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REVIEW ARTICLE

Nosology of genetic skeletal disorders, Pakistan: an updated review

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ABSTRACT

Genetic skeletal disorders (GSDs) are heritably and clinically varied classes of bone and cartilage anomalies, characterized by irregular growth/development of the skeleton. They are rare, but their cases may be upraised with endogamy as it increases homozygosity. Pakistan has the highest rate (55%-60%) of consanguinity, which is quite worrying. Still, Pakistan has no reliable data (geographical prevalence, clinical, and epidemiological data) associated with GSDs and other rare genetic disorders. Unfortunately, due to the lack of adequate clinical/diagnostic resources and genetic knowledge, the suspected cases of genetic disorders are misdiagnosed and hence mistreated, thus, causing psycho-socioeconomic problems. The present study reviewed current literature, published on several Internet databases including the "Nosology of GSDs: (2023 Revision)" from Pakistan. GSDs such as acromesomelic dysplasia, mucopolysaccharidosis, polydactyly, synpolydactyly, and split hand/split foot malformation were reported in several families and have 55.04% of all the reported GSDs from Pakistan. To date, in the literature, 72 different mutated genes have been reported from the Pakistani community. This review will help clinicians and researchers in understanding, diagnosis, and management of GSDs and will offer a descriptive approach to carry out fruitful molecular genetic research in genetically vulnerable and low-resource regions. Moreover, it will also speed up the possible therapy development and may insist the stakeholders to establish a multi-level network to find a path towards the healthcare challenges of GSDs from Pakistan.

Keywords: Prevalence, genetic skeletal disorders, skeletal dysplasia, Pakistani population.

Background

Genetic/hereditary skeletal disorders (GSDs) represent a diverse set of clinical/genetical conditions that arise from the mutations in different candidate genes resulting in disturbances of complex skeletal pathways of growth, development, and homeostasis. In contrast to the prevalent diseases, GSDs are rare and affect a very small fraction of people. However, due to the advent of next-generation sequencing (NGS) technologies, novel candidate genes are reported on a daily basis which has increased the number of rare genetic disorders (RGDs) and is thus currently recognized as one of the most significant global public health issues (1).

In developing countries, there are a number of difficulties like limited advanced clinical resources, and no or far localized genetic services centers, which hampered research and managing studies for GSDs. The proper diagnosis of GSDs is always a challenge because a variety of syndromic and nonsyndromic forms of GSDs affect a large number of people around the world, resulting in substantial healthcare costs and low quality of life (2,3). Despite numerous international initiatives to address the GSDs-associative problems, considerable work still needs to be done to deal with this ignored health sector, especially in Pakistan (4).

In recent times, advanced high-throughput, sequencing technologies such as whole genome sequencing and whole-exome sequencing have greatly increased our understanding of GSDs. The majority of the variants/mutations listed in Table 1 are identified by using recent advanced technology like NGS and with parallel Sanger sequencing method. Though 80% of rare disorders have a genetic origin and significant advances/discoveries are made every day, but still, approximately 65%-70% of causing genes/factors still need to be identified (5).

The nosology classification-2023 revision has classified the 771 different GSDs into 41 groups, on the basis of clinical, molecular, and radiographic diagnostics criteria, while only 552 genes have been associated with RGDs.

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Table 1. *Up-to-date reported mutations and their candidate genes causing GSDs within the Pakistani community.*

Gene name	Phenotype/Disorder	MIM	Total number of variants	Exact alteration in the DNA/Protein	Mode of inheritance	Homo/ Hetero	Reference
ALX1	FND1 (Frontonasal dysplasia)	136,760	5	c.661-1G>C; p.(?)	AR	Homo	(6)
ALX3	FND1	136,760	3	c.604 C>T; p.(Gln202*)	AR	Homo	(7)
BBS1	BBS1 (Bardet-Biedl syndrome1)	616,981	3	c.1339 G>A; p.(Ala447Thr), c.951+1G>A; p.(?)	AD	Homo	(8)
BBS2	BBS2 (Bardet-Biedl syndrome2)	616,981	1	c.443A>T; p.Asn148Ile	AR	Homo	(9)
BBS5	BBS5 (Bardet-Biedl syndrome5)	616,981	1	c.196delA; p.Arg66Glufs*12	AD	Homo	(8)
BHLHA9	MSSD	609,432	3	c.252_270delGCA; p.(Phe85Glufs*108)	AR	Homo	(10)
BHLHA9	MSSD	609,432	5	c.211A>G; p.(Asn71Asp), c.218G>C; p.(Arg73Pro), c.211A>G; p.(Asn71Asp)	AR	Homo	(10)
BHLHA9	MSSD	609,432	4	c.311T>C; p.(Ile104Thr)	AR	Homo	(10)
BHLHA9	MSSD	609,432	3	c.409-409 deletion C p.(His137Thrfs*61)	AR	Homo	(10)
BBIP1	BBS18 (Bardet-Biedl syndrome-18)	616,981	1	c.160A>T; p.(Lys54Ter)	AR	Homo	(8)
BMPR1B	AMDG (Acromesomelic dysplasia)	200,700	3	c.657 G>A; p.(Trp219*)	AR	Homo	(11)
BMPR1B	AMD3 (Acromesomelic dysplasia 3)	201,250	2	c.1190T>G; p.(Met397Arg)	AR	Homo	(10)
Chr 13	PAPA5	263,450	5	Locus on chromosome 13q13.3-q21	AR	Homo	(10)
CC2D2A	JBTS9 (Joubert syndrome 9)	612,285	1	c.4417C>G; p.Pro1473Ala	AR	Homo	(12)
CHST3	SEDCJD	603,799	12	c.802G>T; p.Glu268*	AR	Homo	(10)
CHST3	SEDCJD	603,799	4	c.590T>C; p.(Leu197Pro)	AR	Homo	(13)
CHSY1	TPBS	605,282	3	c.1897 G>A; p.(Asp633Asn)	AR	Homo	(14)
CLCN7	OPTB4	611,490	3	c.610 A>T, c.612 C>G; p.(Ser204Trp)	AR	Homo	(15)
CLCN7	OPTB1 (Osteopetrosis)	259,700	2	c.2416T>A; p.*806Argext*58	AR	Homo	(16)
COL1A1	OI1 (Osteogenesis imperfecta 1)	166,200	1	c.1012G>A; p.Gly338Ser	AR	Homo	(17)
COL10A1	MCDS	156,500	14	c.2011T>C; p.(Ser671Pro)	AD	Hetero	(18)
COL10A1	MCDS	156,500	6	c.133C>T; p.(Pro45Ser)	AD	Hetero	(10)
COMP	PSACH (Pseudoachondroplasia)	177,170	16	c.1423 G>A; p.(Asp475Asn)	AR	Homo	(19)
CTSK	PYCD (Pycnodysostosis/ Osteopetrosis)	265,800	4	c.136C>T; p.(Arg46Trp) c.136C>T; p.(Arg46Trp) c.266_268 del; p.(Lys89del), c.136 C>T; p.(Arg46Trp)	AR	Homo and compound heterozygous	(20)
CTSK	PYCD	265,800	2	c.935C>T; p.(Ala277Val)	AR	Homo	(21)
CTSK	PYCD	265,800	3	c.728G>A; p.(Gly243Glu)	AR	Homo	(22)
DLX5	SHFM	183,600	3	c.482-485dupACCT; p.(Ala163Profs*55)	AD	Hetero	(23)

Continued

Gene name	Phenotype/Disorder	MIM	Total number of variants	Exact alteration in the DNA/Protein	Mode of inheritance	Homo/ Hetero	Reference
DLX6	SHFM	183,600	3	c.632 T>A p.(Val211Glu)	AD	Hetero	(24)
DYM	DMC	223,800	1	c.59T>A; p.(Leu20*)	AR	Homo	(25)
DYM	DMC	223,800	1	c.1205T>A; p.(Leu402Ter)	AR	Homo	(26)
DYM	DMC	223,800	1	c.95_96insT; p.(W33Lfs*14)	AR	Homo	(27)
EPS15L1	SHFM	183,600	3	c.409 deletion A; p.(Ser137Alafs*19)	AR	Homo	(2)
ESCO2	RBS (Roberts syndrome)	268,300	1	c.879_880delAG; p.(Arg293fxX299)	AR	Homo	(28)
EVC	EVC (Ellis–van Creveld syndrome)	225,500	3	c.617G>A; p.(Ser206Asn)	AR	Homo	(10)
EVC	EVC	225,500	1	c.1932_1946dupAGCCCTCCGGAGGCT	AR	Homo	(10)
EVC	EVC	225,500	1	c.731_757del, c.731_757delTCCTTGACCTTCTTCCTAAAAAGAAGT	AR	Homo	(29)
EVC2	EVC	225,500	1	c.702G>A; p.(Try234*)	AR	Homo	(30)
EVC2	EVC	225,500	4	c.30dupC; p.(Thr11Hisfs*45)	AR	Homo	(31)
EXT1	EXT	133,700	22	IVS1 ds +1G-C	AD	Hetero	(10)
EXT1	EXT	133,700	1	c.247delC; p.(Arg83Gly)	AD	Hetero	(32)
FAM92A	PAPA9A	618,219	4	c.478C>T; p.(Arg160*)	AR	Homo	(33)
FBN1	MFS	154,700	15	c.2368 T>A; p.(Cys790Ser)	AD	Hetero	(34)
FBN1	MFS (Marfan syndrome)	134,797	1	c.1402A>G; p.Tyr468Ala	AD	Hetero	(35)
FGFR1	ACH (Achondroplasia)	100,800	1	c.2407C > A; p.Pro803Thr	AD	Hetero	(36)
FGFR3	ACH	100,800	1	c.1779C > G, p.F539L	AD	Hetero	(37)
FGFR3	ACH	100,800	4	c.1138 G>A p.(Gly380Arg)	AD	Hetero	(38)
FGFR3	ACH	100,800	2	c.1144 G>A p.(Gly382Arg)	AD	Hetero	(39)
FKBP10	OI11 (Osteogenesis imperfecta 11)	607,063	7	c.1490 G4A p.(Trp497*), c.344G4A; p.Arg115Gln, and c.831dupC; p.Gly278ArgfsX295	AR	Homo	(40)
GALNS	MPS4A (Mucopolysaccharidosis 4A)	612,222	18	p.(Phe216Ser), p.(Met38Arg), p.(Ala291Ser), p.(Glu121Argfs*37), p.(Pro420Arg), p.(Arg386Cys)	AR	Homo	(10)
GALNS	MPS4A	612,222	1	c.697G>A, p.Asp233Asn	AR	Homo	(41)
GDF5	AMDG (Grebe chondrodysplasia)	200,700	5	c.157_158dupC; p.(Leu53Profs*41), c.872G>A; p.(Trp291*)	AR	Homo	(42)
GDF5	AMDG	200,700	3	c.527 T>C, c.1114 ins GAGT	AR	Homo	(10)
GDF5	AMDG	200,700	1	c.527 T>C, c.1114 ins GAGT	AR	Homo	(10)

Continued

Gene name	Phenotype/Disorder	MIM	Total number of variants	Exact alteration in the DNA/Protein	Mode of inheritance	Homo/ Hetero	Reference
GDF5	BDC (Brachydactyly type C)	113,100	4	c.527 deletion T; p.(Leu176Argfs*17)	AD	Hetero	(43)
GDF5	AMDG	200,700	1	c.404delC; p.(Pro135Gln*12	AR	Homo	(44)
GLB1	GM1G2	230,600	2	c.881-882 dele AT; p.(Tyr294Terfs)	AR	Homo	(45)
GLI1	PAPA8A	618,123	5	c.337 C>T; p.(Arg113*)	AR	Homo	(46)
GLI1	PPD1 (Pre-axial polydactyly)	174,400	3	c.1517 T>A; p.(Leu506Gln)	AR	Homo	(47)
GLI1	PD1 (Polydactyly)	174,400	1	c.1133 C>T; P.(Ser378Leu)	AR	Homo	(48)
GLI1	PAPA8	165,220	1	c.1064 C>A; p.(Thr355Asn	AD	Hetero	(49)
GLI3	PAPA14	174,200	21	c.3635 dele G; p.(Gly1212Alafs*18)	AD	Hetero	(50)
GLI3	GCPS	175,700	5	c.434-435 Inse G; p.(Tyr146Leufs*19), c.295-295 dele G; p.(Glu99Serfs*60), c.1622C>G;p.Thr541Arg; c.2374C>T; p.Arg792*	AD	Hetero	(51)
GLI3	GCPS	175,700	3	c.3790_3791 Inse C, p.(Gly1236Argfs*, c.1692A > G, p.(His536Arg, c.1965_1966delAT; p.(His627Glufs*48	AD	Hetero	(52)
GLI3	PAP	174,200	1	c.3567_3568insG; p.Ala1190Glyfs*57	AD	Hetero	(53)
GNPNAT1	RHZDAN (Rhizomelic dysplasia)	619,598	1	c.226G>A; p.Glu76Lys	AR	Homo	(54)
HOXD13	SPD1 (Synpolydactyly 1)	186,000	14	c.742 C>T; p.(Gln248X)	AD	Hetero	(55)
HOXD13	SPD1 (Synpolydactyly 1)	186,000	60	c.184_210 dup, c.187_207 dup	AD	Hetero	(10)
HOXD13	SPD1 (Synpolydactyly 1)	186,000	1	c.969G>T; p.Trp323Cys	AD	Hetero	(56)
HPGD	PHOAR1	259,100	3	c.577 T>C ;p.(Ser193Pro)		Homo	(15)
IDUA	MPS (Mucopolysaccharidosis)	607,014	11	p.(Leu490Pro)	AR	Homo	(10)
IDUA	MPS (Mucopolysaccharidosis)	607,014	2	c.1456 G>T; p.Glu486*, c.1469T>C; p.Leu490Pro	AR	Homo	(57)
IDUA	MPS (Mucopolysaccharidosis)	607,014	6	c.908T>C; p.L303P	AR	Homo	(58)
IFT27	BBS (Bardet-Biedl syndrome)	616,981	1	c.94C>T; p.Gln32Ter	AR	Homo	(8)
IQCE	PAPA7	617,642	5	c.395-1G>A	AR	Homo	(2,59)
KIAA0825	PAPA1	618,498	1	c.50T>C; p.Leu17Ser	AR	Homo	(60)
KIAA0825	PAPA10	618,498	1	c.143 deletion G; p.Cys48Serfs*28	AR	Homo	(61)
LRP4	CLSS	212,780	6	c.316+1 G>A	AR	Homo	(62)
LRP4	CLSS	212,780	10	c.2858 T>C; p.(Leu953Pro)	AR	Homo	(63)
LRP4	CLSS	212,780	1	c.1151A>G; p.(Tyr384Cys)	AR	Hetero	(10)
LRP4	CLSS	212,780	3	c.295G>C; p.Asp99His, c.1633C>T; p.(Arg545Trp	AR	Homo	(64)

Continued

Gene name	Phenotype/Disorder	MIM	Total number of variants	Exact alteration in the DNA/Protein	Mode of inheritance	Homo/ Hetero	Reference
LZTFL1	BBS17 (Bardet-Biedl syndrome17)	616,981	1	c.505A>T; p.Lys169Ter	AR	Homo	(8)
MATN3	SEMD	602,109	2	c.542G > A, p.Arg181Gln	AR	Homo	(65)
MKKS	BBS6 (Bardet-Biedl syndrome6)	616,981	1	c.775delA; p.Thr259Leufs*21c.119C>G; p.Ser40*	AD	Homo	(66)
MKS1	JBTS (Joubert syndrome)	617,121	7	c.272_285 deletion ACGACCGCCTGGCA; p.(Asn91Ilefs*28)	AR	Homo	(10)
NOTCH2	HJCYS (Hajduv Cheney syndrome)	102,500	1	c.6426_6427 insertion TT; p.(Glu2143Leufs*5)	AD	Hetero	(67)
NPR2	AMDM	602,875	6	c.872 A>G; p.(Gln291Arg)	AR	Homo	(68)
NPR2	AMDM	602,875	15	c.2720 C>T; p.(Thr907Met) c.2986+ 2 T>G	AR	Homo	(69)
NPR2	AMDM	602,875	8	c.1801C>A; p.(Arg601Ser); c.2245C>T; p. (Arg749Trp), c.2986+2 T>G	AR	Homo	(70)
NPR2	AMDM	602,875	1	c.613 C>T, p.R205X	AR	Homo	(71)
OSTM1	OPTB1 (Osteopetrosis)	259,700	1	c.124del; p.Val42Serfs*57	AR	Homo	(10)
PAPSS2	SEMDJL	271,530	1	c.1037G>C; p.R346P	AR	Homo	(72)
PCNT	MOPDII	210,720	1	c.6176_6189delGTC AGC TGC CGA AG;p. Gln2060ArgfsTer48	AD	Hetero	(10)
PRG4	CACP	208,250	11	c.2816_2817 deletion AA; p.(Lys939fsX38)	AR	Homo	(10)
RAB33B	MOPDII	210,720	1	c.174delC; p.Asp60ThrfsTer7	AD	Hetero	(10)
RMRP	CHH (Cartilage-hair hypoplasia)	250,250	2	g.70 A>G	AR	Homo	(73)
ROR2	BDB1 (Brachydactyly type B1)	113,000	11	c.2278 C>T; p.(Gln760*)	AD	Hetero	(74)
SP7	OI12 (Osteogenesis imperfecta 12)	613,848	1	c.824G >A; p.Cys275Tyr	AR	Homo	(75)
SERPINF1	OI6 (Osteogenesis imperfecta 6)	613,982	1	c.397C>T; p.Gln133*	AR	Homo	(76)
SERPINF1	OI 6	613,982	1	c.262_263insCCCTCTC; p.Ala91Profs*23	AR	Homo	(77)
SLCO2A1	PHOAR	259,100	1	c.664G>A; p.Gly222Arg	AR	Homo	(40)
SPARC	OI17 (Osteogenesis imperfecta 17)	616,507	1	c.497G>A; p.Arg166His	AR	Homo	(78)
STKLD1	PPD (Pre-Axial polydactyly)	174,400	3	c.84C>A; p.(Tyr28*)	AR	Homo	(79)
TBX2	OCD (Osteochondrodysplasia)	616,897	1	c.529A>T; p.(Lys177*)	AD	Homo	(80)
TCIRG1	OPTB1 (Osteopetrosis 1)	259,700	2	c.624 deletion C; p.(Pro208fsX)	AR	Homo	(10)
TCIRG1	OPTB1	259,700	7	c.515G>A; p.(Gly172Asp), c.854_855 del; p.(Val285Alafs*204), c.2416 T>A; p.(*806Argext*58), c.971 dup; p.(Cys324Trpfs*166)	AR	Homo	(10,16)

Continued

Gene name	Phenotype/Disorder	MIM	Total number of variants	Exact alteration in the DNA/Protein	Mode of inheritance	Homo/ Hetero	Reference
TMEM67	MKS3 (Meckel syndrome 3)	607,361	2	c.1575+1G>A, c.870-2A>G	AR	Homo	(81)
TP63	SHFM	225,300	1	c.956G>A; p.(Arg319His)	AD	Hetero	(82)
TRPS1	TRPS3	190,351	6	c.2762 G>T; p.(Gly921Val)	AD	Hetero	(10)
TRPS1	TRPS3	190,351	4	c.2762 G>A; p.(Arg921Gln)	AD	Hetero	(5)
WDPCP	BBS15 (Bardet-Biedl syndrome 15)	616981	2	c.720 C>A; p.Cys240Ter	AR	Homo	(8)
WNT1	OI15 (Osteogenesis imperfecta 15)	615,220	7	c.1168 G>T; p.(Gly324Cys)	AR	Homo	(83)
WNT1	OI15	615,220	3	c.359-3C>G	AR	Homo	(2)
WNT1	OI15	615,220	1	c.359-3C>G, c.677 C>T; p.(Ser226Leu)	AR	Homo	(57)
WNT10B	SHFM	225,300	5	c.460C>G; p.(Gln154*), c.300_306 dup AGGGCGG; p.(Leu103Argfs*53)	AR	Homo	(84)
WNT10B	SHFM	225,300	7	c.1165_1168delAAGT, c.300_306 dupAGGGCGG	AR	Homo	(10)
WNT 10B	SHFM	225,300	1	c.1098C>A; p.(Cys366∗)	AR	Homo	(85)
WNT 10B	SHFM	225,300	2	c.338G>A; p.(Gly113Asp), c.884-896delTCCAGCCCCGTCT; p.(Phe295Cysfs*87)	AR	Homo	(77)
WNT10B	SHFM	225,300	9	c.986C>G; p.(Thr329Arg)	AR	Homo	(10)
Xq26.3 loci	SHFM2	313,350	35	Gene position on chromosome Xq26.3	X linked	----------	(10)
ZNF141	PAPA6A	615,226	3	c.1420 C>T p.(Thr474Ile)	AR	Hetero	(10)
ZRS	PPD, PSD, PAPD, TPT (Pre-axial polydactyly, syndactyly, postaxial-polydactyly and triphalangeal thumb)	605,522	14	Intrinsic ZRS 287 C>A	AD	Hetero	(10)
ZRS	TPT/PPD (Triphalangeal Thumb/ Preaxial polydactyly)	605,522	13	Intrinsic ZRS 463 T>G	AD	Hetero	(10)

Table 2. *Province-wise number of GSDs reported and published from each province of Pakistan.*

Province	Total GSDs reported	Percent of total GSDs (%)
Punjab	247	40.56
Sindh	219	35.96
Khyber Pakhtunkhwa	116	19.05
Kashmir	19	3.12
Balochistan	8	1.31
Gilgit-Baltistan	0	0.00

The entire number of GSDs increased to 771 from 461 and the number of genes to 552 from 437; however, groups decreased from 42 to 41 due to regrouping and restructuring in the review of nosology-2023 classification (86).

The nosology classification-2023 revision is more helpful in the identification of novel skeletal disorders and provides an excellent framework for a better understanding of the underlying mechanisms essential for regular skeletal growth, maintenance, and development (86). Based on the nosology classification-2023 revision, this is our second effort at population research studies to display the prevalence and pervasiveness of GSDs in Pakistan (10).

The reasons that stimulate us to compile and publish a second revision of GSDs is to facilitate research and diagnosis by sharing fresh knowledge about the growing number and variety of GSDs. Commonly in Pakistani society, GSD has an autosomal dominant or recessive mode of inheritance.

Skeletal dysplasia

Skeletal dysplasia is the heterogeneous camp of RGDs occurrence rate of 1 in every 5,000 live births (87). Mutations in several genes are associated with skeletal disorders that might affect the development, structure, or function of the skeletal system. They may have autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive or as a de novo mode of inheritance (87). GSDs display varied clinical conditions ranging from a particular organ to multisystematic disorder and are due to defects/mutations in a variety of gene families, including genes encoding transcription factors, extracellular matrix proteins, tumor suppressors, ligands, channel proteins, receptors, enzymes, cellular transporters, intracellular binding and morphogenic proteins, chaperones, RNA processing molecules, cytoplasmic proteins, cilia, and others. Moreover, exposure to teratogen, somatic mosaicism, and imprinting errors may lead to GSDs (87).

In practice, the distinction between different types of skeletal disorders is often implausible due to analogous disease patterns including radiographic and molecular findings and clinical manifestation. GSDs may be classified as skeletal dysplasia or dysostoses on the basis of anomalies in pattern, differentiation, linear development, and maintenance of skeletal tissues (88,89). Skeletal dysplasia is a broad term referring to abnormalities of bone and cartilage that result in unbalanced stature, size, and shape of the skeleton. They primarily affect the development of cartilage and bone (due to the mutation in genes regulating the development, growth, and maintenance of bone/cartilage) but muscles, tendons, and ligaments may also be affected (89,90). On the other hand, dysostosis refers to anomalies in the ossification of one or more bones due to mutation of genes involved in skeletal patterning. They often occur in conjunction with other inherited disorders in the form of spondylocostal dysostosis, cleidocranial dysostosis, and limb deformities such as polydactyly, brachydactyly, and syndactyly (91,92).

To categorize the newly reported genes and disorders, the International Skeletal Dysplasia Society completed its most recent revision in 2023, which revealed a novel molecular and pathological concept of GSDs. In their recent analysis, Unger et al. (86) divide 771 disorders into 41 groups with only 552 known associated candidates' genes.

The present study is coping with sufficient and to-date information on GSD phenotypes reported by the Pakistani community and has systematically evaluated them. The appraisal also comprehensively analyzed, explored, and emphasized all the challenges and concerns associated with accurate diagnosis and proper treatment of GSDs, especially life-threatening GSDs.

Methodology

The current study covered and reported all 552 known GSD candidates' genes, which were grouped into 41 categories in the "Nosology of GSDs (2023 revision)."

Research approaches

All reported GSD genes were obtained from the "Nosology of GSDs (2023 revision)." The search was conducted by entering the mesh "gene name" and "Pakistan" by using various online accessible databases and search browsers such as OMIM, Google Scholar, PubMed, HMGD, and Research Gate.

Results

In the existing literature, 559 cases of GSDs are documented in 21 different groups of the "Nosology of GSDs (2023 revision)" from the Pakistani community. Table 1 lists details of all the pathogenic mutations reported from the Pakistani community till now. SHFM, Synpolydactyly, Polydactyly, Acromesomelic dysplasia/ short-limb dwarfism (AMDH, AMDG, AMDM), and Glycosaminoglycans (Mucopolysaccharidosis) are five most reported GSDs, accounting for 14.19%, 13.18%, 11.51%, 7.8%, and 5.5%, respectively (Tables 1 and 2). Figure 1A and B illustrates the geographical prevalence of GSDs in Pakistan. However, this time a significantly higher number of cases were reported from the Punjab province (40.56%), compared to the GSD 2019, in which Sindh province was at the top with 40.38% GSD cases and Punjab was second with 39.04 of all the cases. All the

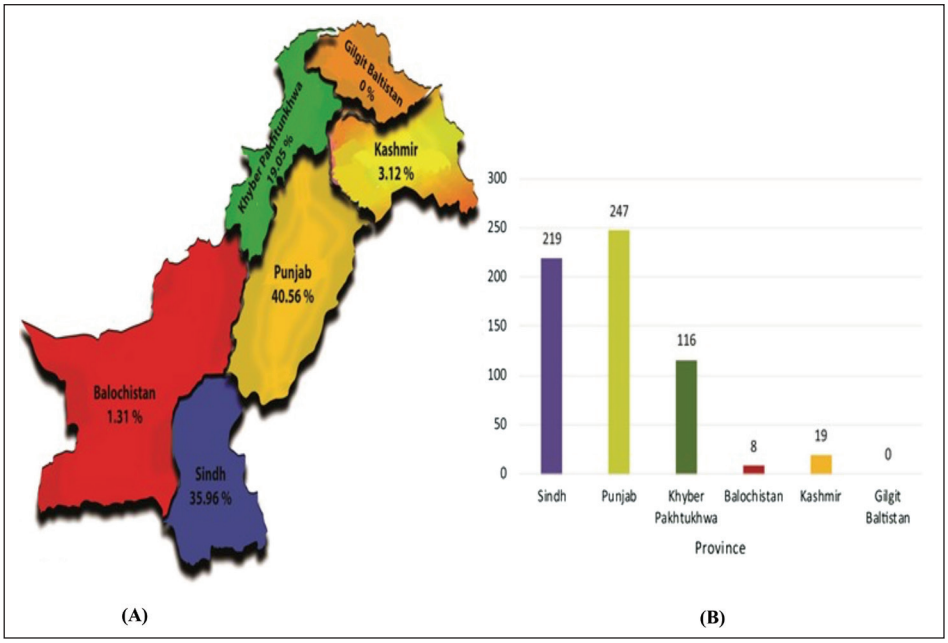

Figure 1. *(A) Provinces-wise percent prevalence of hereditary skeletal disorders reported and published from Pakistan. (B) Number-wise graphical representation of different GSDs reported from Pakistani provinces. Punjab province is showing the highest reports.*

numbers and details of GSDs reported so far from each province (Pakistan) have been listed in Table 2.

Discussion

The term GSD is commonly used to describe bone and cartilage abnormalities. It is a very heterogeneous class of anomalies that result from the mutations of numerous genes, causing disruption in the organization and function of the growth plate. It can range from mild (polydactyly, and so on) to severe/lethal (thoracic hypoplasia, and so on) and from nonsyndromic to syndromic. Genotypically, GSD has both dominant (autosomal/X-linked) and recessive (autosomal/X-linked) forms of inheritance. Keeping in mind the challenges of the precise diagnosis and evaluation of the GSDs, it is important to obtain family history, physical examination, a full set of skeletal radiographs/photographs, audiogram, magnetic resonance imaging, and complete medical records (93).

Currently, Pakistan is the 5th most populous country in the world (241.49 million with a growth rate of 2.55% (census 2023); having five provinces (Balochistan, Gilgit-Baltistan, Khyber Pakhtunkhwa Punjab, and Sindh), and Pakistan administered territories of Azad Jammu and Kashmir (4.045 million populations (census 2017). All GSD cases reported from Pakistan to date include Punjab (40.56%), Sindh (35.96%), KPK (19.05%), Balochistan (1.31%), and Kashmir (3.12%), while from Gilgit-Baltistan still no case has been reported (Figure 1A and B).

Although very little information is available about the prevalence of genetic disorders in Pakistan, the statistics from Europe and golf countries point to a concerning situation for Pakistan, as cousin marriage drastically increases genetic disorders and Pakistan has the highest rate of cousin marriage. For example, Europe has less than 1% cousin marriages with 1/5,000 live births affected by a genetic disorder, while Qatar has 54% consanguinity with 1/1,300 affected birth individuals (94).

According to studies, cousins marry each other in about 55%-60% of marriages in the nation. Numerous cultural, social, and economic factors contribute to this high prevalence. The prevailing cultural and societal norms in Pakistan that encourage cousin marriages are a major contributing factor to the high number of these marriages. In many cultures, getting married within the extended family is seen as a means of preserving inherited wealth and ties to the family. Cousin marriages are also frequently viewed as the best option because of their apparent compatibility and shared morals. However, there are certain negative consequences associated with the prevalence of cousin marriages in Pakistan, including economic burdens. Consanguineous marriages can lead to an increased risk of genetic disorders and disabilities in offspring. Research has shown that the children of cousin marriages are more likely to suffer from birth defects, developmental delays, and other hereditary conditions (85). In addition, the majority of mutations found in the Pakistani population are biallelic; however, heterozygous mutations are also common.

According to Umair (5), 65%-70% of casual genes of RGDs have to be identified; moreover, recently the "Nosology of GSDs (2023)" has reported many novel GSDs worldwide. Developing countries like Pakistan, where 60% of people are below the line in poverty, have no concept of proper testing and have no database or any other organization for the entry and registration of RGDs including GSDs. Even though, the Pakistani population has a high rate of consanguineous marriage, researchers and physicians have little to no documented information.

The current analysis reveals that in the last two decades number and kind of GSDs in Pakistan have rapidly increased due to the powerful NGS screening technologies. Especially, in the last 10 years publications and reports about genetic rare disorders have increased by 99%. That is why GSDs and their causing genes/ mutations have a relatively high novelty rate reporting from Pakistan. The aim of this revision is to provide bridges among clinicians, scientists, and genetics interested in GSDs and in skeletal biology, through the list of GSDs and their causative genes, mutations, pathways, and other associated spectrums. Moreover, it will also ensure a proper diagnosis, as this review holds the treasure of detail and novel information on GSDs (95).

GSDs are a complicated and diverse set of disorders caused by 552 different genes, making it very challenging to identify the exact disorder (5). Monogenetic disorders are very rare but it is helpful to identify the specific gene function and to track down its associated molecular pathways. Studying the pathogenicity of various mutations that occur in different genes sheds light on the potential prevention measures, diagnostic tools, treatment, and a necessary step for providing correct genetic counseling. In modern times, there has been significant progress in molecular/genetic diagnosis (such as NGS, and so on) to confirm clinical/radiographic diagnosis and to predict the risk level of a family for GSDs. Moreover, targeting these molecular pathways has encouraging results both *in vitro* and *in vivo* even though these therapies are still under the research and developmental stage (84).

Despite the paucity of research on GSDs in Pakistan, efforts have been made to comprehend, diagnose, and treat these severe conditions. Pakistan's medical community has been actively involved in the diagnosis, treatment, and management of patients with skeletal dysplasias and other genetic conditions. A significant obstacle in carrying out investigations on GSDs in Pakistan is their uncommon occurrence, which makes it hard to locate enough afflicted people for thorough examinations. Precise diagnosis and treatment of these disorders are further complicated by the fact that certain areas of the nation lack access to specialized genetic testing facilities and knowledge.

The future management of GSDs is likely to be influenced by advancements in genetics, molecular biology, and medical technology. Potential developmental areas that can improve our understanding include precision medicine, CRISPR-Cas9-based gene therapy, stem cell therapies, pre-genetic testing, and early interventions (83,94).

Future studies may focus on the discovery of therapy for GSDs by finding new therapeutic drugs that more specifically affect this integrated signaling network and enhance the delivery of therapeutics to the growth plate. Moreover, in Pakistan, a sound medical policy and establishing robust collaborative partnerships abroad is required. At each big city, a department for genetic counseling through the multidisciplinary approach (including orthopedists, rheumatologists, otolaryngologists, gynecologists, neurologists, ophthalmologists, and so on, having genetically knowledge and experience) should be established for RGDs. This would considerably reduce the likelihood of misdiagnosis and will make it easy to enhance treatment for patients of RGDs.

Conclusion

In conclusion, the main goal of the present systematic revision is to summarize the detailed information on the rare and ultra-rare GSDs on the number, geographic, and molecular genetic bases affecting the Pakistani community. Thus, updating the current literature of GSDs in Pakistan according to the recent nosology classification 2023 (5). Where, it will provide an exact roadmap to proper diagnosis, awareness, and approaches to successful molecular research, as well as it will elaborate on the pathological mechanism of GSDs. Furthermore, it will also accelerate understanding of the potential therapy development and will urge researchers, geneticists, clinicians, and other policymakers to establish a multilevel network organization that might offer a proper solution to diagnosis, treatment, and care to patients suffering from GSDs in Pakistan.

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List of Abbreviations

ACH	Achondroplasia
AMDH	Acromesomelic dysplasia Hunter–Thompson
AMDG	Acromesomelic dysplasia Grebe type
AMD	Acromesomelic dysplasia
AMDM	Acromesomelic dysplasia type Maroteaux
BBS	Bardet-Biedl syndrome
BDB1	Brachydactyly type B1
BDC	Brachydactyly type C
CHH	Cartilage-hair hypoplasia
CLSS	Cenani-Lenz syndactyly syndrome with oro-facial and skeletal symptoms
DMC	Dyggve-Melchior-Clausen disease
EVC	Ellis–van Creveld syndrome
EXT	Multiple hereditary exostoses
FND	Frontonasal dysplasia
GCPS	Greig cephalopolysyndactyly syndrome
GM1G	Infantile GM1 gangliosidosis
GSDs	Genetic skeletal disorders
HJCYS	Hajduv Cheney syndrome
HMGD	Health Ministers Discretionary Grant
ISDS	International Skeletal Dysplasia Society
JBTS	Joubert syndrome
MCDS	Chondrodysplasia
MFS	Marfan syndrome
MKS3	Meckel syndrome
MOPDII	Microcephalic osteodysplastic primordial dwarfism
MPS	Mucopolysaccharidosis
MPS4A	Mucopolysaccharidosis 4A
MSSD	Mesoaxial synostotic syndactyly
NGS	Next-generation sequencing
OCD	Osteochondrodysplasia
OI1	Osteogenesis imperfecta
OMIM	Online Mendelian inheritance in man

OPTP	Osteopetrosis
PAPA	Postaxial polydactyly types
PD1	Polydactyly
PHOAR	Hypertrophic osteoarthropathy autosomal recessives
PPD1	Pre-axial polydactyly
PSACH	Pseudoachondroplasia
PYCD	Pycnodysostosis
RBS	Roberts syndrome
RGDs	Rare genetic disorders
RHZDAN	Rhizomelic dysplasia
SEMD	Spondyloepimetaphyseal dysplasia
SEDCJD	Spondyloepiphyseal dysplasia with congenital joint dislocations
SHFM	Split-hand/foot malformation
SPD	Synpolydactyly
TRPS	Trichorhinophalangeal syndrome type
TPT	Triphalangeal thumb
UMT	University of Management and Technology

Declaration of conflicting interests
The author declares that there is no conflict of interest regarding the publication of this case report.

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