## Characterization of *SHOX* Deletions in Léri-Weill Dyschondrosteosis (LWD) Reveals Genetic Heterogeneity and No Recombination Hotspots

*To the Editor:* In the July 2005 and March 2006 issues of the *Journal,* Schneider et al.[1] and Zinn et al.,[2] respectively, reported mapping studies of *SHOX* (MIM 312865) deletions in patients with Léri-Weill dyschondrosteosis (LWD [MIM 127300]). In their study, Schneider et al.[1] reported that the majority (73%) of patients with LWD who had *SHOX* deletions shared a 3′ deletion breakpoint hotspot located downstream of *SHOX*. Zinn et al.[2] identified a different 3′ breakpoint hotspot located several hundred kilobases farther downstream in 86% of Hispanic patients, whereas the recombination hotspot described by Schneider et al.[1] was not observed.

We characterized the *SHOX* deletion limits in a cohort of 48 European patients with LWD ($n = 47$) and Langer mesomelic dysplasia (LMD [MIM 249700]) ($n = 1$). *SHOX* deletions were originally detected by multiplex ligation probe amplification (MLPA) (MRC Holland) or microsatellite analysis (*DXYS10092, DXYS201, DYS290, DXYS10093, DXYS233,* and *DXYS234*) and subsequently were finely mapped using a dense panel of microsatellites and SNPs.[3] Four newly identified microsatellites (Tandem Repeat Finder), located 133, 54, 31, and 19 kb 5′ of *SHOX* (table 1), and 59 SNPs, 12 of which were previously unreported (table 2), were analyzed.

In our study, the *SHOX*-encompassing deletions were highly heterogeneous for both extension and breakpoint localization, with no recombination hotspot observed (fig. 1). Deletion extensions varied from at least 8 kb to 38 Mb. The majority of deletions (45 of 49) encompassed the entire *SHOX* gene, whereas 4 were partial deletions (deletions 1–4) (fig. 1). The smallest deletion (in proband 3) included exons 4–6a (8–21 kb) and was detected only by MLPA[5] (fig. 1). In seven probands (14%), deletions extended into the Xp-specific region (figs. 1 and 2). The majority (61%) of deletions were interstitial, whereas the remaining 39% encompassed all analyzed telomeric markers, thus possibly extending to the telomere. Because of the lower microsatellite density in the telomeric pseudoautosomal region 1 (PAR1), the 5′ breakpoints of 16 subjects were reevaluated using the commercial SHOX MLPA kit complemented with seven additional synthetic MLPA probes (table 3 and fig. 3). Only three patients—29, 30, and 31—possibly share a 3′ breakpoint between *DXYS10082* and *DXYS10084,* and only probands 35 and 36 possibly share the same 5′ and 3′ breakpoint.

The results from this study are in contrast to previous reports of the presence of 3′ deletion breakpoint hotspots in patients with LWD.[1,2] Schneider et al.[1] reported a common proximal breakpoint in 20 of 27 patients with LWD. In a subset of six patients with LWD, this common breakpoint was refined to an ~5-kb interval 666–671 kb from Xpter, corresponding to a point between *DXYS10083* and *S14*. In contrast, no breakpoint hotspots were observed in our study; moreover, none of our 48 subjects had a breakpoint within this interval. This discrepancy is unlikely to be explained by population differences between studies, since all subjects were of European origin. The presence of multiple 5′ breakpoints in both studies also excludes the possibility of a founder effect. Differences in the methodology used for deletion mapping may explain the discrepancy between the studies. Whereas Schneider et al.[1] initially used microsatellites to identify the deletion limits, subsequent mapping was performed by FISH. They analyzed a number of PAR1 cosmids, by "walking" away from *SHOX* until they identified a probe that gave two hybrid-

**Table 1. Novel Microsatellite Markers**

| Marker[a] | Oligonucleotide (5′→3′) Sense | Oligonucleotide (5′→3′) Antisense | Size Range (bp) | Heterozygosity |
|---|---|---|---|---|
| *DXYS10136* | CTGAACTCAGAATCGGGACC | CCCAGGAGCCCAGGAGATTGA | 303–323 | .85 |
| *DXYS10137* | CCCAGGCCCTGTTTACGCTTCG | TATCCTCACAACTGCGTCTTCC | 180–210 | .90 |
| *DXYS10138* | GTACATAGATGGCAGATAGATG | CTGCATGTATACACACTGTAAT | 197–221 | .73 |
| *DXYS10139* | AGCCCCAACCCTCCATGATACTGA | GCAAAGGCATCTGTTTAAGTAACG | 131–203 | .24 |

NOTE.—PCR conditions for the amplification of microsatellites *DXYS10136, DXYS10137, DXYS10138,* and *DXYS10139* were as follows: 1 × Qiagen Hotstart Taq buffer, 0.5 units of Hotstart Taq polymerase, 2.0 mM $MgCl_2$, 200 $\mu$M dNTPs (50 $\mu$M each), and 400 nM of each primer. Cycling conditions for *DXYS10137, DXYS10138,* and *DXYS10139* were as follows: initial denaturation at 94°C for 15 min; 35 cycles for 30 s at 94°C; 30 s at 49°C, 58°C, and 55°C, respectively; and 40 s at 72°C, with a final extension for 8 min at 72°C. For the amplification of *DXYS10136,* we used a touchdown protocol for easier allele calling. Cycling conditions were as follows: initial denaturation at 94°C for 15 min, 16 cycles for 30 s at 94°C, 30 s at 58°C–66°C ramp (−0.5°C per cycle), and 40 s at 72°C, followed by 16 cycles for 30 s at 94°C, 30 s at 58°C, and 40 s at 72°C. The program terminated with a final extension for 8 min at 72°C.

[a] Further details can be found at the GDB Human Genome Database.

**Table 2. Oligonucleotide Sequences and PCR Conditions of the PAR1 Amplicons That Contain the 18 Analyzed SNPs**

| dbSNP ID | Our Amplicon ID | SNP | Oligonucleotide (5′→3′) Sense | Oligonucleotide (5′→3′) Antisense | Annealing Temperature (°C) | Amplicon Size (bp) |
|---|---|---|---|---|---|---|
| *rs5988284* | S27 | G/A | GTCATGGCCGGATCCT | ACTTGTTACCACGAGCCCG | 52 | 422 |
| *rs6644380* | | G/A | | | | |
| *rs5946512* | | G/A | | | | |
| *rs17148729* | S21 | A/C | GGATTCCTGGTGGTTGCTAT | GCAGTAATCACATTAGGGTAAATAA | 55 | 997 |
| ***ss49845888*** | | **G/A** | | | | |
| ***ss49845889*** | | **T/A** | | | | |
| ***ss49845890*** | S22 | **C/T** | TGGGGACAAATTATTCATTGGATTC | CTTGACCTTGTGATCTGCCCTCTTC | 55 | 986 |
| ***ss49845891*** | | **G/A** | | | | |
| ***ss49845892*** | | **G/A** | | | | |
| ***ss49845893*** | | **T/C** | | | | |
| ***ss49845894*** | | **G/A** | | | | |
| ***ss49845895*** | S23 | T/C | CCACCACCATGCCTAGCTGA | ATGAGAGACAGGTTTCCACTGT | 55 | 377 |
| ***ss49845896*** | S25 | **C/T** | CTCCCCATTGCGGTTGCACGAATTT | CCGTATGCACAATTCATGGGCG | 56 | 1,182 |
| *rs6644384* | | A/G | | | | |
| *rs6644385* | | C/T | | | | |
| ***ss49845885*** | S20 | **T/C** | CAATACCAATCTTGCTTCAACCCAC | GGGATCAACAGACACTAATACGCA | 55 | 720 |
| ***ss49845886*** | | **G/A** | | | | |
| ***ss49845887*** | | **C/T** | | | | |

NOTE.—The 12 previously unreported SNPs are shown in bold.

ization signals. In 20 subjects, the first nondeleted probe downstream of *SHOX* was cosmid P0117. No additional probes downstream of P0117 were reported in these 20 subjects. The deletion breakpoint was defined by cosmids 29B11 distally and P0117 proximally. Further mapping of the breakpoint region was achieved by SNP analysis in 6 of these 20 subjects. A breakpoint hotspot was observed within a 5-kb interval. These findings were then extrapolated to all 20 subjects with a common breakpoint detected by FISH. In our opinion, this inference must be taken with care because of the observation reported elsewhere that PAR1 is enriched for repetitive elements and duplications[6] and the fact that marker P117, located within cosmid P0117, was mapped to multiple Xp locations.[7] Thus, if the cosmid P0117 is misassigned or comprises repetitive sequences, two FISH signals may be observed. This may be misleading, since the presence of the deletion would be masked.

In our study, we employed MLPA and segregation analysis of a large number of microsatellites and SNPs for probands with LWD and their parents. The deletions carried by 42 of 48 patients extended beyond the breakpoint reported by Schneider et al.[1] The large number of polymorphic markers analyzed excludes the possibility of allele dropout and nonpaternity. To investigate the discrepancy between our study and that of Schneider et al.,[1] we tested a subset of subjects with use of FISH. As expected, all four tested subjects had deletion of cosmid 29B11. We also attempted to analyze cosmid P0117 (a kind gift from Dr. G.-J. van Ommen), but we could not obtain hybridization signals for any of the four subjects. However, none of the cases were deleted for a series of fosmids, which mapped to the same region (613–747 kb) (information available from the authors). Furthermore, no deletion breakpoint hotspots were identified in patients with LWD who had PAR1 deletions located downstream of *SHOX*[5] or among the three largest studies of patients with Xp deletions.[8–11]

In the second recent study of *SHOX* deletion mapping of probands with LWD, Zinn et al.[2] employed molecular methods to analyze 30 LWD-affected families with *SHOX* deletions. In 17 of 26 informative cases, the deletion included the *DXYS233* marker—that is, extended beyond the 666–671 kb interval defined by Schneider et al.[1] Detailed STS mapping was performed on a subset of 11 sub-

**Table 3. Novel Synthetic MLPA Probes Incorporated into the MRC Holland SHOX Kit**

| Nomenclature | Approximate Distance from Telomere (kb) | Sequence at Ligation Site |
|---|---|---|
| Probe 1 (*GTPBP6* exon 2) | 169 | AAGATCAGGAAGGCCTTGGACAGG-CTTCGCAAGAAGAGGCACCTGCTC |
| Probe 2 (*PPP2R3B* exon 2) | 292 | CGCAGGACTCCGTCAACGTGGATG-CCGTCATCAGCAAGATCGAGAGCA |
| Probe 3 | 350 | AGCCAGCATCCGTGGTCTCTCTAT-AGTGGCCTCACGGTCTCCAGCCAG |
| Probe 4 | 390 | TCATCTTGTCTCAGAGACCTCGGA-GAGCTCCCAGAGCCTGGCTGCCAC |
| Probe 5 | 430 | GGTGCTCAGAGCCTCTAGGAGGAT-CCTTTCGGAAAGCAAGTCTGCTGT |
| Probe 6 | 470 | TCAGGGCCCAAGCCAGCGGAAGCG-CTGCGCTCACTAAAGACGCTCCGT |
| Probe 7 | 510 | ATGCTGGCAATATGG CGGTCACCA-ATAGTGTTCATCAACTCCAGAGGG |

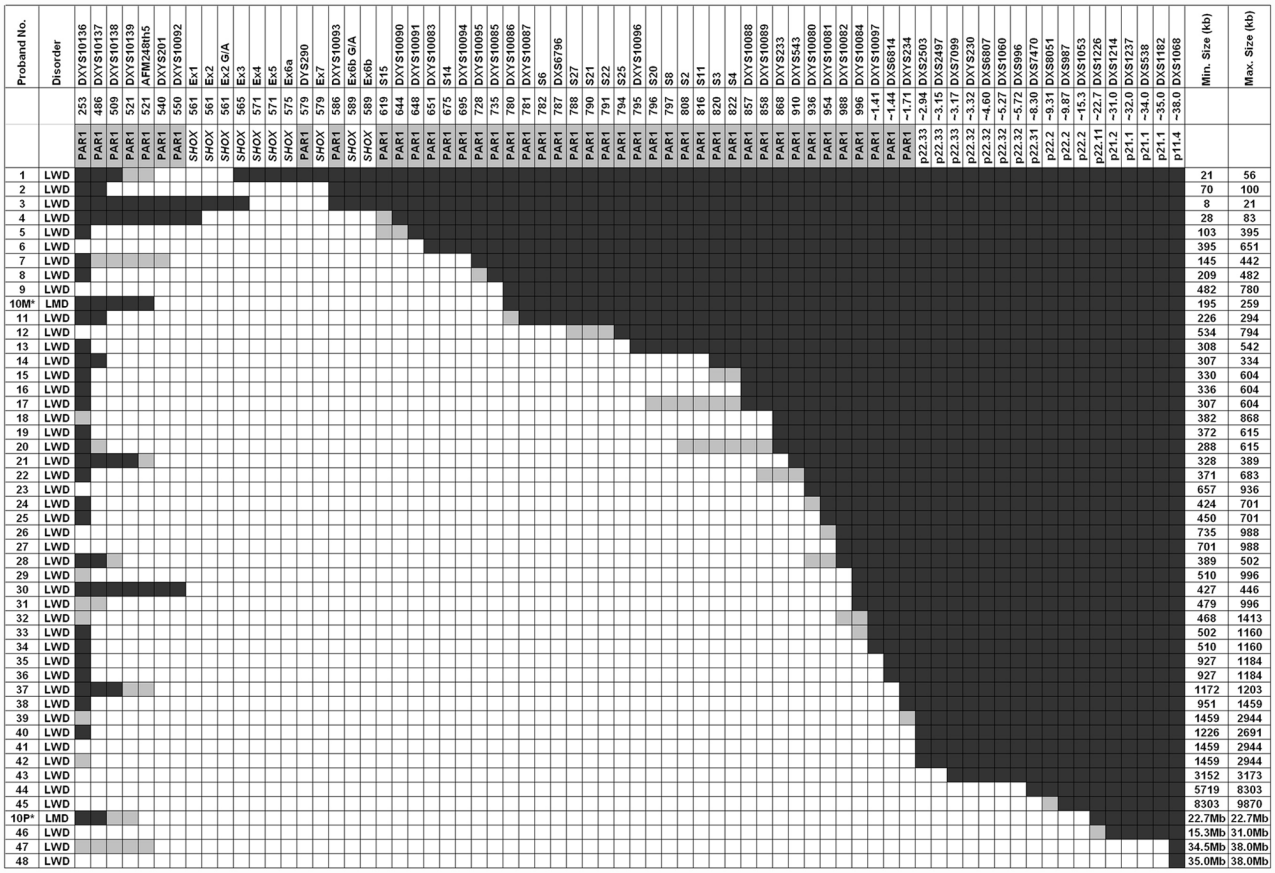


**Figure 1.** Characterization of PAR1 deletions in 47 patients with LWD and 1 patient with LMD, through use of a panel of microsatellites and SNPs (not to scale). Blackened areas indicate the presence of two copies of the marker or SNP, unblackened areas indicate the presence of a deletion, and shaded areas indicate the noninformative areas where the breakpoints are located. Distances are according to Ensembl Genome Browser coordinates; markers *DXYS10136–DXYS234* are stated in kilobases, whereas markers *DXYS10097–DXS1068* are stated in megabases. Deletion sizes are in kilobases unless otherwise stated. Proband 10 (indicated by an asterisk [*]), the subject with LMD, has been reported elsewhere; the proband inherited a familial deletion from her mother (10M), and a de novo deletion of the paternal allele (10P) was also included in the cohort.[4] *AFM248th5* is an STS marker.

jects for whom human-hamster hybrids were constructed. This revealed a second hotspot in 8 of the 11 subjects, between 1.18 and 1.42 Mb, in a region that still contains a number of gaps in the human PAR1 sequence. In contrast to the results of Zinn et al.,[2] only three of our subjects had a 3′ breakpoint within this region. However, a founder effect could not be excluded in their study, since five of the six probands also shared 5′ breakpoints.

Although the underlying molecular mechanism remains to be elucidated, nonhomologous end joining may explain the occurrence of the scattered deletion breakpoints observed in the present study. The architectural features of the PAR1 deletion–flanking sequences include a high incidence of *Alu* and long interspersed nucleotide elements (LINE),[12] which has resulted in a recombination fraction ~20-fold higher per unit of physical distance for the whole PAR1 than for the genome-average rate of 1 cM per Mb.[13] Furthermore, even within different segments of the PAR1, the recombination fraction seems to be variable, with a range from a 13–23-fold greater increase at the telomere to a 26–38-fold increase near the pseudoautosomal boundary.[14] Thus, one can expect—and, indeed, observe—the recurrent incidence of deletions in this region in LWD.

An important diagnostic point was the observation that a significant proportion of probands (14% [7 of 48]) were found to carry PAR1 deletions that extended into the X-specific region of Xp22.3-Xp21.2 (fig. 2). Male offspring of these females would have a 50% chance of inheriting the Xp terminal deletion and therefore could be either inviable or at risk of presenting with severe clinical complications. In the LWD/idiopathic short stature (ISS) cohort studied by Schneider et al.,[1] 3 of 27 subjects with LWD and 1 of 6 subjects with ISS also presented with deletions of the entire analyzed PAR1 and with the likely extension into the Xp22.3 region, although the deletion limits were not available.

In conclusion, we detected a high level of genetic heterogeneity of *SHOX* deletions in a European cohort of 48

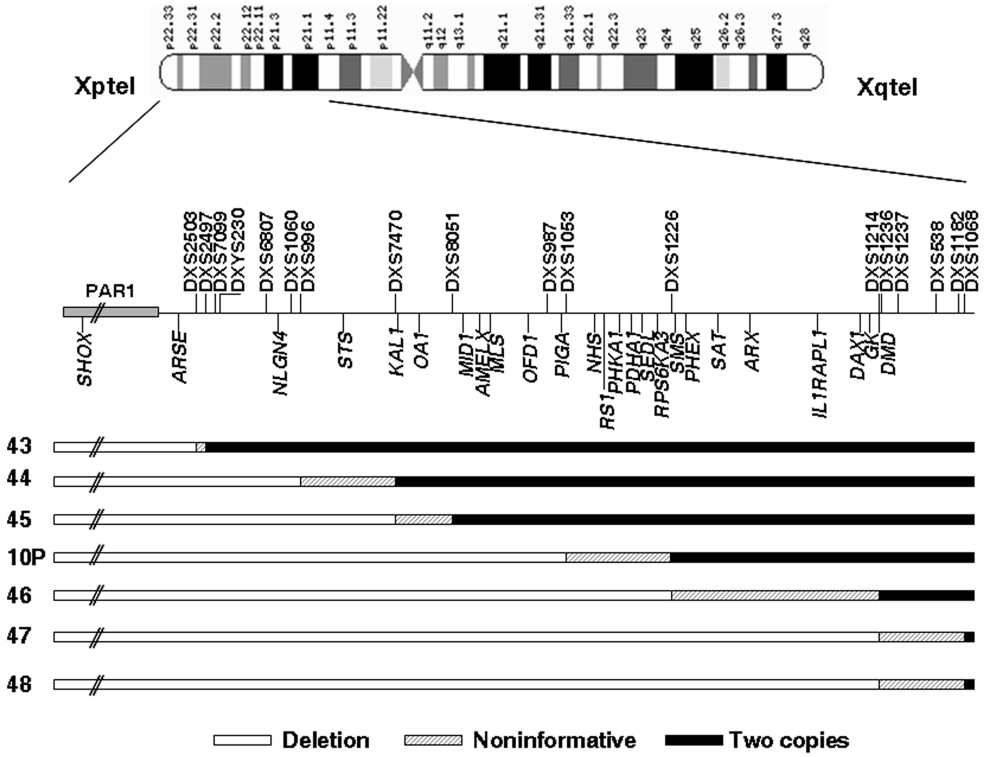


**Figure 2.** Detailed schematic representation of the 3′ deletion limits of probands 10P and 43–48, which extend beyond the PAR1 into X-specific regions. These samples correspond to one male (proband 43), five sporadic females (44, 45, 10P, 47, and 48), and proband 46, a familial case from a family in which only affected females were observed. Blackened areas indicate the presence of two copies of the marker or SNP, unblackened areas indicate the presence of a deletion, and shaded areas indicate the noninformative areas where the breakpoints are located. Localization of the microsatellite markers and the genes located within the deletions are indicated by vertical lines above and below the line, respectively.

patients with LWD/LMD who have a significant proportion of deletions extending beyond the PAR1 boundary. Until recently, molecular analysis of patients with LWD included only the screening of *SHOX* deletions and insertions, deletions, and point mutations within *SHOX*. Our recent findings[3] and those reported here emphasize the necessity of improving the molecular diagnosis given to LWD-, LMD-, and ISS-affected families by means of including deletion screening of the PAR1 region downstream of *SHOX* and, in certain cases, of analyzing whether the 3′ boundaries extend into the Xp22.3 region.

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## Web Resources

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

dbSNP, http://www.ncbi.nlm.nih.gov/SNP/ (for SNP identification numbers [listed in table 2], including the new accession numbers *ss49845885, ss49845886, ss49845887, ss49845888, ss49845889, ss49845890, ss49845891, ss49845892, ss49845893, ss49845894, ss49845895,* and *ss49845896*)

Ensembl Genome Browser, http://www.ensembl.org/ (for sequence information of the human X and Y chromosomes)

GDB Human Genome Database, http://www.gdb.org (for further details about the new microsatellites *DXYS10136, DXYS10137, DXYS10138,* and *DXYS10139*)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *SHOX,* LWD, and LMD)

Tandem Repeat Finder, http://tandem.bu.edu/ (for identifying microsatellites in sequence data)

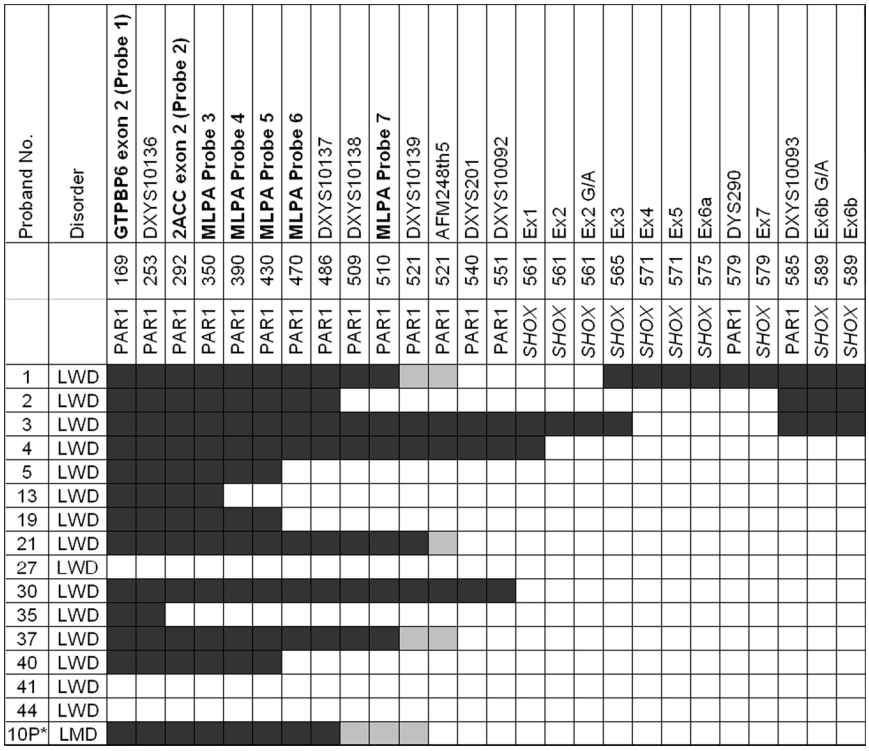


**Figure 3.** Fine mapping of 16 PAR1 deletions in patients with LWD and LMD with use of seven new synthetic Xp telomeric MLPA probes, indicated in bold. Distances are not to scale and are according to Ensembl Genome Browser coordinates (in kb). Blackened areas indicate the presence of two copies of the MLPA probe, marker, or SNP; unblackened areas indicate the presence of a deletion; and shaded areas indicate the noninformative areas where the breakpoints are located. "10P*" indicates the de novo deletion of the paternal allele.

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## Reply to Benito-Sanz et al.

*To the Editor:* We applaud the thorough characterization by Benito-Sanz et al. (in this issue)[1] of deletions encompassing the *SHOX* gene (MIM 312865) in patients with Léri-Weill dyschondrosteosis (MIM 127300). Benito-Sanz et al. suggest a founder effect to explain the apparent recombination hotspot we observed among our probands with *SHOX* deletions.[2] Indeed, four of our five probands who shared both 5′ and 3′ breakpoints were Hispanic. However, the same 3′ breakpoint was present in four non-Hispanic white probands, only one of whom had the common 5′ breakpoint. Additional studies will be required to determine whether the common *SHOX* deletion we observed was recurrent or arose only once. Benito-Sanz et al.[1] also propose that diagnosis of *SHOX* disorders should include testing for deletion of downstream Xp-Yp pseudoautosomal region 1 (PAR1) markers. It will be important to determine whether any of the SNP or microsatellite markers used in their study show deletion polymorphisms among unaffected individuals, since such variations could cause false-positive results in clinical testing. We agree with the statement by Benito-Sanz et al. that Xp deletions extending beyond PAR1 have important genetic counseling implications. Of the 49 deletions they mapped, 5 or 6 were large enough to be visible cytogenetically; our results were similar, but we excluded such deletions from our study. We suggest a low threshold for karyotyping patients with *SHOX* deletions, which may result not only from simple deletions but also from complex chromosomal rearrangements, such as unbalanced translocations or isodicentric chromosomes.[3,4]

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### Web Resource

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for Léri-Weill dyschondrosteosis and *SHOX*)

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