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Report

Mutations in the X-Linked Cyclin-Dependent Kinase–Like 5 (*CDKL5/STK9*) Gene Are Associated with Severe Neurodevelopmental Retardation

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Recently, we showed that truncation of the X-linked cyclin-dependent kinase–like 5 (*CDKL5/STK9*) gene caused mental retardation and severe neurological symptoms in two female patients. Here, we report that de novo missense mutations in *CDKL5* are associated with a severe phenotype of early-onset infantile spasms and clinical features that overlap those of other neurodevelopmental disorders, such as Rett syndrome and Angelman syndrome. The mutations are located within the protein kinase domain and affect highly conserved amino acids; this strongly suggests that impaired CDKL5 catalytic activity plays an important role in the pathogenesis of this neurodevelopmental disorder. In view of the overlapping phenotypic spectrum of *CDKL5* and *MECP2* mutations, it is tempting to speculate that these two genes play a role in a common pathogenic process.

In our recent study of two unrelated females with balanced X;autosome translocations, we showed that truncation of the cyclin-dependent kinase–like 5 (*CDKL5/STK9*) gene causes a severe phenotype of early-onset infantile spasms, global developmental arrest, and profound mental retardation (Kalscheuer et al. 2003). The phenotypes in these patients are reminiscent of the neonatal-onset encephalopathy seen in several patients with a severe form of atypical Rett syndrome (RTT [MIM 312750]) (Schanen et al. 1998; Villard et al. 2000; Zeev et al. 2002). RTT is a progressive neurodevelopmental disorder that affects almost exclusively girls. The classic form of RTT is characterized by apparently normal development, followed by neurological developmental arrest and regression (Hagberg et al. 1983). The increase in cognitive and motor impairments may continue for many years before reaching a plateau; this progression typically leads to profound mental retardation. Patients with a milder RTT variant may retain some speech and motor functions, whereas those with more severe forms develop the disease shortly after birth and often have congenital hypotonia and infantile spasms (Hanefeld 1985; Goutieres and Aicardi 1986; Hagberg and Skjeldal 1994). In ~80% of patients with typical RTT, a mutation has been found in the methyl-CpG–binding protein 2 (*MECP2*) gene, but only 20%–40% of patients with atypical RTT have been shown to carry a mutation in this gene (Buyse et al. 2000; Cheadle et al. 2000; Bourdon et al. 2001). These findings indicate the possible presence of another, as-yet undetected gene on the X chromosome that may play a role in atypical RTT. It is noteworthy that the phenotypic spectrum of *MECP2* mutations is diverse, including autism (Lam et al. 2000; Carney et al. 2003), Angelman syndrome–like features in females (Imessaoudene et al. 2001; Watson et al. 2001), neonatal-onset encephalopathy (Schanen et al. 1998; Villard et al. 2000), and nonsyndromic mental retardation in males (Couvert et al. 2001; Yntema et al. 2002).

We have screened the entire *CDKL5* ORF for mutations in a cohort of 32 patients (25 females and 7 males) who had been diagnosed with RTT syndrome or a variant of RTT and in whom no *MECP2* mutation had been

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identified. All blood samples were obtained after provision of informed consent. PCR primers and denaturing high-performance liquid chromatography (DHPLC) conditions used for mutation analysis are available on request.

Apart from two putative mutations described below, we detected four polymorphisms in *CDKL5*. A c.2372A→C (p.Q791P) change was present in five patients and in 3 of 96 control X chromosomes. Three other nucleotide exchanges—IVS4+17A→G, c.3003C→T (p.H1001H), and c.3084G→A (p.T1028T)—formed a rare conserved haplotype that was found in one patient and in 2 of 267 control X chromosomes from Caucasian individuals (data not shown).

In the patient from family 1 (fig. 1*A* and 1*B*), we found a c.455G→T nucleotide change (GenBank accession number NM_003159) in exon 7 that results in a cysteine-to-phenylalanine substitution at position 152 (p.C152F) of the CDKL5 protein (GenBank accession number NP_003150) (fig. 1*C*). The corresponding sequence of the parents' DNA did not show this change (fig. 1*C*), which strongly suggests that this change is a de novo mutation.

The patient is a female who was born by spontaneous delivery after an uneventful pregnancy. Her parents are healthy and nonconsanguineous, and she has a healthy sister. Her birth weight was 3,500 g, and her length was 53 cm. The neonatal period was normal. At 5 wk of age, she had Blitz-Nick-Salaam–like seizures. At 3 mo of age, her electroencephalogram (EEG) was normal. Therapies with vigabatrin, phenobarbital, and carbamacepine had no effect. After implantation of a vagus-nerve stimulator at the age of 4.5 years, the parents reported that seizures occurred less frequently. At reevaluation at 5 years of age, the patient weighed 13.9 kg (3rd percentile), her length was 115 cm (75th percentile), and her head circumference was 48.8 cm (10th percentile). EEG showed abnormal and generalized theta rhythm, but neither focal disturbances nor any patterns typical of epilepsy were observed. She was very hypotonic, was unable to crawl, and could not sit without support. She understood simple words but could not speak. The patient had initially been diagnosed with Angelman syndrome or atypical RTT syndrome. Methylation analysis of locus *D15S63* was normal, and a mutation search in *UBE3A* and *MECP2* was negative.

In the index patient from family 2 (fig. 2*A* and 2*B*), we found a c.525A→T nucleotide change in exon 8 (fig. 2*C*), which changes an arginine to a serine at position 175 (p.R175S) of the CDKL5 protein. The patient is an MZ twin born to healthy, unrelated parents. Her birth

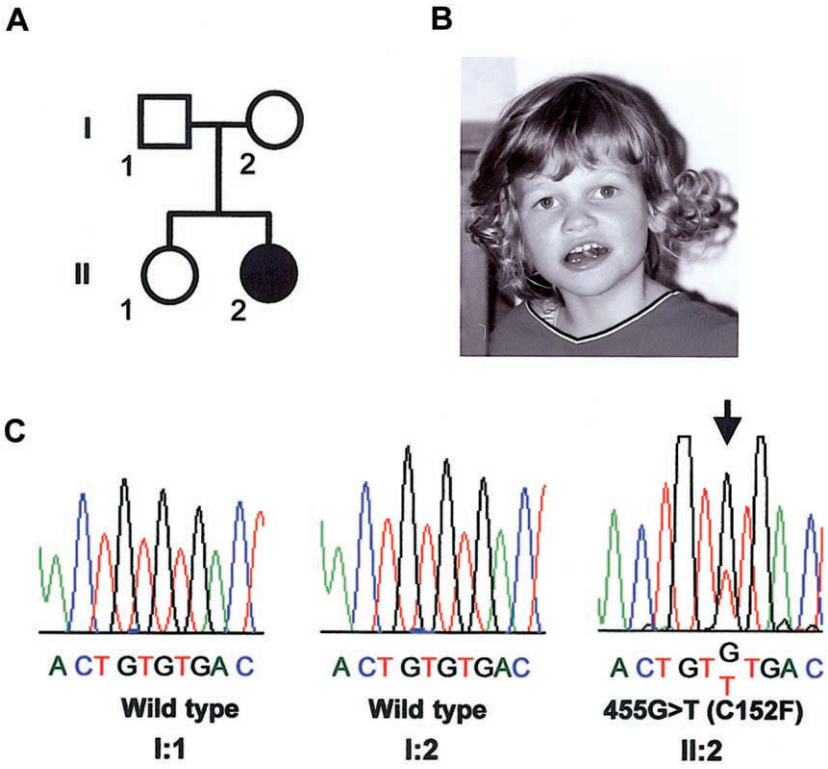

Figure 1 *CDKL5* mutation c.455G→T (p.C152F) in family 1. *A*, Pedigree for family 1. *B*, Patient II:2 at the age of 6.5 years. *C*, Sequence chromatograms from family members I:1, I:2, and the proband (II:2). The affected nucleotide is indicated by a blackened arrow.

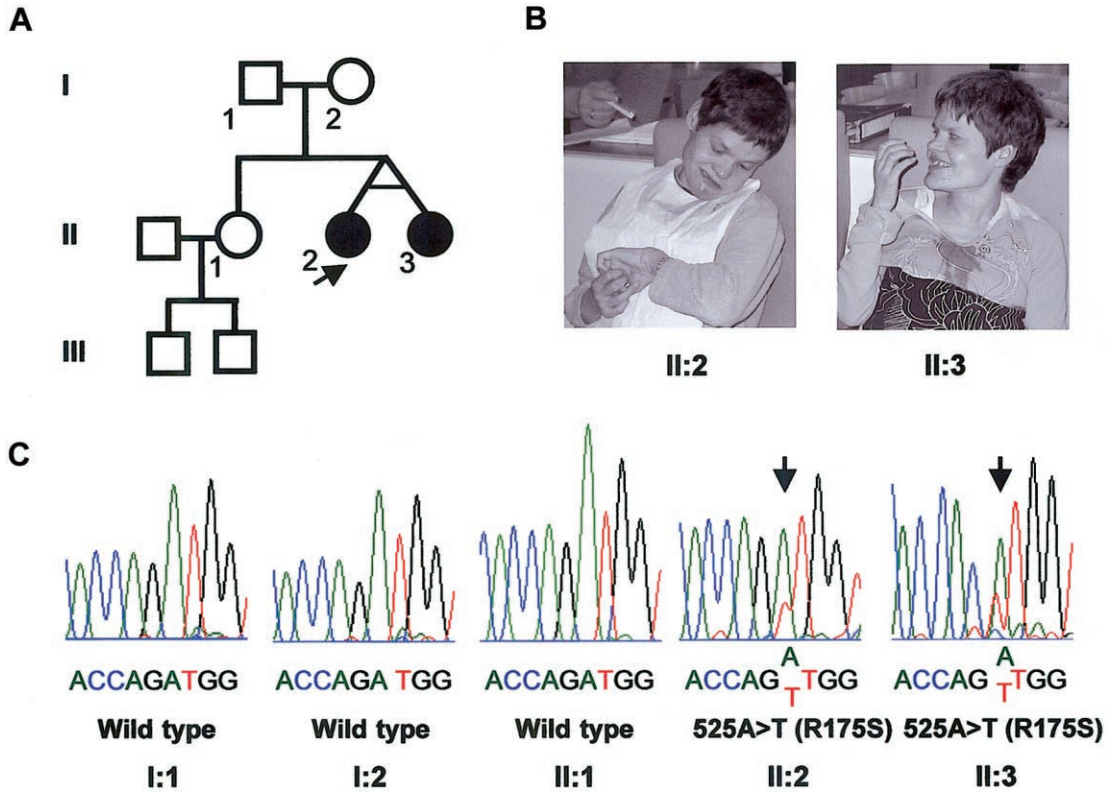

Figure 2 *CDKL5* mutation c.525A→T (p.R175S) in family 2. *A*, Pedigree for family 2. The index patient (II:2) is indicated by a blackened arrow. *B*, Affected twin sisters (II:2 and II:3) at the age of 41 years. Note stereotypic hand movements of the proband (II:2). *C*, Sequence chromatograms from the family members. From left to right: father (I:1), mother (I:2), unaffected sister (II:1), the index patient (II:2), and her MZ sister (II:3). The affected nucleotide is indicated by a blackened arrow.

weight was 3,420 g, and the pregnancy was normal. The mother was being treated for hypothyroidism and had had two previous miscarriages. At 2 mo of age, the patient developed infantile spasms, which disappeared at 6 mo of age, but, later in life, absence seizures were repeatedly observed. During infancy, severe psychomotor retardation was noticed (Bayley mental scale: 2 mo at the age of 12 years). She was able to sit without support at 3 years of age, and, at 10 years of age, she was able to walk a few steps with support. She never developed speech. There was general hypotonia, mild ataxia, and stereotypic movements of the hands. Intentional activity or eye contact was absent. Mood swings were noticed, with alternating bursts of crying and laughter, as well as episodes of hyperventilation. On follow-up, she developed progressive sinistro-convex thoraco-lumbal kyphoscoliosis and hypertonia leading to flexion contractures of the arms. Growth parameters for height, length, and head circumference are within the 5th–25th percentile. Her adult head circumference is 54.5 cm. Now aged 41 years, she is wheelchair bound and still presents with stereotypic hand movements, mood swings, and episodes of hyperventilation. Additional examinations, including brain scan, ophthalmological and hearing tests, routine blood analyses, thyroid hormone tests, metabolic screening, and karyotype analysis, were normal. Repeated EEG analyses exhibited diffuse slow theta activity, but typical epileptiform abnormalities were not observed. Screening for point mutations and deletions in the *MECP2* gene was negative.

The proband's MZ twin sister exhibits a similar phenotype (fig. 2*B*); PCR amplification and sequence analysis of exon 8 confirmed the presence of the same mutation (fig. 2*C*). Like her twin sister, she developed infantile spasms at 10 wk of age, which disappeared at 6 mo of age. During infancy, severe psychomotor retardation was noticed, although the impairment of her motor development was less severe than that in her sister. Her walk is characterized by atactic movements and impaired coordination, but, at 8 years of age, she was able to walk alone. Like her sister, she exhibited stereotypic movements of the hands, made little eye contact, and demonstrated essentially no interaction with her environment. Mood swings and hyperventilation episodes were also present. On further follow-up, she presented with S-shaped dorso-lumbal scoliosis and hypertonia, as well as flexion contractures of the arms, knees, and Achilles ten-

dons. Growth parameters for height, length, and head circumference are within the normal range (5th–15th percentile), and her adult head circumference is 54 cm. Now, at the age of 41 years, she is still able to walk a few steps with support. Both sisters also exhibit abdominal distention because of excessive air swallowing.

The mutation identified in the twin sisters was present neither in their healthy parents nor in an unaffected sister, which suggests that it occurred de novo.

The predicted CDKL5 protein contains a conserved serine/threonine kinase domain in the N-terminus. Sequence comparison revealed that its kinase domain shares high homology with p42 KKIALRE (CDKL1) (Yen et al. 1995), p53 KKIAMRE (CDKL2) (Taglienti et al. 1996), and NKIAMRE (CDKL3) (Midmer et al. 1999), which are members of the protein kinase subfamily with both mitogen-activated protein kinase (MAPK) and cyclin-dependent kinase (CDK) features. The amino acids mutated in the patients lie in critical protein domains that are important for proper kinase function. The Cys152 amino acid in kinase subdomain VII is immediately N-terminal to the conserved Asp-Phe-Gly motif (fig. 3), one of the kinase signatures involved in phosphotransfer (Hanks and Hunter 1995). Although, in other unrelated protein kinases, other small amino acids—such as alanine, glycine, serine, or threonine—may be found at this position, none of the protein kinases present in the GenBank database contains a phenylalanine residue here (see BLAST Web site). The substitution of a cysteine with a phenylalanine residue would likely alter the proper orientation of the adjacent Asp-Phe-Gly motif and therefore would most likely impair the catalytic activity of the protein. The other mutated amino acid, Arg175, lies within kinase subdomain VIII (fig. 3), which is important for substrate recognition (Hanks and Hunter 1995). The sequence context of this amino acid (YVAT**R**WYR) is highly conserved in proline-directed protein kinase subfamilies, such as MAPKs and CDKs, and is required for the selectivity toward substrates containing a proline at the P+1 position, relative to the phosphate acceptor (Russo et al. 1996; Canagarajah et al. 1997). Exchange of a positively charged arginine for an uncharged serine would likely influence substrate-binding specificity.

Taken together, several lines of evidence argue for the pathogenic nature of these missense mutations. First, both mutations most likely occurred de novo. Second, they both lie within critical regions of the serine/threonine kinase domain and therefore most likely have deleterious effects on CDKL5 kinase activity. Third, the mutated amino acids are conserved in mouse and *Fugu rubripes* Cdkl5 orthologs and are also present in other closely related protein kinases, including CDKL1, CDKL2, and CDKL3 (fig. 3). Finally, neither of the missense mutations was found in 427 control X chromosomes.

Additional evidence that implicates *CDKL5* in a severe phenotype with strong similarities to the early-onset RTT variant comes from the recent work of Weaving et al. (2004 [in this issue]), who identified truncating frameshift mutations in two unrelated families. Together, we have found four different mutations, three of which involve the protein kinase domain. These observations, together with our previous identification of disease-causing chromosome translocations that truncate *CDKL5* (Kalscheuer et al. 2003), suggest that mutations in *CDKL5* are associated with a wide range of clinical features, which is also the case for *MECP2* mutations. The associated disorder may be severe, with early-onset encephalopathy, as seen in both translocation patients (Kalscheuer et al. 2003) as well as in one male patient with a frameshift mutation (Weaving et al. 2004 [in this issue]). These patients presented with infantile spasms, severe global developmental delay, and profound intellectual impairment; they never learned to speak, sit, or walk, and they never developed visual or social response. At the other end of the spectrum is the mild mental retardation with autistic features present in one female twin with a frameshift mutation in

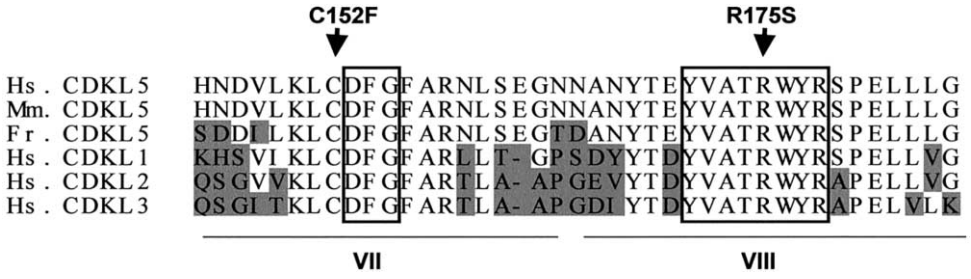

Figure 3 Multiple sequence alignment of human CDKL5 with its vertebrate orthologs and with closely related human protein kinases CDKL1, CDKL2, and CDKL3 in the region of the kinase subdomains VII and VIII (see the ClustalW Web site). In the alignment, the residues that differ from the consensus sequence are shown with a gray background. The invariant DFG motif in subdomain VII and the substrate recognition sequence YVATRWYR in subdomain VIII are boxed. Affected amino acids are indicated by a blackened arrow. Amino acid substitutions are shown above the alignment.

CDKL5. She retains reasonable verbal skills and has no obvious motor deficiencies (Weaving et al. 2004 [in this issue]). The female patients described here and the two female patients reported by Weaving et al. (2004 [in this issue]) have intermediate phenotypes. All of them had an apparently normal pre- and perinatal period but developed severe epileptic activity between 5 wk and 3 mo of age, followed by psychomotor and behavioral development delay, with or without a period of regression. On examination, all of these affected girls exhibited motor deficiency, autistic features, and mental retardation, as well as absence of speech and of purposeful hand use. The affected female patients described in this study did not exhibit the regression period of classic RTT; in particular, in the patient from family 1, no symptoms related to classic RTT, other than those mentioned above, were present, probably because of her young age (6.5 years old at present). However, the cluster of these clinical features meets almost all of the criteria for the early-onset variant of RTT (Goutieres and Aicardi 1986; Hagberg and Skjeldal 1994).

Our data, together with our previous results (Kalscheuer et al. 2003) and the findings of Weaving et al. (2004 [in this issue]), indicate that a subset of patients with a clinical picture resembling the early-onset RTT variant or with a history of early-onset seizures, have mutations in the *CDKL5* gene. In the future, genotype-phenotype correlations in additional patients with a variant of RTT and a mutation in *CDKL5* will probably lead to a reclassification of this subtype of RTT.

The phenotypic heterogeneity observed in female patients with a mutation in this gene may be due to variable X-chromosome inactivation (XCI), since *CDKL5* is subject to XCI. Consistent with this hypothesis, the most severe phenotype, with early-onset encephalopathy, was present in the females who carried the X;autosome translocations, in which the normal X chromosome was completely inactivated (Kalscheuer et al. 2003). Likewise, the hemizygous male with a frameshift mutation was severely affected (Weaving et al. 2004 [in this issue]). In females, expression of the wild-type allele in at least a portion of the cells may mitigate the clinical manifestations. Indeed, a normal XCI pattern was found in the MZ twins in family 2 (data not shown), and a slightly skewed XCI pattern that favored expression of the normal allele was seen in one female patient reported by Weaving et al. (2004 [in this issue]). On the other hand, the twin sisters described by Weaving et al. (2004 [in this issue]) exhibited completely different clinical features from each other but both had a similar XCI pattern in cells from peripheral blood. In this case, the XCI pattern in blood leukocytes may not reflect the XCI patterns in the brain.

The phenotypic overlap between patients carrying *MECP2* and *CDKL5* mutations may indicate that the two genes play a role in a common pathogenic pathway. MeCP2 is known to preferentially bind to methylated CpG dinucleotides through its methyl-CpG–binding domain and to silence downstream target genes (Lewis et al. 1992; Nan et al. 1998). Recently, it has been shown that activation of target genes is associated with increased phosphorylation of MeCP2 (Chen et al. 2003; Stancheva et al. 2003). It is therefore tempting to speculate that CDKL5 may be involved in the regulation of MeCP2 phosphorylation. Further characterization of the CDKL5 signaling pathway, including its upstream activators and downstream substrates, will help to elucidate the potential link between CDKL5 and MeCP2, which will ultimately lead to elucidation of the pathogenesis of this group of diseases.

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Electronic-Database Information

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

BLAST, http://www.ncbi.nlm.nih.gov/BLAST/ (for searching short, nearly exact matches of FDFG sequence)

ClustalW, http://www.ebi.ac.uk/clustalw/ (for alignment of human CDKL5, its orthologs, and closely related CDKL1, CDKL2, and CDKL3)

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for human genomic sequence containing *CDKL5* [accession numbers AL109798 and Z92542], human *CDKL5* cDNA [accession number NM_003159], human CDKL5 protein [accession number NP_003150], mouse Cdkl5 [accession number XP_356367], *Fugu* Cdkl5/Stk9 [accession number AAD28798], human CDKL1 [accession number NP_004187], human CDKL2 [accession number NP_003939], and human CDKL3 [accession number NP_057592])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for RTT)

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