Response to Shaheen et al.

To the Editor: Thank you for the opportunity to respond to the Letter to the Editor, "*FKBP10* and Bruck Syndrome: Phenotypic Heterogeneity or Call for Reclassification?" by Shaheen et al. The findings in the two patients described are interesting and provide more information about the correlation between *FKBP10* (MIM 607063) mutations and phenotype, which is important from a clinical perspective. The index patient has severe osteopenia with flexion deformity and was originally thought to have arthrogryposis multiplex congenita. These findings are highly suggestive of Bruck syndrome (MIM 259450 and 609220), a rare form of osteopenia with congenital contractures that is similar to some forms of OI. However, the patients described in the Alanay et al. 2010 paper did not present with the same phenotypic findings.

We have reviewed the findings in six of our seven Turkish patients with homozgyosity for an *FKBP10* mutation leading to an in-frame p.delGly107_Leu117 deletion and our three Mexican-American patients who were homozygous for a null mutation. All of these patients were diagnosed with osteogenesis imperfecta soon after birth, and all were noted to have excessive joint laxity with neither contractures nor, more importantly, pterygium. Because pterygium was not observed, we infer that there was in utero movement across the joints. Follow-up examination of the Mexican-American family revealed that two of the patients developed contractures at the elbows. Whether the contractures were the direct result of abnormalities in FKBP65 (the protein encoded by the *FKBP10* gene) function or a secondary result of chronic dislocations leading to contractures is unknown.

Shaheen et al. suggest that in the Alanay et al., 2010 article the contractures at the elbow in Figure 2B and the pes planus in Figure 2A are due to "developmental" contractures and thus that the disorder should be reclassified. Radiographs in Figure 2H show severely deformed extremities with a dislocation at the elbow. Because the dislocation was not noted at birth or in the neonatal period, it is our view that any contracture at the elbow would be secondary. Indeed, there are many disorders with chronic joint dislocations that lead to a contracture with "webbing" over the unused joint.

Shaheen et al. identify a mutation in *FKBP10* that alters the third PPIase domain of the FKBP65 molecule. Whether the mutation leads to reduced or absent FKBP65 activity is not clear. However, as in many disorders, a wide phenotypic range of severity can result from different mutations in the same gene. In addition, variability due to the influences of genetic background might also affect phenotypic expression. We welcome further expansion of the phenotypes associated with *FKBP10* mutations because there is so much to learn about the molecule. Previous work on FKBP65 has shown that it has roles in the function of both type I collagen and tropoelastin, and probably other proteins as well, suggesting that much work needs to be done with regard to the role of FKBP65 in mesenchymal-derived tissues in addition to its function in bone.

The issues of semantics and splitters versus lumpers are of on-going debate in the genetics community. There is probably no unified answer to these issues because clinical interpretation occurs over an ever-changing landscape of disease progression and molecular advances. Demonstrating variation in phenotype is important, but categorizing patients into a rare new subgroup with an eponym that does not delineate the phenotype does not serve either the clinical genetics or molecular genetics communities and could lead to confusion. We suggest the phenotype that we have studied and found to be due to mutations in *FKBP10* be categorized as a recessive form of progressive deforming osteogenesis imperfecta with or without joint contractures and that it be recognized that there is a spectrum of phenotypic variability.

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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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