Chapter -1

Introduction
Congenital malformations are a major problem in present society leading to prenatal death as well as socioeconomic burden. In India, congenital malformations are a major cause of death of neonates and its incidence is especially high in stillbirths (Talukder et al., 2006). Globally, at least 7.6 million children are born annually with severe genetic or congenital malformations and 90% of these are born in mid and low income countries. According to March of Dimes (MOD) global report the frequency of congenital malformation worldwide reported to be 6% of total birth (Patel et al., 2017; Singh et al., 2016). In India birth defects prevalence varies from 61 to 69.9/1000 live births (Sharma, 2013). Major congenital developmental disturbances are defined as structural defects of the body and/or organs that impair viability and require intervention (Singh et al., 2014). Minor morphogenetic errors are small structural developmental disturbances that do not impair viability and do not need to be treated. Congenital malformation may occur sporadically or may be the result of various inherited genetic anomalies (Cifuentes et al., 1996). Environmental factors, diet, infections and other causes are much less common. About 20% of all major congenital malformations are genetically transmitted by a monogenic abnormality, 5-10% are due to chromosomal anomalies, and 2-10% are due to viral infections. The rest 60% of the cases, are presumed to be multifactorial i.e., caused due to aggregative effects of more than one genetic risk factors (mutations, polymorphisms, epigenetic changes etc.) together with the effects of extrinsic factors. Recently Patel and Adhia (2005) detected major malformations in 7.92% of 17653 births in India and were able to attribute chromosomal cause to 4%, polygenic to 45.1% and total genetic aetiology to 65.4% (Patel et al., 2005). One study by Bhat and Babu in 1998 from India reported that the overall incidence of malformations was 3.7%. The frequency of malformations was 3.2% among live births, and 15.7% among still births. Musculo-skeletal malformations were the commonest (9.69 per 1000) followed by cutaneous (6.33 per 1000), genitourinary (5.47 per 1000), gastrointestinal (5.47 per 1000), central nervous system (3.99 per 1000) and cardiac anomalies (2.03 per 1000) (Bhat et al., 1998). Recent study carried out in three centers (Mumbai, Delhi and Baroda) on 94610 newborns by using a uniform proforma showed a malformation frequency of 2.03% with neural tube defects and musculo-skeletal disorders were the most common (Verma, 2000).
Congenital limb malformations are among the most frequent congenital malformations in humans caused by genetic mutations or teratogenic effects resulting either in abnormal, loss of, or additional skeletal elements (Zuniga et al. 2012) with a frequency of about 1 in 500 live births for upper limbs (Giele et al. 2001). Upper limb is affected more than the lower limb, although only one study reported the frequencies of upper limb and lower limb deficiencies as 73.3% and 23.7%, respectively among all limb malformations (Gold et al., 2011). Study reported that up to 18% of all children with a congenital limb malformation die before the age of 6 years, usually because of associated, more serious organ malformations and/or dysfunctions (Giele et al. 2001, Talukder et al., 2006; Castilla et al., 1998). The human congenital malformations are caused by alterations affecting the morphoregulatory gene networks that control early limb bud patterning and outgrowth (Zuniga et al. 2012). Specific genes are involved in a number of signaling pathways that regulate different aspects of limb bud growth and patterns of development in three axes: dorsal–ventral, anterior–posterior, and proximal–distal (Barham et al., 2008). Disruptions in such genes have been associated with limb defects (Barham et al., 2008).

Origin of the research problem

Limb defects often result in compromised hand and feet movements that lead to non-ambulation as well as malfunction of hands. Sometimes the limb malformations were too severe (adactyly) that patient have to depend on others to accomplish their daily work. This also leads to psycho-social trauma for both the patients as well as family members. Furthermore, it also disturbs patient’s self-esteem and jeopardizes his or her quality of life. This also leads to huge economic health burden on the family. Limb malformation is not just a cosmetic complication but study suggested that many mutations that cause limb malformation also affect the development of other organ systems. Clinical geneticists use specific patterns and combinations of malformations to delineate specific syndromes and identification of the underlying molecular basis that helps to refine the diagnosis process and provides new developmental links between apparently disparate organ systems. Furthermore the study of inherited human limb malformations throw up new genes not previously suspected to play a role in limb development (Wilkie, 2003). There is need to delineate the precise role of these genes to analyze the underlying developmental
mechanisms. The identification of causative gene mutations is important for genetic counseling and also provides insights into the mechanisms controlling limb development. More specifically limb malformations are important manifestation in clinical medicine not only because of its cosmetic and functional implications but because it can serve as an immediately recognizable indicator that the patient, particularly a newborn, has a multiple congenital anomaly syndrome (pleiotropic developmental anomaly syndrome) (Leslie et al., 2011). For these reasons, it is important for the clinician to be prepared to evaluate the patient for limb malformation and consider the myriad syndromes that may be associated with this anomaly. Analysis of tissue specific gene expressions at development stages would improve our understanding of factors involved in the development and identification of genetic risk factors for limb malformation. Detailed information about global gene expression during human limb bud development is crucial for understanding the gene regulatory networks underlying development and the various signal transduction pathways contributing to morphogenesis.