Aim: Split cord malformation (SCM) is associated with extensive vertebral fusions (Klippel–Feil anomaly). In light of previous embryological theories and recent research findings, we attempt to document the origin of split cord, and vertebral fusions involvement of spectrum of genes is necessary to know better the etiopathogenesis of SCM and its associated diseases. Materials and Methods: We used the various databases such as PubMed/MEDLINE, Cochrane Review, Hinari, and Google Scholar for the recently published medical literature. The women had been living and still born infants had SCM. The relative risk (RR) and possible molecular mechanism are described details of major genes and its variants in details. Although molecular genetics involvement including with recent advances of study add an evidence of both Mendelian and Non-Mendelian fashion is discussed with all genetic components. We mentioned our earlier experience and responsibility of SCM and its associated diseases. Results: Although different mechanisms are suggested for the development of SCM observed in our experience, there is a midline lesion bisecting the neuroepithelium and the notochordal plate, which is responsible for complete splitting of the cervical cord with anterior bony defect. The localized disturbance of cervical neural tube closure accounts for SCM with partial dorsal splitting of the cord with posterior vertebral defect and associated diseases. Conclusions: According to the best of our knowledge, this report is the first one to be documented by wider spectrum of variants from (experimental studies to human subject). This add a complex interaction of mutant variants drive toward an additional second-hit alterations for the SCM. The up-to-date information, documented in proper order, derived the bench-to-bedside approach to overcome this burden of SCM, which is globally noticed with other additional diseases. Keywords: Genes, genetically inherited molecules, split cord malformation

INTRODUCTION

Currently, higher cervical split spinal cords associated with extensive vertebral fusions (Klippel–Feil anomaly) are frequently found in the Indian population. Embryological theories and recent research findings suggest the origin of split cord malformation (SCM) and vertebral fusions. Distinctly separate mechanisms suggested for the development of split cords have been observed in our patients. Basically, midline lesion bisecting the neuroepithelium and the notochordal plate is responsible for complete splitting of cervical cord with anterior bony defect. The cervical neural tube closure (CNTC) is responsible for partial dorsal splitting of the cord in cases with the posterior vertebral defect (PVD). Vertebral fusion anomalies (VFAs) were associated with a disturbance
Table 1: Major table of gene involvement on split cord malformations

| Sl. no | Responsible gene | Chromosomal location | Mutagenicity/polymorphism | Disease-specific |
|--------|------------------|----------------------|---------------------------|-----------------|
| 1.     | Pax-1            | 20p11.22             | Silent                    | Vertebral fusion anomalies + split cord in the cervical region |
| 2.     | Grhl2            | 15; 15 B3.1          | Novel downstream EMT suppressors | Split face malformation + exencephaly |
| 3.     | Grhl3            | 1p36.11              | Conserved                | Spinal closure defect + DLHP |
| 4.     | Grhl2 and Grhl3  | 15; 15 B3.11p36.11   | Novel downstream EMT suppressors + conserved | Rostral and caudal neural tube defects |
| 5.     | SHH              | 7q36.3               | Point                     | CRS + SB |
| 6.     | Zfh-1            | Drosophila zfh-1 gene encodes | Loss of function | Embryonic mesoderm and nervous system |
| 7.     | DeltaEF1         | Heterogeneous DNA-binding domains | Null mutant | Notochord, somites, neural crest, brain, spinal cord, and skeletal defects |
| 8.     | MTHFR            | 11p13                | Missense/Alternative splicing | Complex congenital abnormalities |
| 9.     | MTRR             | rs 1801394rs 1801133 5p15.31 | Alternative splicing | Complex congenital abnormalities + multiple birth defects |
| 10.    | MECP2            | Xq28                 | Duplication              | Neurodevelopmental disabilities + recurrent infection + hydrocephalic |
| 11.    | MECP2 and L1CAM  | Xq28                 | Duplication              | Mental retardation + hydrocephalic + corpus callosumBrain structural abnormalities |
| 12.    | ZRS              | 7q36.3               | Limb bud mutation        | Limb abnormalities, polydactyly, tibial hypoplasia, and syndactyly |
| 13.    | Xq22.1           | X-chromosome         | Deletion                  | Congenital abnormalities |
| 14.    | CLDN16           | W237X                | Sq deletion               | Genetic defects + tubular disorders |
| 15.    | Ring chromosome (r5) | 5p13.2–3 to 5pter | Microdeletion            | Multiple congenital abnormalities |
| 16.    | PAX2PAX6         | 10q24.3111p13        | Germ line                 | Development of optic disc anomalies |
| 17.    | HOX              | 7p15, 17q21.2, 12q13, and 2q31 | Microdeletion | Congenital abnormalities |
| 18.    | TUBA1A           | 12q13.12             | Heterozygous             | Microphthalmia, congenital cataracts, microcephaly, and brain malformation |
| 19.    | ATRX/LICAM       | Xq21.1               | Nonsense                  | MPS + clinical phenotypes |
| 20.    | USP9X            | Xp11.4               | Alternate transcripational splice | MPS + clinical phenotypes + autism |

PAX1 = PAX1 paired box 1 (Homo sapiens [human]), Grhl2 = Grainyhead-like-2 (Drosophila) (Mus musculus [house mouse]), SHH = sonic hedgehog (Homo sapiens [human]), Zfh-1 = zinc finger motifs and one homeodomain, methyl-CpG binding protein 2, DeltaEF1-ZEB1 = zinc finger E-box binding homeobox 1, MTHFR = methylenetetrahydrofolate reductase, MTRR = 5-methyltetrahydrofolate-homocysteine methyltransferase reductase, MECP2 = methyl-CpG binding protein 2, LICAM = Intracellular adhesion molecule-1 (Homo sapiens [human]), ZRS-LMBR1 = (ZRS) limb development membrane protein 1, CLDN16 = Claudin-16 (Homo sapiens [human]), PAX2 = paired box 2, HOX = a subset of homeotic genes, TUBA1A = TUBULIN, ALPHA, brain-specific-Alpha-1, ATRX = alpha thalassemia/mental retardation syndrome X-linked, USP9X = ubiquitin-specific peptidase 9 and X-linked

in PAX1 gene expression. As a developing vertebral column, frequent association of failure of normal segmentation and split cord in the cervical region (CR) located is quite informative.[5] Patients complained of neurological deficit (NLD) as mild and they had no radiological evidence of tethering.[6] The cord and spine and the rarity of a bony spur in the CR are the likely reasons of conservative policy.[7] Primary neurulation in mammals is defined as the distinct anatomical closure sites at the hind brain/cervical spine (closure 1), forebrain/midbrain boundary (closure 2), and rostral end of the forebrain (closure 3).[8] The zones of neurulation were characterized by the morphologic differences in neural fold elevation, with nonneural ectoderm-induced formation of paired dorso lateral hinge points (DLHP) necessary for neural tube closure in both the cranial and the lower spinal cord regions.[9] The notochord-induced bending at the median hinge point is sufficient for the closure in the upper spinal region (USR).[10] The function of the nonneural ectoderm-specific Grainy head-like genes in human subject is important now.[11] Grhl2 gene-targeting approach is deletion of Grhl2, resulting in failed closure 3, mutants exhibiting a split face malformation, and exencephaly.[12] Failure of neuroepithelial folding
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at the DLHP has loss of Grhl3 alone, which defined the distinct lower spinal closure defect. DLHP formation genes contribute equally to closure 2, and only Grhl gene dosage is limiting. Deletion of Grhl2 and Grhl3 induces rostral and caudal neural tube defects. DLHP-independent closure 1 proceeds in the USR. The DLPH findings on the basis of non neural ectoderm mediated by the formation of DLHP is critical for complete neuraxis closure (CNC). Male infant of healthy non-consanguineous parents was born with congenital malformations (CMFs) is the one of challenges for the society, which include bilateral cleft palate and lip, mild microphthalmia with iris coloboma and glaucoma of the right eye, and blepharophimosis with severe microphthalmia of the left eye as well [Table 2].

The spine radiograph, computed-tomography image and magnetic resonance imaging (MRI), showed first sacral hemivertebra with spina bifida (SB) and agenesis of the 2nd, 3rd, 4th, and 5th sacral vertebrae and coccyx. The spine MRI showed caudal tethering of spinal cord at L(3) level, filum terminalis lipoma, and syringomyelia. Anophthalmia-plus syndrome (APS) had a distinct syndrome having gene locus of APS research is now in progress with this new subjects. Human development series of first-trimester abortions were studied in the embryo with expression of sonic hedgehog (SHH) was found in both domains SCM. SCM corresponding with duplicated part of the notochord, single signal observed that no duplicated part located on development. The cervical level of the open neural tube with SHH expression domain and with two or even three domains in its lumbar region is quite important.

Multiple functional floor plates (MFFPs) along with two embryos leads SB. SHH expression found in the ventral neural tube (VNT) frequently. Static magnetic fields involved in the pathogenesis of CR and similar notochord abnormality and altered expression of the SHH gene observed in Lp mice with neural tube defect (NTD). Lp gene is a candidate gene (CG) for human CR. The notochord splitting and for the abnormal expression of the SHH gene in the floor plate in embryos with CRS and SB questionable. DeltaEF1 is a DNA-binding protein containing a home domain and two zinc finger clusters. Located in vertebrate homologue of zfh-1 (zinc finger homeodomain-containing factor-1) in Drosophila species. DeltaEF1 is expressed in the notochord, somites, limb, neural crest derivatives (NCD), and few restricted sites of the brain and spinal cord. Regulatory function of deltaEF1 helps in embryogenesis. DeltaEF1 has a role in regulating the development of skeletal structures. DeltaEF1, deltaC727, and deltaEF1 having various regulatory activities (VRA) are dependent on different domains.

### MATERIALS AND METHODS

We used different databases PubMed/MEDLINE, Cochrane Review, Hinari, Google Scholar for recent medical literature. The women who had live-and stillborn infants, of whom had SCMs are also in relative risk of SCMs. The possible molecular mechanisms we were described details in the table major genes and its variants through molecular genetics involvement clearly. This including with recent advances and future prospective. It add an evidence of both Mendelian and Non-Mendelian fashion. We are trying to document and summarize all responsible possible genes and recent advances approach with bench to bedside approach.

### RESULTS

The association of polymorphisms in folate metabolism genes (FMG), methionine synthase reductase (MTRR) gene, and 5, 10-methylenetetrahydrofolate reductase (MTHFR) gene, with complex congenital abnormalities (CCA) and its association with CCA are derived from three germ layers. MTRR single nucleotide polymorphisms (SNPs) (rs1801394) and MTHFR SNP (rs1801133) are genotyped with multiple birth defects. The homozygous recessive genotype (HRG) at rs1801133 served as a protective factor (PF). Ectoderm- or endoderm-derived CCA are HRG (rs1801394) and served as a PF SNPs in
FMG (MTRR and MTHFR) associated with CCA and related to ectoderm, mesoderm, or endoderm development significantly.[33] Chromothripsis is an extreme class of complex chromosomal rearrangements (CCR) with major work on chromosomal architecture (CA).[34] Chromothripsis with congenital abnormalities (CCA) has incidence of pathogenic effects.[35] Human genome tolerates extreme reshuffling of CA.[36] Basically, in breakage point of multiple protein-coding genes (MPCGs) had a nature without noticeable phenotypic effects.[37] Chromothripsis in healthy individuals affects reproduction and increases the risk of miscarriages, abortions, severe congenital disease, and direct involvement with birth defects.[38]

MECP2 duplication is a well-recognized syndrome in 100% of the affected male children with neurodevelopmental disabilities and recurrent infections.[39] MECP2 and L1CAM genes in the Xq28 region in family with severe X-linked mental retardation (MR) are higher.[40] Prenatal fetus with the brain structural abnormalities is identified from the fetuses with MECP2 duplication.[41] Hydrocephalus, agenesis of the corpus callosum, choroid plexus cysts, fetal growth restriction, and hydrenephrosis might be the common ultrasound findings in prenatal fetuses with MECP2 duplication, which is now more challengeable and newly recognized.[42]

In ZRS, a highly conserved cis-regulator, long-range gene regulation is noticed.[43] It acts over approximately 1 Mb to control spatiotemporal expression of SHH in the limb bud.[44] ZRS mutations promote limb abnormalities, including polydactyly, tibial hypoplasia, and syndactyly.[45] Prenatal diagnosis (PD) found a duplication on the long arm of chromosome X from chromosomal band Xq13.2 to q21.31 in a male fetus with increased nuchal translucency in the first trimester and polyhydramnios at 22 weeks of gestation period.[46] The amniocentesis with cytogenetic analysis (CA) revealed chromosomal material (CM) in the long arm of chromosome X at position Xq13.[47] Analysis with higher resolution array CGH revealed the additional material is in fact a duplication of the region Xq13.2-q21.13.[48] Duplication is 14.8 Mb in size and includes the following genes: SLC16A2, KIAA2022, ABCB7, ZDHHC15, ATRX, MAGT1, ATP7A, PGK1, TBX22, BRWD3, POU3F4, ZNF711, POF1B, and CHM.[49] In according to analysis of the parents revealed that mother to be the carrier of the same duplication also a causal factor of SCM. After elective termination of the pregnancy at 28 weeks, a detailed autopsy of the fetus allowing genotype-phenotype correlations is required for necessary investigations.[49]

Multiple congenital abnormalities (MCAs) are caused by the chromosomal aberrations, mutant major genes and teratogens.[48] Patients are identified as with syndromes but the major part belonged to the group of unclassified multiple CAs (UMCAs).[50] Young-aged mothers are associated with the higher risk of UMCA.[51] Birth order 4 or more is associated with the higher risk for UMCA with 2 and 3 component CAs.[52] The possible maternal and birth order effect for cases with UMCA, and the young age and higher birth order associated with a higher risk for UMCA were analyzed.[50]

Chromosomal microarray analysis (CMA) identified a novel 1.1-Mb deletion at Xq22.1. A similar deletion has been described once in the literature.[47] Female patient and her mother both have intellectual disability (ID) and dysmorphic facial features of a 0.35-Mb subregion[53] containing four genes, which is sufficient to cause majority of the Xq22.1 deletion phenotypes. Male and female patients contain 30 common genes, including the 4 described in the 0.35-Mb subregion.[54] Male with deletion of the 0.35 Mb subregion died prenatally from respiratory failure due to pulmonary hyperplasia, consistent with the breathing problem and potential neonatal fatality in male patients.[55] The patients were strikingly affected with similar fashion. The deletion of these five genes (ARMCX5, ARMCX5-GPRASP2, GPRASP1, GPRASP2, and BHLHB9) is likely responsible for the novel Xq22.1 deletion syndrome.[56]

Congenital anorectal malformation (ARM) is one of the most common gastrointestinal congenital diseases accounting for one-fourth of digestive tract malformations[57] and is one of the CMFs in routine surveillance by the World Health Organization.[58] Of the variety of risk factors and the complexity of the pathological changes, etiology of ARM is a unique one.[49] ARM results from hereditary factors and environmental factors in the development of embryogenesis.[59] Through all the animal experiments, we have observed that HOX, SHH, FGF, WNT, Cdx, and TCF4, Eph, and ephrin play a crucial role during the development of digestive tract because of the genes/signaling pathway dysfunction.[59] ARM is the external factor in pregnancy.[60] Because of this complexity in SCM and related factors are responsible in the development process of human embryogenesis,[62] research on the progress of human ARM is still going on. Reviewing in appropriate genetic and environmental factors we provide the theoretical/practical basis for the treatment and prevention of ARM is quite necessary.[63] Fetal lung interstitial tumor (FLIT) is a
newly recognized lung lesion in infants.\[^64\] Histological examination revealed immature airspaces and interstitium, containing bronchioles and cartilage.\[^65\] The epithelial and interstitial cells (EIC) contained abundant glycogen granules. Immunohistochemistry (IHC) showed nuclear/cytoplasmic expression of β-catenin in the EIC, report are very interesting to know the disease progression and aetiopathogenesis.\[^66\]

β-Catenin gene mutations and trisomy 8 are neoplastic origin could not be confirmed till date.\[^67\] Histological findings (H and E) were partly consistent with normal fetal lung at the canalicular stage, pulmonary interstitial glycogenesis, and congenital cystic adenomatoid malformation/congenital pulmonary airway malformation (CPAM) type 3.\[^68\] However, we compare the above conditions and discuss the pathogenesis of FLIT.\[^69\] Familial hypomagnesemia (FH) with hypercalciuria and nephrocalcinosis is an autosomal-recessive renal tubular disorder.\[^70\] It is characterized by renal magnesium wasting, hypercalciuria, advanced nephrocalcinosis, and progressive renal failure with mutations.\[^71\] Paracellin-1 (CLDN16) gene been as the underlying genetic defect frequently.\[^72\] Tubular disorders and progression in renal failure are usually resistant to magnesium substitution and hydrochlorothiazide therapy.\[^73\] Hypomagnesemia improves with advanced renal insufficiency. A patient was presented with a homozygous truncating CLDN16 gene mutation (W237X)\[^74\] who had an early onset of renal insufficiency despite early diagnosis at 2 months. The patient also had horseshoe kidney, neonatal teeth, atypical face, cardiac abnormalities including coarctation of the aorta associated with atrial and ventricular septal defects, umbilical hernia, and hypertrichosis.\[^75\] FH with hypercalciuria and nephrocalcinosis and additional congenital abnormalities (ACAs) were independent of the disease.\[^76\]

A child with a ring chromosome 5 (r(5)) associated with facial dysmorphology and MCAs was noticed by researchers.\[^77\] Fluorescent in situ hybridization (FISH) using bacterial artificial chromosome clones was performed to determine the breakpoints involved in the r(5).\[^78\] The 5p deletion extended from 5p13.2-3 to 5pter and measured 34.61 Mb (range, 33.7–35.52 Mb), whereas the 5q deletion extended from 5q35.3-5qter deletion.\[^79\] NKX2-5 gene had been related to congenital heart defects (CHDs), patients including with 5q35.3-5qter deletion is important cause for SCM.\[^80\] Additionally, VEGFR3, deleted in patient, a Ctg for the congenital heart abnormalities (CHAs) were observed with SCM and also associated diseases.\[^81\]

**DISCUSSION**

Recently, MSX1 gene, which helps in outflow tract morphogenesis, was found in a fetus with isolated heart (IH) in hypermethylation of the GATA4 gene. Fetuses with Down syndrome with or without CHDs are newly recognized. In fetuses with IH malformations, epigenetic alterations of relevant genes are present in developing heart DNA. In fetuses with both isolated and syndrome heart malformations, pathogenesis is related to the malformation by cis-acting effects and gene expression.\[^82\] Optic nerve malformations are common causes of congenital blindness and are recognized with increasing prevalence. These malformations help not only in determining the cause and level of visual impairment but also in looking for associated treatable or life-threatening systemic conditions such as PAX2 or PAX6 gene. Recent advances in genetic testing such as array technology distinguished the comparative genomic hybridization and allow to detect the micro deletions.\[^83\]

PAX2 provides the clue for further research and avoids publication bias.\[^84\] Congenital anomalies in the kidney and urinary tract (CAKUT) are common genetic malformations. PAX2 gene has a role in kidney organogenesis and antenatal hydronephrosis in healthy controls. In genotyping and allelic discrimination find out by probes were rs2077642, rs4244341, rs6421335, rs11190698, and rs11190693. PAX2 gene involved with the pathogenesis of Vesicoureteral Reflux (VUR) in children subject is one important information.\[^85\] Defects in these processes are the common causes of CMF syndromes, and rapid progress is being made in elucidating their embryological and genetic basis. Perturbation in the DiGeorge syndrome is the second induction at differentiation of the forebrain. Holoprosencephaly the third role played by the human HOX genes in CMFs.\[^86\]

TUBA1A mutation is responsible to creating microphthalmia.\[^87\] Congenital nephrotic syndrome (CNS) is a rare disease inherited as an autosomal recessive trait and defined as proteinuria manifesting at birth or in the first 3 months of life. The classical form is the Finnish type is one classical example of SCM.
The classical findings included prematurity, large placenta, and massive proteinuria. Minor cardiac findings have been reported as a minor functional disorder, but CNS with major cardiac malformation is rare. Child with CNS with small indel mutation (c.614_621delCACCACC GGinsTT) in exon 6 of NPHS1 had major role in cardiac malformation and developed end-stage renal disease (ESRD). Patients with occlusive vascular Ehlers–Danlos syndrome accompanying a congenital cystic adenomatoid malformation of lung, in addition to duplicated infrarenal vena cava, have been reported.

Type 2 CPAM is reported in association with other congenital anomalies. Type 2 CPAM with CNS has not been reported. First report of such an association in a boy had a PD of cystic lung malformation and was found to have CNS (diffuse mesangial sclerosis) at 1 month of age. CAKUT was seen in approximately 45% of the children with ESRD in Indian population. Mutations in 30 genes were described as causing autosomal-dominant isolated CAKUT in human subjects. The degree of an intrauterine fetal growth retardation (IUFGR) is depends on number of component CA in UMCA cases were newly Observed by the researchers.

Menkes disease (MNK) is an X-linked recessive disorder. Incidence of live-born infants with MNK is 2.8 per million live births in Japan and varies in the Indian scenario. Sudden death occurred in MNK patients with CM conditions. Developmental delay (DD) and/or ID affects 1%–3% of children. Causative variants are identified in patients who had a nonsense mutation. ATRX gene and a canonical splice site mutation in the L1CAM gene with splice site variant in the USP9X gene help clinical phenotypes. Gene MPS is likely to provide a genetic diagnosis for children with autism phenotype. A typical presentation of anterior meningocele in a young adult with urinary incontinence, a sacral defect, ARM and headaches during bicycle riding also a great example in rare cases.

Heart- and NCD-expressed (Hand) proteins are the Twist family of the basic helix-loop-helix (bHLH) transcription factors. TWIST plays crucial role in the development. Hand2 results in developmental defects of limbs, craniofacial, and lumbar vertebrae, and trisomy of the Hand2 gene is involved with congenital disorder. Polymorphisms of OSR1 gene rs12329305, rs9936833 near FOXF1, and HOXA1 rs10951154 polymorphism in the development of CMFs stillborn/ neonatal death occurred with congenital kidney (CK) and heart developmental defects (HDDs) were still a challenging task.

Periconceptional folate supplementation prevents a number of congenital anomalies (CA). MTHFR C677T and MTR A2756G loci were increased the risk of CA-affected pregnancy. MTHFR A1298C and its associated of MTR A2756G increased the risk of CA. Locus A2756G in MTHFRR gene susceptibility also counted as an important information for the SCM. CMF of external and middle ear is a common disease in the ENT department. External and middle ear malformations an important ear symptom of the systemic syndrome confirmed with genetic research progress of CMF of external and middle ear. Identical twins with lethal CPAM type 0 an autosomal-recessive inheritance pattern responsible in familial recurrence (FR). Congenital cardiovascular malformation (CCVM) exhibits familial predisposition, the specific genetic factors involvement are unknown. Genes of the bone morphogenetic protein (BMP) signaling pathway for novel variants are exonic, splice site, and untranslated regions of BMPRIA, BMPR2, and SMAD6 genes. Researchers believe that low-frequency deleterious variants in SMAD6 predispose into CV human disease phenotype genetic variation with SMAD6 is one of the new message for student.

P63-positive cells are epithelium of the apical urorectal septum (AUS), hindgut, and cloacal membrane. Mutation identified that P63 strongly causal factors among the ARM phenotype and P63. P63 helps in incessant septation of the cloaca and hindgut in the morphogenesis. Apert, Fibroblast Growth Factor (FG), Floating–Harbor, Shprintzen–Goldberg, and Rett syndromes and craniosynostosis diseases are developed through the MECP2 gene mutation globally. CCR, is important for balanced or unbalanced structural rearrangements, are cytogenetic break points on CMA. Submicroscopic deletions at 3p12.3 (467 kb) and 12q13.12 (442 kb) are having important role for CMA. Microdeletion within ROBO1 gene at 3p12.3 played a role in the patient’s DD, potential activity-dependent role in neurons, and IQ. Neural elements are proper interaction with the brain. So, congenital spinal deformities had normal embryologic development. Hmx1 expression in neural-crest-derived CM and deregulation of Hmx1 expression acted candidate mechanism for congenital ear malformation. Split hand/split foot malformation (SHFM) type 1 missing central digital rays with efts of the hands and/or feet, which was linked to chromosome 7q21.3. DLx5 and DLx6 help limb defects in human subject. SHFM1 caused heterozygous paternal deletion, enhancers the osteoblast-specific maternally imprinted through these (DLX6 and DLX5 genes).
HUB genes were identified that (UBC, APP, HUWE1 and SRC) are potential biomarkers for CHD in DS.[111] Novel mutations, c.559C>G (p.P178A) and c.682T>A (p.C228S), in the SYM1 and atypical SYNS1 families changes found in the protein-coding regions, exon-intron boundaries or promoter regions. The NOG, GDF5 or FGF9 genes were found in the SABTT family. These syndromes are help in the diagnostic purpose for “NOG-related-symphalangism spectrum disorder”. [112]

Microtia is a complicated congenital anomaly had a genetic and environmental predisposition. miR-200c expression of miR-451 and miR-486-5p expression in microtic causes abnormal development of the external ear. OSR1 and TRPS1 genes were complementary target of mRNAs had an important role during the development.[113] FOXI3 gene responsible for patient with SCM and its associated diseases for new information for further study.[114]

Congenital vertebral malformation (CVM) is a congenital vertebral structural deformity caused by abnormal somitogenesis during embryonic development. Copy number Variations (CNV) of chromosome 16p11.2, 10q24.31, 17p11.2, 20p11, 22q11.2 like few other regions is associated with CVM. This gene dosage plays an important role in the development of the spinal cord and SCM.[115] lp36 deletion (monosomy 1p36) is a common terminal deletion observed in human subjects. Patients with limb, CHDs, and other malformations with SNP array report proved they having small deletion. Additionally, lp36.33-p36.32 had SKI (Sloan–Kettering Institute proto-oncoprotein) also one causal factor for CHDs. Dominant mutations in SKI identified are with Shprintzen–Goldberg syndrome. lp36.33-lp36.32 deletion encompassing SKI represents a previous undescribed microdeletion disorder.[116] Presently, ITI (inter-trypsin inhibitor) gene family consisting of five genes (ITIH1 to ITIH5) encodes proteins involved in the dynamics in the extracellular matrix. ITIH5 found inactivated by partial deletion in a case of congenital uterovaginal aplasia among human subject rare diseases are called Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome.[117] Female reproductive tract and ITIH5 considered as putative CG for MRKH syndrome. MR and MCA's are associated with microdeletion/duplication syndromes noticed by the earlier researchers.[118]

Persistent hyperplastic primary vitreous (PHPV) is identically same as persistent fetal vasculature, rare congenital developmental malformation of the eye, and failure of regression of the primary vitreous. Norrie disease with FZD4 genes is found to be mutated in unilateral and bilateral PHPV. Potential CGs are the future and provide a better understanding of the pathogenesis, therapeutic approach, and better management for SCM.[119] CMFs in the female population are estimated to be 5:1000 live births associated with infertility, abortion, stillbirth, preterm delivery, and other organ abnormalities. The homeobox (HOX) genes (HOXA10 and HOXA13) are involved in the development of human genitalia. HOXA10 gene helps in misdevelopment of female internal genitalia, which should not be ignored.[120]

Mitogen-activated protein kinase (MAPK) pathway and genes (FGF18, FGF12, PDGFRA, MAPK11, AMH, and CTBPI) are involved in organ development and morphogenesis. Genome level shown that no genetic factors also involved in pathogenesis of renal agenesis.[121] SHFM had variable degree of median clefts on hands and feet. Genes (TP63, WNT10B, and DLX5) are promoting SHFM phenotype with involvement of hands and feet. Genotyping using microsatellite markers to map the families to WNT10B gene at SHFM6 on chromosome 12q13.11-q13 is newly discussed.[122] Sequence analysis of WNT10B gene revealed a novel 4-bp deletion mutation (c.1165_1168delAAGT) and 7-bp duplication (c.300_306dupAGGGCGG). Structure-based analysis showed conformational shift within active binding site mutated by WNT10B (p.Lys388Glufs*36). It influences in binding with FZD4. The WNT10B gene extends the body of evidence and helps in the pathogenesis of SHFM.[123]

Congenital hypothyroidism (CHT) and mutations in genes involved in thyroid development, patients according to their CH-T etiology, types, and patterns in morphological findings helpful in how thyroid development.[124] Karyotype is found patients chromosomal rearrangement, different break points the identified genes (NRCAM, NPTX1, NMT1, MAPT, HDAC5 and MEF2C) associated with SCM and its associated diseases (due to a position effect).[125]

SHFM along with -bone deficiency is the rarest condition in SHFM. Which associated with long-bone malformation (LBM) involved with the tibia. SHFM had located on 17p13.3 duplication and BHLHA9 copy number gains similarly associated with limb defect presenting ectrodactyly and harboring a BHLHA9 duplication is one important information mentioned in Table 1.[126] DNA sequence analysis provides the fundamentals of gene study of the congenital craniofacial abnormalities. Human genome project paved the confirmation of CG of the congenital craniofacial abnormalities and enlighten to know the association of SCM with its associated diseases.[127]
**FUTURE PROSPECTIVE AND RECOMMENDATIONS**

The first success in cloning sheep, the production of viable animals somatic cell nuclear transfer (SCNT) developed is now time to remember and analyze. The most successfully cloned cattle species. Newer techniques are still associated with a higher incidence of pregnancy failure and accompanying by the placental and fetal pathologies. Pre- and early postimplantation losses affected up to 75% of the pregnancies. The SCNT placenta appears normal, placental vascularization modified and fetal-to-maternal tissue ratios are slightly increased in the SCNT placentomes.[128] Gsc gene and BMP5 gene mutation both environmental and genetic factors contribute to congenital microtia. So that Gsc gene and BMP5 maternal peptide gene predisposing genes of microtia.[129] Molecular genetics study in molecular level, genetic information is stored, inherited, expressed, and influenced by the structure and function of cells in SCM and its associated diseases progression is more important. Several molecular approaches been used for decades in the laboratory and core of modern medical education are only now beginning to influence clinical practice and research. Newer techniques permit rapid and affordable DNA sequencing, gene expression profiling, gene cloning, gene manipulation, gene transfer, recombinant protein production, gene editing, and other technologies of enormous biomedical importance for SCM and associated diseases. As a genomics era grown up including proteomics, pharmacogenomics, and bioinformatics. Recently newer techniques are providing diagnostic, prognostic, and therapeutic opportunities in all areas of medicine and promote translational research. Presently, somatic and germ line variants in genes at the PI3K-AKT pathway (AKT3, PIK3R2 and PIK3CA) associated with MCAP and/or other related megalencephaly syndromes. Clinical features are macrocephaly, cutis marmorata, angiomata, asymmetric overgrowth, DD, discrete midline facial nevus flammeus, toe syndactyly, and postaxial polydactyly—thus, clearly an MCAP phenotype are very clear cut message for recent young researchers. Nowadays, an exome-based sequencing helps pathogenic de novo germ line variants [PTPN11 gene (c.1529A>G; p.(Gln510Arg)], a PTPN11], germ line variant in MCAP patient had major impact. The new data from experimental studies have shown the complex interaction of SHP2 (gene product of PTPN11) within PI3K-AKT pathway. PTPN11 germ line variants drive toward an additional second-hit alterations for SCM and its associated diseases are very unique information for researchers and neurosurgeon as well.

**Split cord malformation treatment in India**

In the 2-year period, 2008–2009, a total of 53 cases with SCM, an uncommon condition, were examined. With all cases of progressive scoliosis, an MRI was carried out. All asymptomatic patients were subjected to surgery and none developed post-op deterioration. The post-op neurological deterioration (ND) was noticed in 15% patients, of which 8% had transient postoperative deterioration. The new type I SCM subclassification system proposed by Borkar and Mahapatra is found to have a significant prognostic value in assessing postoperative ND in patients with type I SCM.[130] With decreasing incidence of NTD in the West, the reports of SCM are getting lesser and lesser. However, in India, spinal dysraphism is still a major problem encountered by the neurosurgeons. SCM is rare and not many large series are available in literature. We operated 300 cases and noticed a large number of associated anomalies with multilevel and multisite splits. Improvement or stabilization was noted in 94% and deterioration in 6% of the cases, and prophylactic surgery for asymptomatic patients was recommended.[131] Again complete neural axis scan is the first instance to determine associated lesions. Very good results were expected in about 90% patients, with minimal complications documented in 48 cases.[132] Incidence of SCM with Meningomyelocele (MMC) amounts to 41% of total SCM cases. Progressive NLD was higher among these groups (SCM with MMC) in comparison to the group harboring SCM without MMC. In view of a significant association of SCM in MMC cases, associated with other craniospinal anomalies, a thorough screening of neuraxis (by MRI) is recommended to treat all treatable anomalies simultaneously for desired outcome.[133] In a retrospective analysis study consisting of 19 cases with SCM, 13 were grouped under (Pang) type I and 6 under type II, including the age range from 1 month to 9 years (mean, 3.5 years). Kumar et al.[134] observed that surgery seemed to be effective, particularly in patients with neurological dysfunction (NLDF). Venkataramana[135] recommended that surgery before the onset of NLDs is quite important and surgical results are excellent with good microsurgical technique is helpful for the patients.

**CONCLUSION**

In conclusion, not only genes but also many signaling pathways, proteins, and enzymes are responsible for SCM and its associated diseases. In our experience, next-generation sequencing and genome-wide association study may help and support to know the better etiopathogenesis, future management, and may
help improve further development research for SCM and its associated diseases.

LIMITATION
More samples are required and a strong database with appropriate tools is mandatory.

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Conflict of interest
There are no conflicts of interest.

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