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Brief communication (Original)

Epidemiological study of congenital limb defects in individuals or families from the interior Sindh region of Pakistan

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Background: Congenital limb defects (CLDs) are a significant cause of morbidity and depending upon the severity, result in varying degrees of disability. Data on CLDs is scarce for South Asian populations.
Objective: To obtain insight into the spectrum of CLDs in the population of the interior Sindh region Pakistan.
Methods: A cross-sectional study was conducted in seven districts of interior Sindh and individuals or families were recruited from various hospitals and through door-to-door surveys.
Results: We recruited 165 independent individuals or families with certain type of CLDs during 2010–2013. The CLDs were categorized into 10 broad categories, and the five major types witnessed were: polydactyly, syndactyly, reduction deformities, musculoskeletal defects, and brachydactyly. CLDs depicted great phenotypic variability, but collectively, upper limbs were more commonly involved than lower limbs, right arms more than the left, left legs more than the right, and distal limb segments more than proximal segments. The pattern of malformations was not different between Muslims and Hindus.
Conclusions: These data established detailed distributions of CLDs across the vital sociodemographic attributes of the studied population, and are helpful in quantifying the impact of CLDs on the study population. Future molecular analyses of this cohort are anticipated to improve the clinical classifications and would also be of tremendous help to the affected individuals or families in risk estimation and genetic counseling.

Keywords: Congenital limb defects, genetic epidemiology, limb anomalies, polydactyly, syndactyly

Congenital limb defects (CLDs) are commonly observed in clinical practice; they are readily identified and are frequently reported in the medical literature. Descriptions of hand malformations are as old as recorded medical history [1]. CLDs affect approximately 1 in 500 live births. Depending upon their severity, they cause disability of varying grades and usually require surgical intervention to improve functional and aesthetic outcome. Up to 18% of children with a CLD die before the age of 6 years, usually because of associated malformations [2]. CLDs exhibit a broad spectrum of phenotypic manifestations. The majority of CLDs have an isolated appearance; however, there are a number of limb anomalies occurring in association with malformations in other organ-systems [3].

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The medical literature describes various approaches to the classification of limb malformations. Different researchers have employed various classification methods based on anatomy, etiology, severity, and genetics. The major categories identified for limb anomalies include: absence deformity, brachydactyly, carpal-tarsal synostosis, contracture deformity, digital malformations with congenital ring constrictions, macrodactyly, polydactyly, symphalangism, and syndactyly [1]. In many instances it is possible to subclassify the type of anomaly by the site of the malformation. For instance, polydactyly can be subclassified into preaxial, postaxial, and complex types [4]. Furthermore, each major class can be subdivided into one of two main groups according to whether abnormalities are essentially limited to the limbs or associated with malformation in other organs [1].

Corresponding to their diverse phenotypic manifestations, the etiology of CLDs is highly heterogeneous, ranging from genetic to environmental

and stochastic factors. These CLDs may serve as indicators in a search for genetic and environmental causes of dysmorphology. Therefore, it is pertinent to explore the nature of CLDs in a given population, in order to estimate their morbidity, social, psychological, and economic impacts on the society. For the Pakistani population, a few hospital-based studies have reported broader categories of skeletal anomalies without further characterizing limb defects [5]. Therefore, the present study was conducted to establish the spectrum of CLDs in the population of the interior Sindh region of Pakistan.

Methods and participants

Study population

This study was conducted in seven districts of interior Sindh, Pakistan namely: Tando Allahyar, Umerkot, Sanghar, Mirpur Khas, Khairpur, Hyderabad, and Tando Adam (Fig. 1). Interior Sindh is one of the poorly developed regions of Pakistan with prevailing poverty (about 30% live below poverty level) and low literacy rate. It has an agro-based economy, and the majority of the population resides in rural areas. Interior Sindh is a diverse assemblage of various ethnicities both native and migrated. One of the peculiar features of interior Sindh is the largest minority population of Hindus which are residing here from centuries and are considered to be the old settlers. Major languages are Sindhi, Urdu, Saraiki, Marwari, and Dhatki [6].

Methodology and case ascertainment

After approval by our Institutional Ethical Review Committee (approval No. DAS/10-854), a cross-sectional epidemiological study was conducted from July 2010 to July 2013. Individuals with CLDs were ascertained through door-to-door surveys, and from various public places like schools, community centers and hospitals. Cases were not ascertained from the institutes for the handicapped or special-education. Before recruitment, all the subjects provided documented informed verbal ascent or consent for their voluntary participation in our study, for those participants less than 18 years old or were otherwise incapable of providing consent, their parents or legal guardians provided documented informed verbal consent. Many of those included in the study were illiterate. All the data were obtained according to the ethical principles of the current Declaration of Helsinki. Data from individuals who were not the permanent residents of the study area or the respondents providing incomplete information were excluded. Limb anomalies with clear nongenetic or traumatic nature were not included.

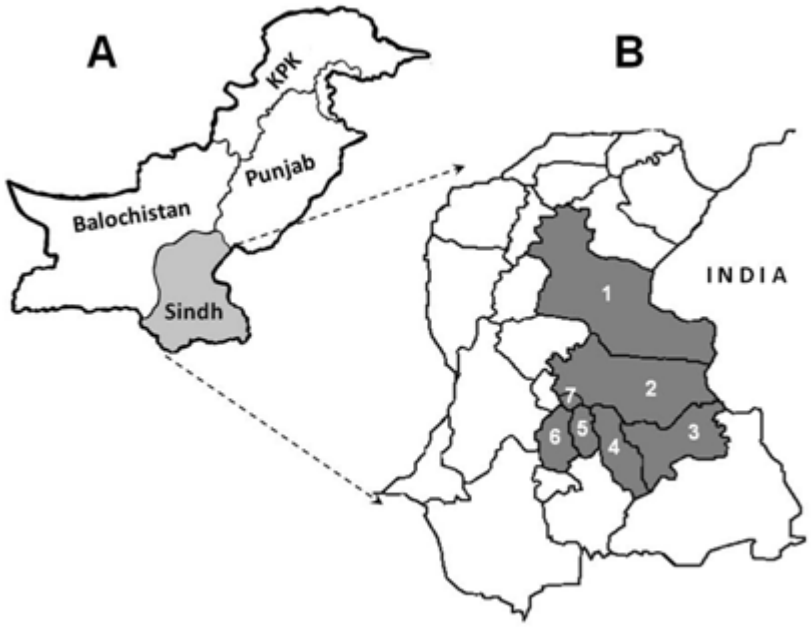

Figure 1. Map of Pakistan (A) with zoom-in image of Sindh province (B). Seven districts of interior Sindh from where subjects were recruited: 1. Khairpur, 2. Sanghar, 3. Umerkot, 4. Mirpur Khas, 5. Tando Allahyar, 6. Hyderabad, 7. Tando Adam.

Detailed information regarding sociodemographic variables including origin, ethnicity, language, age, family type, and parental marriage type, was obtained from each participant. Data regarding the clinical variability and associated malformations were also acquired. Photographs of almost all the participants and roentgenographs of the selected individuals were obtained with due respect for their privacy.

Only the index participants (n = 165) were included in the analyses. The limb anomalies were grouped into ten major categories (with further subdivisions): polydactyly, syndactyly, absence deformities, musculoskeletal anomalies, brachydactyly, leg defects, camptodactyly, clubfoot, clinodactyly, and club fingers [1-3,7-10]. Distribution of limb anomalies was established across the sociodemographic variables of study participants. Descriptive summaries were generated and the departure from random distributions was evaluated with a χ^2 test and Fisher exact test. Proportions of individual malformation types were calculated within the total anomalies. No attempt was made to estimate the prevalence of CLDs in the total population.

Results

There were a total of 165 independent individuals or families with CLDs that fulfilled the inclusion criteria (**Table 1**). Among the index cases, 80% (n = 132) were in males and 20% (n = 33) were in females, and there were 50.3% (n=83) cases in Muslims and 49.7% (n = 82)cases in Hindus.

Spectrum of congenial limb defects (CLDs)

CLDs were categorized into 10 major groups (**Table 1**). Polydactyly was most represented (n = 80; 48.5%), followed by syndactyly (n = 34; 20.6%), absence deformities (n = 13), musculoskeletal defects (n = 11), and brachydactyly (n = 11). The remaining five categories with low representations were leg defects, camptodactyly, clubfoot, clinodactyly, and club finger. The distributions of CLDs with respect to the sex of the index subject and subpopulation are shown in **Table 1**. The types and distribution of CLDs in the Muslim and Hindu communities were not different ($\chi^2 = 5.026$; $P = 0.83$). By contrast, there were more affected males in almost every category (male:female = 4:1).

Expressivity analyses: involvement of upper/lower limbs

In the cohort of 165 cases, a total of 315 limbs were affected; the involvement of upper limbs was more common than the lower (172 vs 143, respectively) (**Table 2**). In the affected upper or lower limbs, there was no significant preference for the involvement of the right or the left limb (**Figure 2**). However, certain individual CLDs types preferentially affected the upper or the lower limbs (and/or right or left limb). For example, polydactyly affected the upper limbs significantly more commonly than the lower limbs (88 vs 51, respectively; $P = 0.03$). Absence deformities and camptodactyly also preferentially affected the upper limbs. By contrast, brachydactyly involved the lower limbs more commonly than the upper limbs.

Table 1. Major categories of CLDs: distributions with respect to sex, subpopulation, and proportions

Limb defect	Index participants (n = 165)		Subpopulation		Total	Proportion	95% CI
	Male	Female	Muslim	Hindu			
Polydactyly	62	18	40	40	**80**	0.4848	0.4086–0.5611
Syndactyly	29	5	17	17	**34**	0.2061	0.1443–0.2678
Absence deformities	10	3	4	9	**13**	0.0788	0.0377–0.1199
Musculoskeletal defects	9	2	5	6	**11**	0.0667	0.0286–0.1047
Brachydactyly	7	4	7	4	**11**	0.0667	0.0286–0.1047
Leg defects	5		3	2	**5**	0.0303	0.0041–0.0565
Camptodactyly	4		3	1	**4**	0.0242	0.0008–0.0477
Clubfoot	4		2	2	**4**	0.0242	0.0008–0.0477
Clinodactyly	1	1	1	1	**2**	0.0121	–0.0046–0.0288
Club finger	1		1	0	**1**	0.0061	–0.0058–0.0179
Total	**132**	**33**	**83**	**82**	**165**	**1.000**	**1**

Table 2. Pattern of affected limbs and the combination of involved limbs in the study subjects

Limb defects	No. of cases (n = 165)	Total affected limbs (n = 315)	Upper limb (n = 172)		Lower limb (n = 143)		No. of cases with involvement			No. of limbs involved (n = 165)			
			RA	LA	RL	LL	Hands only	Feet only	Both	Any 1	Any 2	Any 3	All 4
Polydactyly	80	139	47	41	23	28	47	17	16	44	23	3	10
Syndactyly	34	77	16	18	22	21	12	14	8	5	21	2	6
Absence deformities	13	25	9	9	3	4	8	1	4	6	4	1	2
Musculoskeletal defects	11	25	8	6	6	5	5	3	3	3	5		3
Brachydactyly	11	20	2	2	9	7	1	9	1	4	6		1
Leg defects	5	6			1	5		5		4	1		
Camptodactyly	4	8	4	4			4				4		
Clubfoot	4	7			4	3		4		1	3		
Clinodactyly	2	4	2	2			2				2		
Club finger	1	4	1	1	1	1			1				1
Subpopulation													
Muslim	83	174	45	45	41	43	34	25	24	31	31	3	18
Hindu	82	141	44	38	28	31	45	28	9	36	38	3	5
Total	**165**	**315**	**89**	**83**	**69**	**74**	**79**	**53**	**33**	**67**	**69**	**6**	**23**

RA = right arm, LA = left arm, RL = right leg, LL = left leg

Involvement of only the upper limbs tended to be more frequent than the involvement of only the lower limbs, but the difference was not significant (79 vs 53, respectively; $P = 0.14$). Involvement of both upper and lower limbs was seen in 33 cases. In majority of the index cases, either one or only two limbs were observed to be affected (n = 67 and 69, respectively) (**Table 2** and **Figure 2**).

Involvement of limb segments

To understand the severity of the malformation, CLDs were typed with respect to the affected limb segments (stylopod, zeugopod, autopod, and digits), i.e., the more severe the malformation, the more proximally it ascended the affected limb/segments. Generally, the distal limb segments were more frequently affected than the proximal, and the autopods only were observed to be affected in 176 cases (**Figure 3**).

In the cohort from Muslim population, there was no specific preference for the involvement of any of the upper or lower limbs; however, in the Hindu subjects, upper limbs tended to be more commonly affected than the lower limbs, but the difference was not significant (82 vs 59, respectively; $P < 0.19$), (and right limb was the most affected limb) (**Table 2**). Involvement of only the hands was the most common presentation in both Muslim and Hindu samples. Furthermore, in both communities, either one or two limbs were most often involved in the CLDs. All four limbs were involved in 23 cases, while combinations of any three limbs were seen in only six cases.

Clinical subtypes

CLDs could be further subtyped into 30 entities (**Table 3**). There were four polydactyly types. Preaxial type I was highest in number (54%), followed by postaxial type A (36%). Among the syndactylies (n = 34), six distinct entities were established, and types Ia and Ic were common (n = 11 each). There were 13 cases of absence deformities, the most prominent of which were constriction rings (n = 4). There were 11 cases of musculoskeletal defects, majority of which (n = 6) had dwarfism, while other types included radial hemimelia (n = 2), and neuromuscular defects (n = 3).

Laterality and symmetry

The majority of the CLDs had bilateral presentation (n = 92; 55.8%) (**Table 3**). Among the five major categories, syndactyly was frequently bilateral (85%), followed by musculoskeletal defects (73%) and brachydactyly (64%). By contrast, absence deformities and polydactyly were generally unilateral (62% and 60%, respectively). Among the bilateral CLDs, 44 (48%) had symmetrical phenotypes. Brachydactyly exhibited symmetrical presentations most often (5/8; 71%), followed by musculoskeletal defects (63%). Polydactyly and syndactyly demonstrated symmetrical phenotypes in 50% and 45% cases, respectively (**Table 3**).

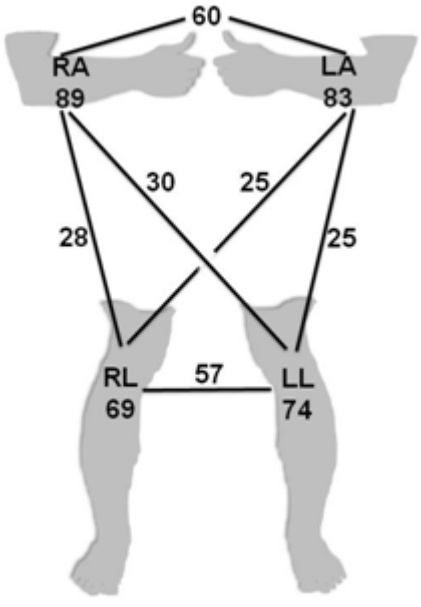

Figure 2. Schematic showing the frequency of involvement of CLDs in each limb and the combinations of two limbs involved in a malformation. (RA = right arm; LA = left arm; RL = right leg; LL = left leg)

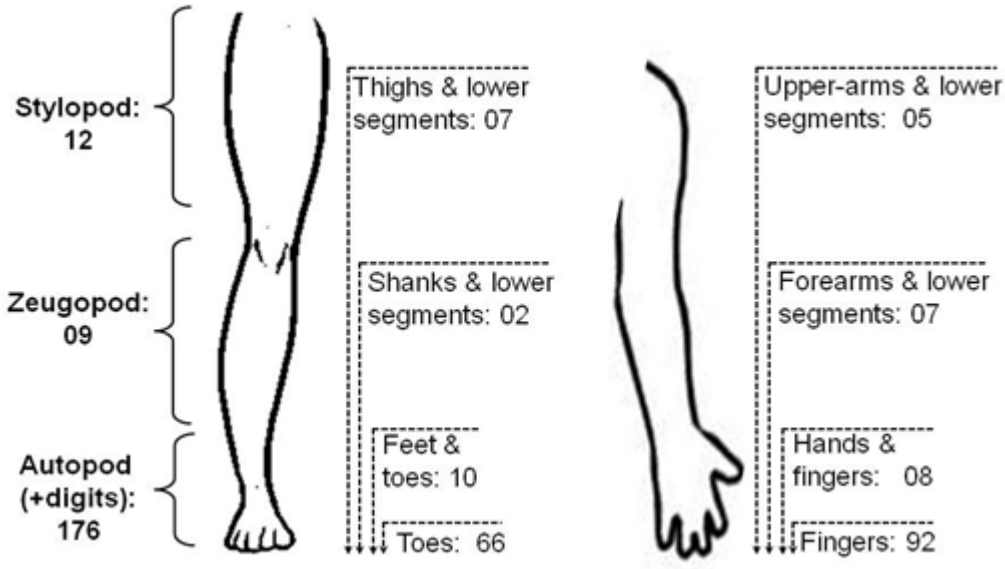

Figure 3. Involvement of different segments of limbs (stylopod, zeugopod, autopod, and digits). Composite numbers are presented for the total, upper, and lower limbs

Table 3. Clinical subtypes, laterality, and symmetry in CLDs

Limb defect	Total	Subtypes	Unilateral	Bilateral	Symm[a]
Polydactyly	80	4	48	32	16
Syndactyly	34	6	5	29	13
Absence deformities	13	5	8	5	
Musculoskeletal defects	11	4	3	8	5
Brachydactyly	11	4	4	7	5
Leg defects	5	3	4	1	
Camptodactyly	4	1		4	3
Clubfoot	4	1	1	3	1
Clinodactyly	2	1		2	
Club finger	1	1		1	1
Total	**165**	**30**	**73**	**92**	**44**

Associated anomalies among the CLDs

CLDs had isolated presentations in 85% (n = 140) of cases. There were 25 cases associated with certain type of malformations, majority of which (n = 18) involved the digit defects (data not shown). Furthermore, 31.5% participants with CLDs had a positive family history, while 68.5% cases were sporadic. In the familial cases, most of the anomalies segregated in autosomal dominant fashion (data not shown).

Demographic distribution of CLDs

The distributions of CLDs across the key demographic attributes in the gender and subpopulation specific samples were established (**Table 4**). The differences in the distributions of CLDs among Muslim and Hindu participants were statistically significant with respect to variables including district, age range, occupation, literacy, socioeconomic status, marital status, and family type ($P < 0.05$).

Table 4. Demographic distribution of 165 index subjects with CLDs (with respect to gender and subpopulation)

Demographic variable	Sex		Subpopulation		Total
	Male	Female	Muslim	Hindu	
District (n = 165)					
Tando Allahyar	66	15	38	43	81
Umerkot	21	13	8	26	34
Sanghar	16	2	12	6	18
Mirpur Khas	9	1	6	4	10
Khairpur	8	1	7	2	9
Hyderabad	6	1	7	0	7
Tando Adam	6	0	5	1	6
Total	**132**	**33**	**83**	**82**	**165**
	$P = 0.11$		$P = 0.004$*		
Origin (n = 165)					
Rural	99	21	56	64	120
Urban	33	12	27	18	45
	$P = 0.19$		$P = 0.13$		
Age range (y; n = 165)					
≤9	21	9	14	16	30
10–19	42	10	19	33	52
20–29	33	7	28	12	40
≥30	36	7	22	21	43
	$P = 0.49$		$P = 0.02$*		
Occupation (age≥ 6 y; n = 144)[a]					
Labor/manual jobs	50	11	30	31	61
Student	28	5	23	10	33
Farmer/agriculture	24	5	9	20	29
Skilled worker	14	0	8	6	14
Housewife (women)	2	5	1	6	7
	$P = 0.006$*		$P = 0.01$*		
Literacy (age≥ 6 y; n = 144)[a]					
Illiterate	50	21	25	46	71
Literate	68	5	42	31	73
	$P = 0.0004$*		$P = 0.007$*		
Socioeconomic status (n = 155)[a]					
Poor	85	21	39	67	106
Lower middle	23	8	22	9	31
Upper middle	12	2	11	3	14
Upper	4	0	3	1	4
	$P = 0.64$		$P = 0.0004$*		
Marital status (age ≥18; n = 85)[a]					
Single	29	4	30	3	33
Married	42	10	20	32	52
	$P = 0.55$		$P < 0.0001$*		
Family type/structure (n = 150)[a]					
Single	3	0	1	2	3
Nuclear	74	15	28	61	89
Extended	42	16	42	16	58
	$P = 0.15$		$P < 0.0001$*		
Mother tongue (Muslim, n = 83)					
Sindhi	40	6			46
Urdu	8	2			10
Saraiki	7	1			8
Balochi	5	3			8
Punjabi	7	1			8
Others	2	1			3
	$P = 0.58$				

Table 4. Demographic distribution of 165 index subjects with CLDs (with respect to gender and subpopulation) (Continous)

Demographic variable	Sex		Subpopulation		Total
	Male	Female	Muslim	Hindu	
Mother tongue (Hindu, n = 82)					
Marwari			33	11	44
Dhatki			17	3	20
Gujarati			9	3	12
Sindhi			5	1	6
			$P = 0.81$		
Caste systems (Muslim, n = 83)					
Baloch	5	3			8
Khanzada	6	1			7
Solangi	3	4			7
Abbasi	4	0			4
Arain	4	0			4
Khaskheli	0	4			4
Khumbhar	0	4			4
Others	20	14			34
Caste systems (Hindu, n = 82)					
Bheel			31	9	40
Menghwar			10	5	15
Kohli			8	0	8
Rathore			7	0	7
Others			8	4	12
Total	**132**	**33**	**64**	**18**	**165**

[a]Only data of these cases was available, *statistically significant ($P < 0.05$). Categories with nonzero values were employed in the analyses.

Discussion

Various epidemiological studies have made certain generalizations of CLDs [1]. For instance, CLDs occur bilaterally in around half of cases, in unilateral presentations the right and left sides are affected with approximately equal frequency, and the upper limbs are more frequently affected than the lower limbs [11, 12]. The present study iterates several of these findings. For instance, 44% cases were unilateral and 56% were bilateral, and the upper limbs were more commonly involved than the lower limbs.

Polydactyly was the predominant type of anomaly among the limb defects examined by Frias et al. [13] in Spain and Latin America. Shawky et al. [14] showed that polydactyly comprised 25% of cases of the total isolated limb anomalies. In the present cohort, polydactyly affected the upper limbs approximately 42% more commonly than the lower limbs. By contrast, syndactyly, the second most common CLD in the present cohort, was more prevalent in the lower limbs than the upper limbs. Absence defects have not been much ascertained in Pakistanis [15, 16]. Studies published elsewhere present a diverse picture. Absence defects were observed to be the largest group (25%) among Egyptian children with CLDs [14]. In the present cohort, there were 13 cases of absence defects, which affected the upper limbs more often than the lower limbs. Swinyard and Pinner [11] noted in a series of limb-reduction defect cases in the United States that when only one limb was affected, it was the arm only in 85% of the cases. They also found that the left side was affected nearly twice as often as the right.

CLDs had isolated presentations in 85% of the cases in the present study. In the experience of Shawky et al. [14], isolated anomalies were 39% of the 140 CLDs. Population based studies have demonstrated that limb defects are the most frequent associations with neurological and cardiac malformations [1, 3]. Such malformations may provide insights into limb development that may be useful for etiologic studies and public health monitoring.

The pattern of limb anomalies is quite variable in different populations [1]. The current analyses revealed that sex-specific differences in the distribution of CLDs across most of the sociodemographic variables of the Sindhi population were not significant (with the exception of occupational status and education). However, differences were highly significant in several variables when subpopulation-specific data were analyzed, demonstrating disparities in the sociodemographic attributes in the Muslim and Hindu samples. There were differences in the samples with respect to geographic origin, age, occupation, and marital status. There was high representation of literate participants in the sample obtained from Muslim community compared to Hindus where illiterate participants were common. Likewise, with respect to socioeconomic status, majority of the Hindu participants belonged to 'poor' category; most common family type in Muslims was 'extended' type compared with 'nuclear family' in Hindus.

However, differences in the distribution of CLDs were not obvious in either community. According to the most common tradition, Muslims in Sindh are either converts at the arrival of Arabs in 8th century, or immigrated after the partition of the Indo-Pakistani subcontinent in 1947 [12]. Hindus are the representatives of the most ancient settlers of this region and are ethnically and linguistically quite distinct from the Muslim majority. The biosocial structure of the Hindu community is also distinct because of the lack of consanguineous marriages, which may be a contributory factor in the incidence of morbidity/mortality in the Muslim populations (at least for the recessively segregating disorders). However, no statistically significant differences were witnessed between these communities with respect to the distribution of CLDs. The similar pattern of morbidity may suggest common genetic and nongenetic etiologies in both populations. This scenario may further necessitate similar patterns of genetic burden in both. Secondly, sporadic CLDs, which are major representations in both sample types may also have common environmental etiologies. Alternatively, consanguineous marriages, which are exclusively present in the Muslim community, are likely to have changed the genetic structure of this population. Higher consanguinity is known to be associated with elevated prevalence of recessively segregating disorders [17]. However, the majority of the CLDs observed in this study were segregating autosomal dominantly, and are less likely to be influenced by consanguineous marriages. Further studies at molecular genetic levels are warranted to explore the genetic burden in both communities and to explore their affinities.

Towards the elucidation of etiological factors of CLDs it would be pertinent to conduct a molecular genetics study on the recruited individuals and families. The results of that prospective study would not only complement the clinical and phenotypic categorization of these limb malformations, but would also be of tremendous help to the respective individuals and families in risk estimation and genetic counseling.

Acknowledgments

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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