Review Paper:

The genetic complexity of anorectal malformations

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Abstract

Anorectal malformations (ARMs) are a heterogeneous group of congenital anomalies having an incidence of 1 per 5000 live births. ARM is among the most common surgically treated congenital anomalies. The genetic causes of anorectal malformations are complex and varied including chromosomal aberrations, single-gene disorders and phenotype with multifactorial inheritance.

However, the exact aetiology remains largely unknown. It can be syndromic or nonsyndromic, sporadic, or familiar with a different mode of inheritance. Genetic information can provide a deeper understanding of genotype-phenotype correlation, disease nature and prognosis of the anorectal malformations. This review provides an overview of the genetic causes associated with ARMs. More emphasis is given to the monogenic syndromes with a brief overview of associated anomalies which play an essential role in genetic diagnosis, management and prevention strategies.

Keywords: Anorectal malformation, associated anomalies, chromosomal abnormality, mutations, syndromes.

Introduction

Anorectal malformations (ARMs) comprise a broad spectrum of congenital defects that continue to present a challenge for paediatric surgeons. ARMs are the most common congenital anomalies in neonates with an incidence of 1 in 5000 live births, although there are differences in incidence in different ethnic groups[1]. It is estimated that nearly 15000 babies with anorectal malformations are born every year in the state of Uttar Pradesh with one of the highest birth rates in India[61].

ARM is characterized by the presence of an ectopic anus at birth and has a variable clinical presentation ranging from mild to more complicated cases. According to several statistical studies, it is a male preponderance. According to several studies, 55% to 70% of anorectal malformation cases found in males, with more severe malformation tend to be more common [9,44,54]. In more severe malformation, bowel outlet opens in an ectopic position in the urogenital tract or genital tract in males and females respectively[39]. The knowledge of genotype-phenotype correlation is essential for the planning and management of anorectal malformations.

This review aims to provide the genetic basis of anorectal malformations and available genetic markers for the diagnosis of disease. The published literature search was carried out by using PubMed, MedLine databases and CrossRef (Google).

Epidemiology: The average incidence of ARMs is approximately 1 in 5000 live births, although this incidence is more common in some geographic regions. The majority of anorectal malformation is more common in males as compared to females. Recto-urethral and recto-vestibular fistula are frequently observed as anorectal malformations in male and female patients respectively. Wingspread classification (1984) is widely accepted. In this classification, anorectal anomalies are classified as high, intermediate and low[55].

Aetiology: The exact aetiology of anorectal malformation remains unclear due to its multifactorial behaviour. Many reports suggested that genetic factors play an important role in their development. It can be syndromic, sporadic (single affected individual), or familiar (more than one affected individual) with a different mode of inheritance[29,58]. Some syndromes with an autosomal dominant mode of inheritance including Townes-Broks syndrome, Currarino's syndrome and Pallister-Hall syndrome are associated with ARMs[7,25,26]. Some studies demonstrated that several gene mutations (such as *SALL1*, *GLI3* and *HLXB9*), microdeletions (22q11.2) and trisomy (trisomy 21, trisomy 18) are also associated with anorectal malformations[4,67].

There are also some data to support the role of environmental factors that may be related to the development of ARMs including maternal diabetes mellitus, obesity, *in-vitro* fertilization and illicit drugs or occupational hazards[63,68]. Different animal models showed a significant correlation with trans-retinoic acid and ethylene thiourea with the development of anorectal malformations[37].

Associated malformations: ARMs are frequently associated with other congenital anomalies. It is estimated that approximately 50-60% of all cases with ARMs have at least one other associated malformation[34]. The VACTERL (Vertebral, Anal, Cardiac, Tracheo-Esophageal, Renal and Limb) anomalies are severe in high and intermediate ARMs with frequency up to 93% in different types of ARMs. The incidence of reported anomalies is variable in different studies[46,47].

In a study of 216 neonates with ARM, associated anomalies were found in 67 cases (31.02%) and Esophageal atresia was the most common associated anomaly. High-type ARM was

seen in 81.94% cases while low-type ARM in 18.06%. The associated malformation with ARM was more common in females (44.19%) than males (27.75%). Associated malformations were slightly higher in high type ARM (31.64%) than low type ARM (28.20%)[18,33]. Kumar et al[28] also reported that the associated anomalies in patients with ARM were 68%. The associated malformations were more in high type ARM (72%) than the low type of ARM (50%). Ratan et al[45] stated that males with high ARM had more vertebral and gastrointestinal tract anomalies while in low, ARM had a higher incidence of genital malformations.

On the other hand, females with high ARM have more skeletal anomalies and urinary tract malformations, while in low, ARM frequently suffered from vesicoureteric reflux[45]. Table 1 shows the most common associated anomalies and their frequencies in ARMs patients.

Genetic basis: Anorectal malformation (ARM) is a heterogeneous group of congenital anomalies. It can be syndromic, nonsyndromic, sporadic, or familial with different modes of inheritance. The aetiology of nonsyndromic ARMs remain unclear due to the multifactorial involvement of genetic and non-genetic risk factors. Several researchers found that about 2-8% of patients with ARM have an affected first or second-degree relative[30,37]. The occurrence of familial ARMs seems to be higher in such patients with the presence of a perineal or vestibular fistula. The association of ARM and common chromosomal anomalies is well known with an incidence of approximately 5-10%[14]. It is also observed that ARMs have been associated with mutations in almost all chromosomes.

Microdeletion of chromosome 22q11.2 (DiGeorge syndrome) and Trisomy 21 (Down syndrome) are leading causes of anorectal malformations. Other genetic syndromes are also associated with ARMs including Townes-Brocks syndrome, Opitz Frias, Johanson-Blizzard, Lowe syndrome, Mckusick- Kaufman, Pallister-Hall and Fragile X syndrome[32,67]. Some epidemiological studies also support the role of teratogenic agents in the development of ARMs[63,68]. Different animal models showed that the SHH, WNT, FGF and BMP signalling pathways are essential in the development of the hindgut[43,52].

Chromosomal anomalies associated with ARM

The incidence rate of ARMs with chromosomal abnormalities is ranging from 5-10%. Microdeletion of chromosome 22q11.2 and trisomy 21 are the most common chromosomal mutation in patients with ARMs. Clark et al found a significantly higher incidence of chromosomal anomalies among 1,846 babies with ARM. They found the number of cases of trisomy 13, 18, 21 and 22 among babies with ARM was 12, 20, 39 and 3 respectively which were very high in comparison to the same age group in the general population (Table 2)[10,11]. Wong et al[66] identified 12 chromosomal aberrations that were unique in ARM patients. In the same study, they noted that these chromosomal aberrations were unique in the patients and they were not identified in controls or the healthy individuals of the Database (Genomic Variants).

Trisomy 21: The association between trisomy 21 (Down syndrome) and ARM is well known. Trisomy 21 is more frequent in the general population with a higher rate of deformities without fistula (35-40%) and less than 0.5% in patients with a fistula. Gupta et al[17] have reported 4 cases (17%) out of 24 children with ARM. Of the 4 down syndrome cases, 3 were males and one was female. In one study of Japan, 5.1% of the patients had down syndrome without any gender variation.

Table 1
Most common associated anomalies and their frequency in ARMs Patients[33,47].

S. N.	Affected System	Incidence (%)	Anomalies
1.	Cardiovascular	30-35	Tetralogy of Fallot, atrial septal defect, ventricular septal defect, dextrocardia, coarctation of the aorta
2.	Gastrointestinal	5-10	Oesophagal atresia; duodenal, jejunal, or ileal atresia; absent colon; intestinal malrotation; volvulus; Meckel diverticulum
3.	Other skeletal	13-16	Hip dislocation or dysplasia, a fusion of iliac bones, Madelung deformity, arthrogryposis, clubfoot, polydactyly, limb deficiency
4.	Spinal cord and spine	25-30	Sacral agenesis, vertebral dysplasia, spina bifida, tethered cord, myelomeningocele
5.	Urogenital	29	Vesicoureteral reflux, hydronephrosis, bilateral or unilateral renal agenesis, renal dysplasia, renal ectopia, horseshoe kidney, polycystic kidney, renal duplication, megaureter, exstrophy of the bladder, micropenis, hypospadias, double uterus or double vagina, vulvovaginal atresia, ambiguous genitalia

Table 2
Some chromosomal anomalies associated with ARM patients[11].

Chromosomal anomalies	Number of cases (out of 1,846 ARM patients)	Per cent
Trisomy 8 mosaic	1	0.05%
Trisomy 13	12	0.65%
Trisomy18	20	1.08%
Trisomy 21	39	2.11%
Trisomy 22	3	0.16%
Sex chromosome aneuploidy	4	0.22%
Triploidy	1	0.05%
Tetrasomy 12 p	2	0.11%
Ring (13)	3	0.16%
Deletion 5p	3	0.16%
Extra fragment	3	0.16%
Partial tri/monosomy	21	1.14%
Other chromosome anomalies	17	0.92%

In the same study, the incidence of high ARM, intermediate ARM and low ARM was 2.7%, 18.7% and 4.1% respectively[5,13,59]. In another large series study of 5,581 patients with ARM, down Syndrome was found in 50 cases (0.9%)[24].

Trisomy 18: Many authors have described the association between trisomy 18 (Edward syndrome) and ARM. Cuschieri et al[11] reported an incidence of 1.08% for trisomy 18 cases among all cases of ARM. Cho et al[9] also observed a similar result[9]. Brantberg et al[6] found 1 case (1.7%) of trisomy 18 among 59 cases with imperforate anus. Schinzel had reported the association of anal atresia and stenosis with trisomy 18 in men. The medical literature on trisomy 18 does not unveil on the cause of anorectal malformation.

Trisomy 13: The phenotype of trisomy 13 is widely variable but well recognized. The spectrum includes holoprosencephaly, microcephaly, scalp defects, ocular abnormalities, cleft lip and palate, low-set ears, dysplastic auricles, micrognathia, overlapping fingers, polydactyly, congenital heart defects, renal and genital abnormalities[23,38]. According to reports in the medical literature, the association of trisomy 13 with anorectal malformation is unusual and not frequently reported. Chen et al[8] suggested that trisomy 13 is responsible for the high rate of spontaneous abortion and intrauterine death. In a study of 1,846 patients with ARM, 0.65% of the patients had trisomy 13[11].

Endo et al[13] has reported 5% cases of trisomy 21, but none had found any trisomy in 13 patients with ARM out of 1,992 patients. In a study of 103 patients with an anorectal malformation, one had trisomy 13[9]. This prevalence shows a genuine association between trisomy 13 and ARM with an unusual anorectal anomaly.

Genetic syndromes associated with ARM

Other genetic syndromes are associated with ARMs such as Townes-Brocks syndrome, Pallister-Hall syndrome, Kaufman-Mckusick Lowe syndrome, Fragile X syndrome and Johanson-Blizzard syndrome. The occurrence of familial ARM has been reported 2. 4 and 8%. Some studies showed that the genes *SHH, EN2 and HLXB9* are associated with anorectal malformation. *HLXB9* is responsible for Curranino syndrome which is autosomal dominant[19,32].

Townes-Brocks syndrome: Townes-Brocks syndrome (TBS) is a rare autosomal dominant syndrome which was first described in 1972 by Townes and Brocks[58] with an estimated incidence rate of 1:250,000 live births. TBS is the most common anal anomaly including the imperforate anus and anal stenosis. Serville et al[53] outlined some typical features including imperforate anus, anal stenosis, dysplastic ears and thumb malformations with some minor features including hearing impairment, foot malformation, renal impairment, genitourinary malformation and congenital heart malformations. Cameron et al[7] noted that TBS patients with ARMs might have mild/severe mental retardation.

TBS is caused by a mutation in the *SALL1* gene located on the long arm of chromosome 16 (16q12.1). The underlying molecular mechanism for TBS is still under investigation. At least 29 mutations have been reported in affected individuals with scattered mutations, all over the *SALL1* gene. The *SALL1* gene is part of a group of the SALL family. This gene is responsible for the formation of tissue and organ before birth. In some patients, TBS has a mutation in the *SALL4* gene[27].

TBS is inherited by an autosomal dominant fashion which means that one copy of the mutant gene in each cell is sufficient to cause the disease. Surka et al[57] found a 3-generation family in which seven individuals had TBS and they suggested that cardiac evaluation is essential in all patients with this disorder.

Pallister-Hall syndrome: Pallister- Hall syndrome (PHS) is a pleiotropic autosomal dominant disorder. It is

characterized by hypothalamic hamartoma, polydactyly, imperforate anus and respiratory tract anomalies. PHS was initially described in 1980 in six infants by Hall et al[20]. This syndrome is sporadic with unknown prevalence.

It is caused by a mutation in the *GLI3* gene which is inherited in an autosomal dominant fashion. The *GLI3* gene family is responsible for the natural shaping of many tissues and organs during the early stage of development before birth. *GLI3* gene is located on the short arm of chromosome 7 at position 14.1 (7p14.1). Up to 40 mutations in the *GLI3* gene were reported to cause Pallister-Hall syndrome. Most of these mutations occur near the middle of the gene which is involved in premature stop signals for making the *GLI3* protein[22,60].

The *GLI3* gene encodes a downstream member of the Sonic Hedgehog (*SHH*) signalling pathway. Motoyama[36] suggested that the *SHH* mutations may cause holoprosencephaly in humans. Although, in humans, no mutations have been identified in patients with ARM. However, Mo et al[35] reported that some genes from the Sonic Hedgehog signalling pathway show abnormal anorectal development. A similar report has been found for clocal development in Zebrafish[40].

Currarino Syndrome: Currarino syndrome (CS) was first described by Guido Currarino, an American radiologist in 1981. It is a multiple anomalies syndrome and the main characteristic features are partial sacral dysgenesis, presacral mass and anorectal malformation. The estimated incidence rate of CS is approximately 1 in 100,000 people[26]. The female and male ratio of CS is 1.7:1. Lynch et al[31] noticed CS is more frequent in females than males due to the coexistence of the gynaecological or urological problems. In the same study, about 33% of cases may be asymptomatic. Most of the cases with this syndrome related to an autosomal dominant pattern with highly variable expression[31,41].

The *HLXB9* gene has been found as the major causative gene in Currarino syndrome. This gene is located on the long arm of chromosome 7. Some studies showed that the 7q39 locus of chromosome 7 plays a significant role in CS. This region was identified by linkage analysis of the causative gene of CS. The locus 7q39 includes three important genes, the first is Sonic Hedgehog (*SHH*) which is a crucial molecular factor for early embryogenesis. The mutations of this gene are responsible for holoprosencephaly in humans. The remaining second and third genes, namely *EN2* and *HLXB9*, are also essential for early development before birth. The *HLXB9* gene mutation is a major cause of Currarino syndrome.

Horn et al[21] reported four cases of holoprosencephaly and CS due to mutation of *HLXB9* and *SHH* gene at 7q36.3 location. Many reports have been identified that there are approximately 82 causative mutations in this gene is mapped to the 7q36 region and encodes a transcription factor with no genotype-phenotype correlation so far. A variety of different kinds of mutations are found causing CS in total nine missense, two nonsense, two splicing and six homozygous microdeletions[19,21,48].

Caudal Regression Syndrome: Caudal Regression Syndrome (CRS) is a heterogeneous group of caudal anomalies. CRS is a rare syndrome with an incidence of 1:7500-100,000 while some authors found a higher incidence of 1:200-1000[12,64]. The male and female ration of CRS is 2.7:1. Maternal diabetes, genetic factors and hypoperfusion are the leading causes of the development of CRS. It may also be associated with pulmonary hypoplasia and congenital heart disease with some other anomalies like anorectal atresia, imperforate anus, tethered cord, lipomyelomeningocoele, scoliosis hip dislocation and contraction and club foot. CRS is about 200-400 times higher in patients with a maternal history of Insulin-Dependent Diabetes Mellitus type I or types II than non-diabetic mothers. The authors also found that the incidence of CRS is 16% to 22% in the offspring of the diabetic mother against 0.2% to 1% in the offspring of a non-diabetic mother[15,56].

These findings support the association between environmental factors (hyperglycemia, insulin, hormonal imbalance) and the development of CRS. The contrary of the several cases has no association with maternal diabetes and it may be associated with *VANGL1* gene mutation. This gene is located on the short arm of chromosome 1 (1p13) inherited as an autosomal dominant fashion.

Battaglia et al[2] described three cases with anal anomalies, two with anteriorly displaced and one with imperforate out of 60 cases with a 1p36 deletion, while Gajecka et al[16] did not find any anal anomalies in 59 cases with 1p36 deletion syndrome.

Cat Eye Syndrome: Cat Eye Syndrome (CES) is a type of a rare chromosomal anomaly which was first described in 1965 by Schachenmann and co-workers.[49] The classical features of this syndrome are Ocular coloboma, anorectal, heart, ear, renal malformations and variable intellectual disabilities. CES is often associated with variable phenotypes ranging from normal to severe abnormalities. It is estimated to have an incidence rate of 1:50,000-150,000[4].

It is hard to define exact clinical criteria for this syndrome but a preauricular tag or pit is the characteristic feature in CES. This syndrome is usually associated with a supernumerary marker chromosome consisting of duplicate material of chromosome 22[50]. Many authors found the incomplete trisomy for chromosome 22 and 11 in cases of CES[49,65]. Mosaicism can be a particular feature of familial CES. Wenger et al[62] reported the marker chromosome in a proband and his mother by conventional cytogenetic techniques. The 22q11 region of chromosome 22 is playing a vital role in the expression of all or most of the features

associated with CES. This region is a CES critical region which contains approximately 12 genes.

Other Syndromes: Further genetic syndromes associated with anorectal malformation include Mckusick- Kaufman, Fragile X syndrome, Lowe syndrome, Johanson-Blizzard syndrome, Opitz Frias syndrome, Opitz G syndrome, Charge syndrome and Fraser syndrome. These syndromes are summarized in table 3.

Conclusion

The genetics of anorectal malformation is very complicated. The genetic classification of ARM is not so easy because they are influenced by different factors such as sex and associated anomalies. It can be only nonsyndromic or syndromic and may occur in a sporadic or familial with varying modes of inheritance. The present knowledge of the genetics of ARM is still in developing stage due to its phenotypic variability and their multigenic origin. The genetic information related to anorectal malformation may provide a greater understanding of the development of the disease. Hence, the knowledge of the genetics of anorectal defects may be beneficial for paediatric surgeons, physicians and researchers for risk prediction, accurate diagnosis, focused treatment and preventive screening and patient care. Genetic counselling can play a significant role in the estimation of recurrence risk in patients and their family members.

Several syndromes associated with anorectal malformations usually tend to repeat itself in the successive generation of affected individuals with a 50% recurrence risk variable expression. Congenital anomalies are a subject of intense interest and much research.

Table 3
Genetic syndromes associated with ARMs.

S. N.	Syndrome	Features	Mode of inheritance	Genes (Chromosomal location)
1.	Mckusick- Kaufman	Genitourinary malformations, especially hydrometrocolpos, polydactyly and, more rarely, heart or gastrointestinal malformations	Autosomal recessive	*MKKS* (20p12.2)
2.	Fragile X syndrome	Moderate to severe mental retardation, macroorchidism and distinct facial features, including long face, large ears and prominent jaw.	X linked dominant	*FMR1* (Xq27.3)
3.	Lowe syndrome	Hydrophthalmia, cataract, mental retardation, vitamin D-resistant rickets, aminoaciduria and reduced ammonia production	X Linked recessive	*OCRl* (Xq26.1)
4.	Johanson-Blizzard	Pancreatic insufficiency, failure to thrive, short stature, abnormalities of permanent teeth, distinctive skull and facial features, intellectual disability.	Autosomal recessive	*UBR1* (15q15.2)
5.	Opitz Frias	Hypertelorism or telecanthus, laryngotracheoesophageal cleft, clefts of lip, palate and uvula, swallowing difficulty and hoarse cry, genitourinary defects, mental retardation, developmental delay and congenital heart defects.	Autosomal dominant	*SPECC1L* 22q11.2
6.	Opitz G	Hypertelorism, hypospadias, swallowing difficulties.	X linked recessive	*MID1* gene (Xp22.2)
7.	CHARGE	Congenital anomalies, including choanal atresia and malformations of the heart, inner ear and retina	Sporadic or autosomal dominant	*CHD7* (8q12.2)
8.	Fraser	Cryptophthalmos with other malformations, cryptophthalmos-syndactyly syndrome.	Autosomal recessive	*FRAS1* (4q21.21), *FREM2* (13q13.3), *GRIP1* (12q14.3)

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