Letters to the Editor

Am. J. Hum. Genet. 63:1559, 1998

Reply to Shanske et al.

To the Editor:

Clinical overlap often confounds accurate diagnosis. For a number of pleiotropic genetic syndromes, sophisticated biochemical, molecular, and cytogenetic tests have mitigated this problem. However, for a laboratory result to be of value to the practitioner, there must be no doubt about the accuracy of the diagnosis for those patients on which the laboratory test was validated. In their foregoing letter to the Editor, Shanske et al. express concern about our clinical diagnosis of Marshall syndrome in a family in which we found a mutation in a gene encoding a subunit of type XI collagen. To address their concern, we shall review the clinical findings in the family described by Marshall (1958), for whom the syndrome is named, and compare these findings to those reported for our patients (Griffith et al. 1998) and for the patients described by Shanske et al. (1997), who also were thought to have Marshall syndrome.

Marshall (1958) reported "a kindred of seven individuals in three generations, who showed the following ocular abnormalities: congenital and juvenile cataracts,…basic myopia; fluid vitreous; and one instance of retinal detachment…; these patients also had defective hearing, a congenital defect of the nose and the associated facies, and other evidence suggestive that they may represent incomplete examples of hereditary anhidrotic ectodermal dysplasia" (p. 143). In addition to anhidrotic ectodermal dysplasia, Marshall included in his differential diagnosis "congenital syphilis, gargoylism, achondroplasia, and (distinct facies) even alone in an otherwise normal body" (pp. 144–145). Not included in his differential diagnosis were Stickler syndrome (Stickler et al. 1965) and Weissenbacher-Zweymüller syndrome (Weissenbacher and Zweymüller 1964), which had not yet been described. After careful clinical assessment and examination of the dermal histology of two family members, Marshall stated, "This kindred lacks the triad found basically in the major, anhidrotic type of ectodermal dysplasia: hypotrichosis, hypodontia, and hypohidrosis. There is some evidence of the presence of the latter two conditions, but this is not strongly convincing" (p. 155). Did these patients really have a form of ectodermal dysplasia, or did Marshall expand the differential diagnosis of congenital nasal defect by describing a new nonectodermal dysplasia syndrome that now bears his name? We and others (Cohen et al. 1974; Zellweger et al. 1974; Lyons-Jones 1997, pp. 252–253) think that the latter conclusion is more likely. Shanske et al. (1997) disagree and refer to a four-generation kindred with ectodermal abnormalities and hypertelorism, which they feel is consistent with Marshall syndrome.

As detailed below, a comparison of the principal findings reported by Marshall (1958) with the findings reported for our patients (Griffith et al. 1998) reveals high concordance, whereas comparison with the patients reported by Shanske et al. (1997) shows low concordance. Marshall's patients and our patients all had congenital or juvenile cataracts and fluid vitreous; none of the patients described by Shanske et al. had these conditions. Marshall's patients and our patients all had significant hearing loss; none of the patients described by Shanske et al. had hearing loss. Marshall's patients had "ample and normal hair," as did our patients; the patients described by Shanske et al. all had "sparse" hair or a "paucity of hair." Two of Marshall's patients were studied radiographically; each had nasal bones that were "small, short, and far back of their normal position." These patients also had "prominence of the frontal bossae," which served to "accentuate the flatness or depression of the bridge of the nose," and "thickening of the outer table of the skull and absent frontal sinuses." In our report (Griffith et al. 1998), we included a patient photograph and cranial CT scan that showed nearly identical features. In contrast, the patients described by Shanske et al. had "significant frontal recession" and normal skeletal surveys.

Why did Shanske et al. conclude that their patients had Marshall syndrome? One reason seems to be the presence of ectodermal abnormalities, including sparse hair, eyebrows, and eyelashes, in their patients. However, Marshall's patients did not have these ectodermal abnormalities. Instead, Marshall thought that his patients had an altered ability to sweat. When comparing his patients with a 32-year-old female control, Marshall observed that sweat production was "diminished, perhaps

25 percent below normal" (p. 148). However, the patients described by Shanske et al. did not have problems with sweating. A second reason that Shanske et al. favored a diagnosis of Marshall syndrome was the presence of myopia in their patients; however, in addition to basic myopia, Marshall's patients had cataracts and fluid vitreous, which the patients described by Shanske et al. lacked. A third reason that Shanske et al. considered Marshall syndrome was the presence of ocular hypertelorism in all of their patients. After inspecting the published facial photographs of six of Marshall's patients, Shanske et al. noted that one of the six (patient 6) had "striking ocular hypertelorism." We tend to agree with this assessment and suspect that Marshall's patients 2, 4, and 7 also might have had mild ocular hypertelorism. However, "mild orbital hypertelorism" was included in the figure legend accompanying the published photograph of one of our patients (Griffith et al. 1998, p. 819).

We feel strongly that this detailed comparison supports the clinical diagnosis of Marshall syndrome in our kindred. A separate issue is whether the clinically defined Marshall, Stickler, Weissenbacher-Zweymüller, and Wagner syndromes represent locus heterogeneity, allelic heterogeneity, or variable expression of the same mutation. In our report (Griffith et al. 1998), we discussed the similarity and possible identity of Marshall syndrome and Stickler syndrome. Yet, there are precedents for consideration of the possibility that clinically distinct phenotypes also can result from allelic heterogeneity; for example, FGFR3 mutations cause both achondroplasia and thanatophoric dysplasia. On the basis of published studies, we suggest the following conclusions: First, Stickler syndrome exhibits locus heterogeneity with mutations identified and shown to cosegregate in at least three different genes, COL2A1, COL11A1, and COL11A2; thus far, COL11A2 mutations have been identified only in families lacking eye involvement but otherwise having other component features of Stickler syndrome. Second, the autosomal recessive disorder oto-spondylo-megaepiphyseal dysplasia (Giedion et al. [1982] concluded that the patient described by Weissenbacher and Zweymüller [1964] had this disorder) also appears to be due to mutation within the COL11A2 gene. Third, Wagner syndrome is genetically distinct from both Stickler and Marshall syndromes, having been mapped by linkage analysis to a novel locus on human chromosome 5, by use of DNA from the kindred originally reported by Wagner (Brown et al. 1995). This kindred had ocular involvement without the systemic findings reported to occur with Marshall and Stickler syndromes (Graemiger et al. 1995). Last, in at least one kindred, Marshall syndrome is caused by a mutation within COL11A1 (Griffith et al. 1998).

We fully agree with Shanske et al. (1997) that accurate syndrome diagnosis is necessary in order to draw meaningful conclusions about the molecular pathogenesis of a disease phenotype. Results from one family are not sufficient to determine whether COL11A1 will be the sole Marshall syndrome locus or whether identical mutations in COL11A1 (or in other loci) can cause Marshall syndrome in one instance and Stickler syndrome in another. If the unexpected, yet exciting, findings from studies of other collagens are any indication (e.g., O'Reilly et al. 1997), studies of collagen XI will continue to yield intriguing results. For now, we speculate that mutations in COL11A1 cause Marshall syndrome, and we invite our clinical and scientific colleagues to assist us in testing this hypothesis.

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0002-9297/98/6305-0038$02.00