accompanying leukoencephalopathy may carry mutations in eIF2B genes. Episodic liver or bone marrow failure may occur in children provoked by fever but without an identifiable cause. These episodes are usually ascribed to "viral infections." Considering the episodic encephalopathy with fever in patients with VWM/CACH, easily mistaken for "viral encephalitis," and the recurrent "hepatitis" in patients with Wolcott-Rallison syndrome, an important next step is to investigate whether failure of other organs under fever can be caused by mutations in *EIF2B1–EIF2B5*.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for VWM and Wolcott-Rallison syndrome)

VU University Medical Center site, http://www.vumc.nl/whitematter

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