FKBP10 and Bruck Syndrome: Phenotypic Heterogeneity or Call for Reclassification?

To the Editor: We read with interest the recent paper by Alanay et al., who describe the first human patients with *FKBP10* (MIM 607063) mutations and conclude that this adds to the growing list of autosomal-recessive nonsyndromic osteogenesis imperfecta (OI) genes (MIM 610968).[1] This is in contrast to our experience with an extremely rare form of OI called Bruck syndrome (MIM 259450 and 609220), in which multiple joint contracture is a prominent finding.[2] Below we show this syndrome to be caused by a mutation in the same gene.

The index patient in the study family was referred to us as a neonate after he was found to have severe flexion deformity of knees, ankles, and to a lesser extent, elbows. His working diagnosis was arthrogryposis multiplex congenita. After an initial fracture of the femur because of trivial trauma at the age of 7 months, osteogenesis imperfecta was suspected and subsequently clinically confirmed when he had multiple other long bone fractures in early childhood. He was started on parenteral bisphosphanate therapy, which seems to have helped with his fracture frequency. He had normal appearance of the sclera and teeth. Surgical soft tissue release was only partially successful, and the patient, currently 9 years old, is still unable to walk but has normal use of the hands and is of normal intelligence (Figure 1). His radiological findings consist of evidence of old healed fractures, severe flexion deformities of knees and ankles, wormian bones, and generalized osteopenia (Figure 1). Family history is notable for a similarly affected older brother, currently 13 years old, who has frequent fractures and multiple joint contractures and who was also treated successfully with parenteral bisphosphonate. There are four healthy siblings and parents, who are healthy and denied consanguinity, but they can trace their ancestry to the same village in central Saudi Arabia.

Clinical testing for *COL1A1* (MIM 120150) and *COL1A2* (MIM 120160) in both patients revealed homozygosity for a previously reported sequence variant (P205A) in *COL1A1*, although the pathogenicity is unclear.[3] Given the ambiguity of the result and the fact that Bruck syndrome has not been linked to *COL1A1*, we recruited this family under a protocol approved by the King Faisal Specialist Hospital and Research Center institutional review board and obtained written informed consent. We performed genome-wide SNP genotyping of both patients as described before assuming that the parents might be distantly related.[4,5] Indeed, only very few blocks of apparent homozygosity were identified per patient, and none of them overlapped with either of the two previously described Bruck syndrome loci, confirming that these patients have Bruck syndrome 3 (BKS3).[6,7] One area of overlap between the two patients was identified on 17q21.2, spanning 1.5Mb of genomic DNA that contains 91 genes. *FKBP10*, which encodes FKBP65, an extracellular matrix binding protein,[8] was an attractive candidate in that interval. Sequencing of the entire coding and the flanking intronic sequence revealed the presence of a homozygous 8 bp insertion (c.1023insGGAGAATT) along with resulting frameshift and premature truncation of the protein (p.T342G*f*sX367).

Interestingly, the OI phenotype that Alanay et al. described in association with the two mutations is much more severe than the one we describe here.[1] It may be hard to attribute this to the allelic difference because one of the two mutations described by Alanay et al. causes in-frame deletion of 11 amino acids from the first peptidyl-prolyl cis-trans isomerase (PPI) domain, whereas our mutation predicts complete loss of the fourth PPI domain (Figure 1), so it is quite possible that bisophosphanate therapy might have played a role in ameliorating the phenotype in our patients.[9] More importantly, the phenotype of our patients is classical for Bruck syndrome, whereas Alanay and colleagues described an apparently isolated form of osteogenesis imperfecta. The clinical description by Alanay and colleagues does not focus on the presence of contractures, and the "severe deformities" are assumed to be related to fractures. Upon review of Figure 2A of the Alanay paper, we suggest that the patient has a plantar and forefoot flexion deformity of the right foot. In addition, the webbing formation shown in Figure 2B suggests the possibility that a pterygium formation preceded the onset of the bending fracture of that limb.

In view of our findings above, it would be very helpful if Alanay and colleagues could evaluate in detail the contracture phenotype of their patients, with particular emphasis on early infancy prior to the onset of fractures. This would enable us to determine whether mutations in *FKBP10* cause nonsyndromic OI as well as Bruck syndrome or whether perhaps the patients described in the Alanay paper should be re-classified as patients with Bruck syndrome (BKS3).

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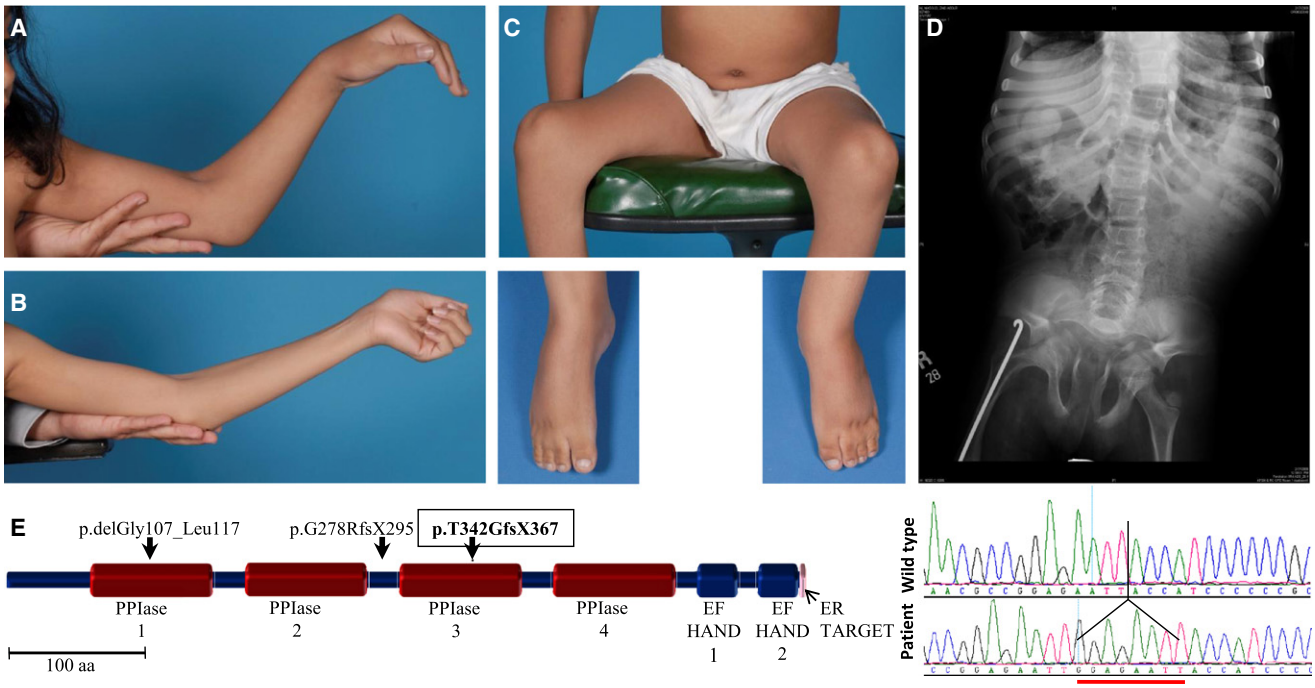

Figure 1. A Novel *FKBP10* Mutation in Two Siblings with Bruck Syndrome
(A) Clinical photographs of the index patient and (B) his brother showing fixed flexion deformity of the elbows. (C) Note the severe flexion deformity of the knees in the index patient; the ankles are less severely involved. (D) Thoracolumar spine X-ray showing scoliosis and osteopenia. Severe protrusion acetabuli and intrmedullary rod fixation of the right femur fracture can also be seen. (E) Schematic representation of FKBP65 with the location of mutations indicated by arrows. Our mutation is boxed and shown next to the sequence chromatogram; the inserted 8 bp are indicated by a red line.

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Web Resources

The URL for data presented herein is as follows:

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

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