

# Mutations in *HODX13* and *ZRS/LMBR1* genes and chromosomal abnormalities cause congenital limb defects

## Abstract

Congenital limb defects occur when a portion or the entire upper or lower limb fails to form normally. The most common congenital limb defects include complete or partial absence of the limb, failure of the portion of the limb to separate, duplication, overgrowth or undergrowth of the limb. Presently, congenital limb defects are treated by the use of prosthetic devices, which are mostly valuable for lower-limb deficiencies and for completely or almost completely absent upper limbs. The most common known causes for congenital limb defects are genetic mutations and chromosomal abnormalities. However, details about how they exert their effect are still less understood.

**Keywords:** genes, upper limbs, lower limb, congenital limb defects, genetic mutations, chromosomal abnormalities

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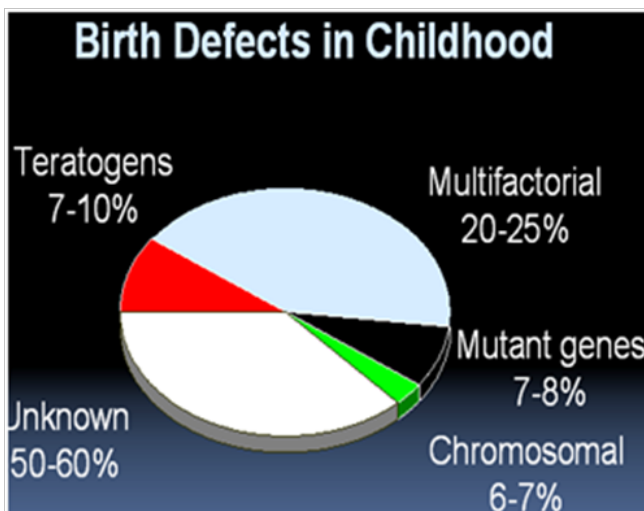
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## Introduction

Congenital limb defects (CLDs) are common and exhibit broad phenotypic variability. Depending upon the severity, they cause varying degrees of disability which may severely affect the quality of life of the affected subject. Genetic factors and chromosomal defects are the most common causes of congenital malformations and account for approximately one fourth of them (Figure 1). Congenital limb defects (CLDs) are common and readily identifiable. Their detection rate is expected to be less affected by geographical and temporal factors. Consequently, these defects can serve as indicators in a search for genetic and environmental causes.<sup>1</sup>



**Figure 1** Most common causes of congenital malformations.

## Literature survey

Different classification schemes have been used for limb

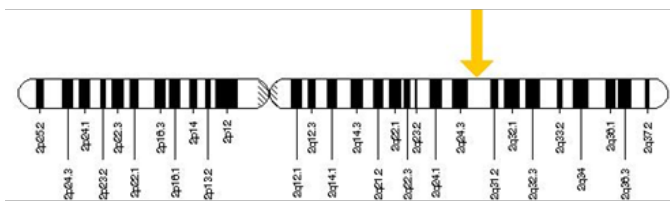
malformations.<sup>2,3</sup> The major categories of limb defects include:

- Presence of deformity,
- Brachydactyly,
- Syndactyly,
- Polydactyly,
- Macroductyly,
- Arachnodactyly,
- Contracture deformity,
- Carpal-tarsal synostosis,
- Symphalangism,
- Digital malformations with congenital ring constrictions.

In many instances, it is possible to sub-classify the type by the site of the malformation.<sup>4</sup> Furthermore, each major class is subdivided into one of two main groups according to whether abnormalities are essentially limited to the limbs or associated with malformation in other organs. Finally, mode of inheritance is also considered in the precise categorization of limb abnormality.<sup>1</sup> The different genes and chromosomal abnormalities involved in limb malformations are:

### HOXD13 gene

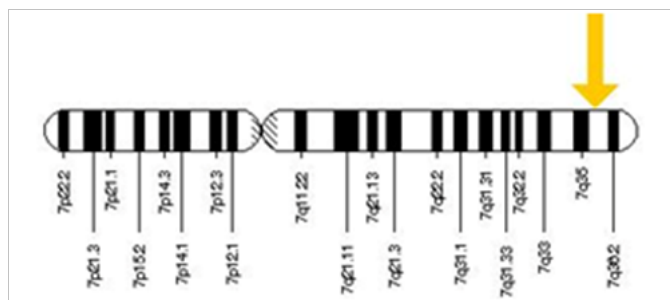
The HOXD gene cluster is located on chromosome 2 (Figure 2). Deletions of the entire HOXD gene cluster or only the 5' end of this cluster have been shown to result in limb and genital abnormalities. Mutations in HOXD13 gene can cause synpolydactyly and brachydactyly. This gene encodes a transcription factor, Homeobox protein (Hox-D13), which plays an important role in morphogenesis.<sup>5</sup> Hox-D13 protein plays a role in axial skeleton and forelimb development.<sup>6</sup>



**Figure 2** HOXD gene cluster located on chromosome 2.

### ZRS/LMBR1 gene

The ZRS/LMBR1 gene (Figure 3) encodes for a member of the LMBR1-like membrane protein family.<sup>7</sup> A cis-acting transcription factor for the sonic hedgehog gene is located in the intron of this gene. Mutations in this gene can alter limb development in sonic hedgehog. However, it is not known if this gene functions directly in limb development and can result in chiropody and pre-axial polydactyl.



**Figure 3** LMBR1 gene located on the long (q) arm of chromosome 7 at position 36.

### Chromosomal abnormalities

A correct amount of chromosomal material is essential for normal body formation and function. Common kinds of chromosomal abnormalities include chromosomal trisomies, deletions, duplications and mosaics. The majority of chromosomal trisomies arise from non-disjunction at meiosis. There are a few well recognized syndromes associated with autosomal trisomies such as Down's syndrome (trisomies 21),<sup>8</sup> Edward's syndrome (trisomies 18)<sup>9</sup> (Figure 4) and Patau's syndrome (trisomies 13).<sup>10</sup> In the case of trisomies 18, there is absence of the thumb. The characteristic hand deformity is tight flexion of the fingers with the 2<sup>nd</sup> and 5<sup>th</sup> digits and overlapping 3<sup>rd</sup> and 4<sup>th</sup> digits.



**Figure 4** Trisomy 18 (Edward's syndrome) is caused by an abnormality in chromosome 18 (shown by an arrow).

### Future direction

Regenerative medicine is an interdisciplinary field which applies engineering and life science principles to promote regeneration. It can be used to restore diseased and injured tissues and whole organs. It has the potential to correct for congenital defects. The field of regenerative medicine contains various strategies that include the use of materials and de novo generated cells to replace missing tissue, both structurally and functionally.

### Acknowledgements

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### Conflict of interest

The author declares no conflict of interest.

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