Publisher Name: ZenToks Books
Editorial Book: Emerging trends in medical research and practice
ISBN: 978-81-986895-9-7

Chapter 1

Molecular mechanism of dysmorphology

Prashant Kumar Verma[1*]

[1]*Additional Professor Department of pediatrics, Medical Genetics Division AIIMS Rishikesh, Uttarakhand, India*
[*]*Corresponding Author:*

Dysmorphology is a discipline of medical genetics that studies body structural changes from normal to abnormal for understanding the patterns of variation, etiologies, classification, and pathophysiology and utilizing that knowledge in the management of structural birth defects. Structural birth defects (SBDs) are congenital birth defects that all have changes in size or shape or symmetry of any tissue(s), and they can be recognized as anomalies through clinical or non-molecular investigations at birth or later in life [1].

Major and minor anomalies are two broad categories of SBD on the basis of severity of tissue dysfunction. Major anomalies (1-3 %) need urgent attention due to incompatibility with normal life expectancy without management, as do most structural developmental defects of internal organs for example, congenital heart disease, omphalocele, and myelomeningocele. Minor anomalies, the most common types of anomalies (12-15%), do not need any specific management at birth. A minor anomaly is called a variant in case of its presence in family members in isolated form. Minor anomalies usually do not associate with any significant tissue dysfunction, and they are often not recognized in milder form. The number of minor anomalies is directly proportionate to the increased possibility of major anomalies and syndromic diagnosis. Various syndromes are recognized at birth by the presence of a specific unique anomaly or constellation of anomalies. There are well defined criteria for each anomaly in the literature. It is always preferable to take medical photography, video recording, and standard anthropometry for dysmorphic structure with adequate consent [1, 2].

Understanding the mechanism of anomaly helps in the patient's overall management and genetic counselling. In the pre-molecular era, the primary mechanisms for all birth defects are classified in four categories malformation, deformation, disruption, and dysplasia. Malformations are further divided into four categories as unrecognized malformation(s), malformation sequence, malformation association, and malformation syndrome [3]. Deformation and disruption both have primary normal structure, and there are secondary changes in the tissues. In deformation, changes are limited to musculoskeletal due to mechanical forces without any tissue loss. While significant targeted fetus tissue damage by apoptosis in disruption likely hampers the blood supply by various causes[4, 5].

Primary tissues are not normal in case of dysplasia and malformation. Malformation happens due to a primary error of morphogenesis and usually involves two or more than two organ systems. Whereas a morphogenesis defect in only one tissue lineage leads to tissue dysplasia like skeletal, cortical, and ectodermal dysplasia, and so on. A pattern of events after a first primary insult is called a malformation Sequence; however, an undefine pattern without any available literature database is called an unrecognized malformation. Syndrome and association both have characteristic constellations of findings[6].

Most of this nomenclature is based on clinical evaluation with limited molecular diagnosis and knowledge. These all nomenclatures have overlapped phenotypes and several exceptions for classifying a phenotype in various categories. Many dysplasias are also counted as malformations; dysplasia can be presented as a sequence, deformation could be part of any other phenotype, and so on. Even the same phenotype is named differently in different resources as amniotic band sequence, amniotic band syndrome, or Streeter's dysplasia [7, 8]. Besides that, the phenotypic spectrums in all categories of SBDs originate from a single event, that initiate the further secondary changes, so all should be called sequences ideally.

So, with our recent knowledge of molecular science, all SBD can be classified on the basis of intrinsically normal or abnormal DNA. Figure 1 is displaying that all SBDs are in the sequence due to the cascade of secondary events after the primary defect. In an intrinsically

How To Cite: P.K Verma. *Molecular mechanism of dysmorphology*. In J.E. Anieche (Eds). Emerging Trends in Medical Research and Practice. Pages 1-3, 2025. ZenToks Books, India. ISBN: 978-81-986895-9-7

normal group, deformation and disruption events occur even without obstinacy or alternation of protein or RNA functions, while all malformations with teratogenic agents usually affect proteins or RNAs level at early developmental stages in the cells. All recognized or unrecognized SBDs with normal antenatal history could have possibilities of intrinsic abnormal DNA.

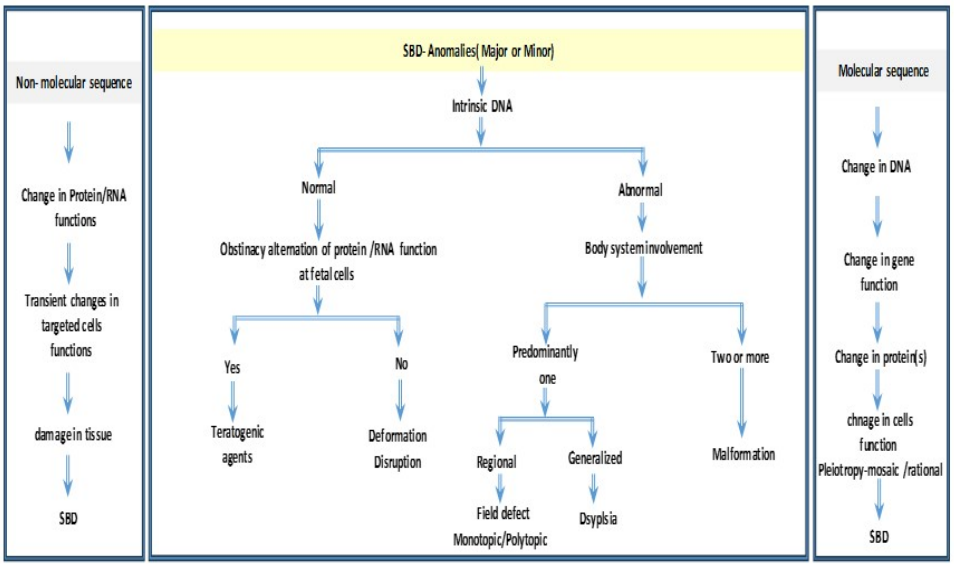

Figure 1: Diagram

Intrinsically abnormal DNA-based malformations can be divided into two broad categories on the basis of body system involvement. Tissue dysplasia usually involves the whole body but primarily a single body system due to the gene dominantly expressed in particular cell lines; however, the mosaic molecular defect or in field development, only a region of the body, such as the heart, kidney, or brain, develops a structural abnormality.

The malformations are related to the genes or gene pathways that express in various tissues. Understanding the molecular sequencing helps to know the initial step of cellular dysfunction and might guide us for identification of a specific anomaly from all anomalies, which is useful for identification of a syndrome that is also likely correlated with the gene family of the gene pathway. Despite next-generation sequencing, it is quite common to fail to detect genotyping without a clinical diagnostic clue; besides that, getting a variation of unknown significance requires reevaluating the case to match genotype with phenotype.

Most of Gene' family and pathways have a distinctive anomaly with variable levels of severity and penetration. Indirectly, the gene pathway has specific role at the cellular level, and altering the gene function leads to a particular chain of events, a molecular sequence, which can be recognized clinically. There is a paucity of literature with this correlation due to the very wide subject, lack of availability of easy-handling syndromic searching software and dysmorphologists, genetic heterogenicity, and presence of a newer phenotype or locus. Third-world medical centers with low resources fail to detect these DBD and having the list of phenotypic clues by understanding molecular sequencing can help for both physician and family in many aspects, such as initial counselling, future planning, and further research.

Wingless type (Wnt), Sonic hedgehog (SHH), tumor necrosis factor (TNF), transforming growth factor-β (TGF-β), the Endothelin, Fibroblast growth factors (FGF) , the Neurogenic locus notch homolog protein (NOTCH), the Rat sarcoma (Ras)- mitogen activated protein kinases (MAPK), the phosphoinositol 3-kinase (PI3K), and Liver kinase B1 (LKB1) are nine signaling pathways are well studied in the literature and those have a strong contribution to the initial development and differentiation of the embryo, although many of them have lifelong other functions for cellular maintenance and modification in a certain extent, and dysregulation of these developmental pathways usually associated with a precancerous state [9, 10].

Figure 1 depicting these, displaying common genetic syndromes reported with these developmentally related signaling pathways. Involvement of the appendicular system is a predominant feature in the genes related to Wnt pathways, while facial & cephalic anomalies are prime features of SHH pathways. Ectodermal findings are characteristic features of TNF pathway genes. Superfamily TGF-β is involved in midline orientation, cartilage differentiation, and regulation of vascular development. Neural crest cell migration-related disorders are broadly recognized as neurocristopathies related to dysfunction of endothelian signaling pathway [11].

FGFS pathways-related genes are well known for being the leading cause of bone dysplasia and craniosynostosis principally, but other genes in this pathway are also related to kinase and also lead to vascular malformation, eyelid abnormalities, and hypogonadotropic hypogonadism [12]. While various types of Waardenburg syndrome are reported with genes (EDNRB, EDN3, and SOX10) of the endothelian signaling pathway[13].

The RAS pathway regulates cell proliferation and survival, so all syndromes reported with RAS pathways have a slightly increased risk of malignancy overlapping features like coarse facies, short stature, and subtle to significant facial dysmorphology [14].

Predominantly congenital vertebral defects are seen with defects in the NOTCH signal pathway with variable other system tissue

involvement [15] .P13K-LKB1 pathway genes regulate the cellular growth at the tissue level, so defects in their functions lead to various hamartoma related syndromes [16].

Especially, RECQL, and ERCC Gene families' disorders usually have variable progeria phenotype, which characterized by ectodermal changes of aging including lipodystrophy, metabolic syndrome, and increase risk of tumors because they are related to DNA repair and maintenance [17, 18].

Genes in those gene families that are not yet in pathways, like the PAX, TBX, SOX, FOX, and HOX gene families, do not share common phenotypes in their families.

Understanding the molecular mechanism explain the phenotype, further evolution of complete phenotype and possible evolving new therapies at different steps of disease progress at cellular level.

References

[1] A. M. St Louis, K. Kim, M. L. Browne, G. Liu, R. F. Liberman, W. N. Nembhard, et al. Prevalence trends of selected major birth defects: A multi-state population-based retrospective study, united states, 1999 to 2007. *Birth Defects Res.*, 109(18):1442–50, 2017.

[2] X. Zhou, D. Xie, Y. Jiang, and J. Fang. Prevalence and death rate of birth defects from population-based surveillance in hunan province, china, 2010-2020. *Sci Rep*, 14(1):14609, 2024.

[3] W. Reardon and D. Donnai. Dysmorphology demystified. *Arch Dis Child Fetal Neonatal Ed*, 92(3):F225–9, 2007.

[4] S. Grubesa Raguz, M. Jerkovic Raguz, J. Brzica, S. Dzida, S. Mikulic, A. Kolobaric, et al. Meaning and clinical interest of minor malformations and normal variants in neonatology. *Balkan J Med Genet*, 27(1):37–42, 2024.

[5] M. I. Van Allen. Structural anomalies resulting from vascular disruption. *Pediatr Clin North Am*, 39(2):255–77, 1992.

[6] M. M. Howley, E. Williford, A. J. Agopian, A. E. Lin, L. D. Botto, C. M. Cunniff, et al. Patterns of multiple congenital anomalies in the national birth defect prevention study: Challenges and insights. *Birth Defects Res.*, 115(1):43–55, 2023.

[7] J. E. H. Bergman, I. Barisic, M. C. Addor, P. Braz, C. Cavero-Carbonell, E. S. Draper, et al. Amniotic band syndrome and limb body wall complex in europe 1980-2019. *Am J Med Genet A*, 191(4):995–1006, 2023.

[8] E. Lopez-Munoz and L. E. Becerra-Solano. An update on amniotic bands sequence. *Arch Argent Pediatr*, 116(3):e409–e20, 2018.

[9] R. Hayat, M. Manzoor, and A. Hussain. Wnt signaling pathway: A comprehensive review. *Cell Biol Int*, 46(6):863–77, 2022.

[10] B. T. MacDonald, K. Tamai, and X. He. Wnt/beta-catenin signaling: components, mechanisms, and diseases. *Dev Cell*, 17(1):9–26, 2009.

[11] N. Sasai, M. Toriyama, and T. Kondo. Hedgehog signal and genetic disorders. *Front Genet*, 10:1103, 2019.

[12] D. M. Ornitz and N. Itoh. The fibroblast growth factor signaling pathway. *Wiley Interdiscip Rev Dev Biol*, 4(3):215–66, 2015.

[13] S. Huang, J. Song, C. He, X. Cai, K. Yuan, L. Mei, et al. Genetic insights, disease mechanisms, and biological therapeutics for waardenburg syndrome. *Gene Ther.*, 29(9):479–97, 2022.

[14] M. Zenker. Clinical overview on rasopathies. *Am J Med Genet C Semin Med Genet*, 190(4):414–24, 2022.

[15] B. Zhou, W. Lin, Y. Long, Y. Yang, H. Zhang, K. Wu, et al. Notch signaling pathway: architecture, disease, and therapeutics. *Signal Transduct Target Ther*, 7(1):95, 2022.

[16] T. Ersahin, N. Tuncbag, and R. Cetin-Atalay. The pi3k/akt/mtor interactive pathway. *Mol Biosyst*, 11(7):1946–54, 2015.

[17] S. Sharma, D. J. Stumpo, A. S. Balajee, C. B. Bock, P. M. Lansdorp, Brosh R. M. Jr., et al. Recql, a member of the recq family of dna helicases, suppresses chromosomal instability. *Mol Cell Biol*, 27(5):1784–94, 2007.

[18] M. Manandhar, K. S. Boulware, and R. D. Wood. The ercc1 and ercc4 (xpf) genes and gene products. *Gene*, 569(2):153–61, 2015.