AUCTORES
Globalize your Research

Journal of Pharmaceutics and Pharmacology Research
Bechan Sharma *

Open Access

Review Article

A Brief Review on Molecular Mechanisms of Congenital Diseases

Aradhna Gupta [1], Bechan Sharma [2]*

[1]Department of MLT, Delhi Skill Entreprenur University, New Delhi

[2]Department of Biochemistry, University of Allahabad, Uttar Pradesh 211002, India

***Corresponding Author:** Bechan Sharma, Department of Medical Laboratory Science, College of Medicine and Health Sciences Rhema University, Aba Abia State, Nigeria.

Received date: December 18, 2024; Accepted date: December 23, 2024; Published date: December 31, 2024

Citation: Aradhna Gupta, Bechan Sharma, (2024), A Brief Review on Molecular Mechanisms of Congenital Diseases, *J. Pharmaceutics and Pharmacology Research*, 7(12); **DOI:10.31579/2688-7517/224**

Abstract

Congenital diseases, present from birth, encompass a diverse range of disorders caused by genetic abnormalities, chromosomal defects, and environmental influences. These conditions can affect multiple organ systems and vary in severity. The molecular basis of congenital diseases includes single-gene mutations, which can disrupt protein function, and chromosomal abnormalities, such as aneuploidy, which alter gene dosage and expression. Understanding the molecular mechanisms of congenital diseases is essential for accurate diagnosis, effective treatment, and the development of preventative strategies. In this article we have discussed in brief about congenital diseases, types, cause and molecular basis of congenital disease of glycosylation, congenital hypopituitarism, and other disorders. Advances in genetic and molecular research may help in understanding the complexities conditions, offering hope for improved patient outcomes.

Key words: congenital; mutation genes; enzymes; phenylketonuria; galactosemia

Introduction

Congenital diseases (CD), or birth defects, are conditions that are present from birth. These disorders arise due to genetic, environmental, or unknown causes and can affect various parts of the body, including the structure, function, or metabolism. Congenital diseases can be inherited from parents or occur as a result of issues during fetal development.

There are mainly five types of CD briefly described here:

(1) Genetic Disorders includes (a) single gene disorders which are caused by mutations in a single gene examples cystic fibrosis, sickle cell anaemia, and Huntington's disease; (b) chromosomal disorders are due to abnormality in the number or structure of chromosomes like Down syndrome (trisomy 21), Turner syndrome (monosomy X), and Klinefelter syndrome (XXY) (c) multifactorial inheritance disorders which are again caused by a combination of genetic and environmental factors examples are congenital heart defects, cleft lip and palate, and neural tube defects like spina bifida.

(2) Structural Disorders includes (a) congenital heart defects which is mainly abnormality in a heart structure like holes in the heart (septal defects), abnormal heart valves, or abnormal connections between heart chambers; (b) Cleft Lip and Palate in this there is an opening in the lip and/or the roof of the mouth due to incomplete fusion during fetal development; (c) neural tube defects are defects in the development of the spinal cord and brain, such as spina bifida and anencephaly.

(3) Metabolic Disorders include (a) phenylketonuria (PKU) due to missing enzyme phenylalanine hydroxylase as a result body cannot properly break down the amino acid phenylalanine, leading to its accumulation resulting in brain damage if untreated; (b) galactosemia in this galactose gets accumulated in body due to missing enzyme galactose-1-phosphate uridyl transferase which catalyzes galactose degradation. The symptoms are liver damage, intellectual disability, and other health issues if not managed.

(4) Infectious Causes like infections during pregnancy, such as rubella, cytomegalovirus (CMV), or Zika virus, can lead to congenital disorders in the baby, such as hearing loss, intellectual disabilities, or microcephaly.

(5) Environmental Causes includes (a) teratogens exposure to harmful substances during pregnancy, such as alcohol leading to fetal alcohol syndrome, certain medications, or radiation (b) maternal health conditions such as uncontrolled diabetes, thyroid disorders, or malnutrition in the mother can contribute to congenital disorders. Figure 1 shows a different type of congenital diseases.

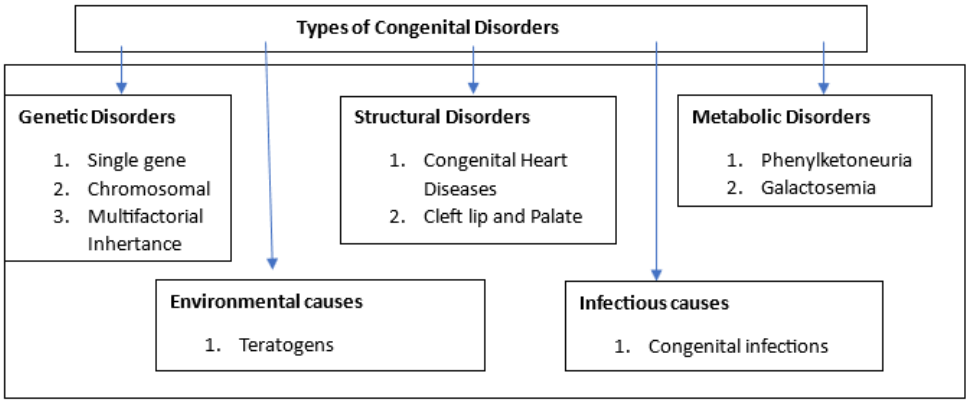

Figure 1: Types of Congenital diseases

(2) **Diagnosis/Detection** can be done before or after birth through various screening and diagnostic methods:

(1) Prenatal Screening: includes ultrasound, maternal blood tests, and non-invasive prenatal testing (NIPT) to assess the risk of congenital abnormalities.

(2) Prenatal Diagnostic Tests: procedures like amniocentesis and chorionic villus sampling (CVS) can diagnose certain genetic and chromosomal disorders before birth.

(3) Newborn Screening: after birth, babies are screened for certain metabolic, genetic, and other congenital conditions using blood tests, hearing tests, and other assessments.

(3) Treatment and Management

(1) Medical Interventions depends on the disorder condition, treatments may include medications, surgeries, or other medical procedures.

(2) Nutritional Management metabolic related disorders like PKU (phenylketonuria), dietary restrictions can prevent complications.

(3) Therapeutic Support: therapies like physical, occupational, and speech can help manage developmental delays or disabilities resulting from congenital disorders.

(4) Genetic Counselling: families affected by congenital disorders may benefit from genetic counselling to understand the risks of recurrence in future pregnancies.

(4) Prognosis/ Prevention

The prognosis for individuals with congenital diseases varies widely depending on the specific condition, its severity, and the available treatments. Some congenital diseases are manageable with early intervention and ongoing care, while others may lead to significant challenges or reduced life expectancy.

Though not all congenital diseases can be prevented, certain measures can reduce the risk: (1) prenatal care: regular prenatal check-ups, proper nutrition, and avoiding harmful substances can reduce the risk of congenital disorders (2) vaccination against infections like rubella before pregnancy can prevent certain congenital infections (3) genetic counselling for those with a family history of genetic disorders, genetic counselling can help assess risks and guide reproductive decisions.

(5) Molecular basis of some disorders:

Disorders of Glycosylation (CDG): Glycosylation is a process which occurs in post translational modifications, are a group of rare, inherited metabolic disorders that impact the process of glycosylation, a common biochemical pathway in which sugars (glycans) are attached to proteins and lipids. Its biogenesis occurs primarily in the endoplasmic reticulum (ER) and Golgi apparatus. Glycosylation is essential for the proper function and stability of many proteins, and defects in this process can lead to a wide array of clinical manifestations, reflecting the importance of glycosylated molecules in numerous physiological processes. Approximately there are at least 18 different types of CDG identified, each resulting from mutations in specific genes involved in the glycosylation pathway. These types are classified based on the step in the glycosylation process that is affected. In **Type I CDG:** involves defects in the early stages of glycan precursor synthesis or the assembly of the glycan chain before it is transferred to the protein and in **Type II CDG:** it relates to defects in the processing and modification of glycan chains after they are attached to proteins.

Defects in glycosylation affects the neurons leading to developmental delays, intellectual disabilities, seizures, hypotonia (reduced muscle tone), and ataxia (lack of muscle coordination) liver dysfunction, and gastrointestinal problems like chronic diarrhoea, and failure to thrive are common in CDG patients. [1]

Congenital hypopituitarism (CH) is a group of disorders characterized by the underdevelopment or malfunction of the pituitary gland by birth, leading to a deficiency in one or more pituitary hormones. The pituitary gland, often called the "master gland," is located at the base of the brain and is divided into the anterior and posterior lobes. It produces hormones that regulate various endocrine functions, including growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin. These hormones are crucial for growth, metabolism, and overall homeostasis.[2] At gene level the disease is due to mutations that affect the development and function of the pituitary gland, as well as the hypothalamus and other related structures. These mutations can affect transcription factors, signalling pathways, and structural proteins necessary for pituitary gland development.[3-7] Genes like PROP1, PIT1, SOX3 gene are a common cause of combined pituitary hormone deficiency (CPHD). PROP1 is a transcription factor essential for the development of pituitary cells that produce growth hormone (GH), thyroid stimulating hormone (TSH), prolactin and rare in luteinizing hormone (LH) and follicle stimulating hormone (FSH).[8-10]

Mutations in the HESX1 gene can cause septo-optic dysplasia a condition associated with congenital hypopitutarism, optic nerve hypoplasia, and

midline brain abnormalities.[11-13] HESX1 plays a role in early forebrain and pituitary development. Mutations in LIM homeobox genes LHX3 and LHX4 genes are involved in the early development of the pituitary gland. Mutations can lead to CPHD and structural abnormalities of the pituitary gland and surrounding brain structures.[14-15]

Mutations in signalling pathways: FGFR1 (Fibroblast Growth Factor Receptor 1) can cause Kallmann syndrome, which is characterized by hypogonadotropic hypogonadism and anosmia (loss of smell). FGFR1 is involved in the signalling pathways that guide the migration of gonadotropin-releasing hormone (GnRH) neurons from the olfactory region to the hypothalamus.[16-18] GLI2 is part of the Hedgehog signalling pathway, which is crucial for the development of the hypothalamus and pituitary gland. Mutations can cause holoprosencephaly, a disorder where the forebrain fails to divide into two hemispheres, and associated pituitary hormone deficiencies.[19-21]

Mutations in structural protein: Mutations in OTX2, a gene involved in head and brain development, can lead to combined pituitary hormone deficiency and eye abnormalities, including anophthalmia or microphthalmia (absent or small eyes).[22-24]

Receptor and Enzyme Deficiencies: Mutations in GHRHR (Growth Hormone-Releasing Hormone Receptor) can cause isolated growth hormone deficiency (IGHD) by impairing the response of pituitary somatotroph cells to growth hormone-releasing hormone (GHRH). Mutations in the GH1 (Growth Hormone Gene) gene itself can also lead to IGHD by affecting the production or secretion of growth hormone.

Symptoms and Diagnosis: The clinical manifestations of congenital hypopituitarism depend on the specific hormones that are deficient. Common symptoms include growth failure, delayed puberty, hypoglycemia, jaundice, and micropenis in males. In more severe cases, multiple hormone deficiencies can lead to life-threatening complications, especially in the neonatal period.

Diagnosing CH involves hormonal assays to measure the levels of pituitary hormones, imaging studies (MRI) to assess the pituitary gland's structure, and genetic testing to identify causative mutations.

Treatments include hormone replacement therapy like administration of growth hormone, thyroid hormone, cortisol, and sex steroids as needed, depending on the specific deficiencies.

(6) Other Disorders

Developmental Pathway Disruptions: Mutations in genes involved in embryonic development can also lead to congenital malformations. As, mutations in the SHH (Sonic Hedgehog) gene can cause holoprosencephaly, a disorder where the brain fails to properly divide into two hemispheres.[25-27]

Epigenetic Changes: Alterations in gene expression without changes in DNA sequence, often due to environmental influences, can result in improper imprinting of genes can cause syndromes like Prader-Willi and Angelman.

Conclusion

Congenital diseases arise from a variety of molecular mechanisms, like genetic mutations, chromosomal abnormalities, and disruptions in metabolic or developmental pathways. Understanding these mechanisms is crucial for diagnosing, managing, and potentially preventing these conditions.

Acknowledgments

The authors are grateful to the University of Allahabad for providing facilities for carrying out the present work. AG acknowledges UGC-New Delhi for providing financial support in the form of a fellowship.

Conflict of interest

The authors declare no conflict of interest.

References

1. Freeze HH, Aebi M. (2005). Altered glycan structures: the molecular basis of congenital disorders of glycosylation. Curr Opin Struct Biol. ;15(5):490-498.
2. Christopher J. Romero, Suzana Nesi-França, Sally Radovick, (2009). The molecular basis of hypopituitarism, Trends in Endocrinology & Metabolism,Volume 20(10), ,Pages 506-516, ISSN 1043-2760.
3. Kelberman D, Dattani MT. (2007). Genetics of septo-optic dysplasia. Pituitary. ;10(4):393-407.
4. Blum WF, Klammt J, Amselem S, Pfaffle HM, Legendre M, Sobrier ML, Luton MP, Child CJ, Jones C, Zimmermann AG, Quigley CA, Cutler GB Jr, Deal CL, Lebl J, Rosenfeld RG, Parks JS, Pfaffle RW. (2018). Screening a large pediatric cohort with GH deficiency for mutations in genes regulating pituitary development and GH secretion: Frequencies, phenotypes and growth outcomes. Biomedicine. ; 36:390–400.
5. Williamson KA, Yates TM, FitzPatrick DR. (1993). SOX2 Disorder. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, eds. GeneReviews((R)). Seattle (WA)
6. McCabe MJ, Alatzoglou KS, Dattani MT. (2011). Septo-optic dysplasia and other midline defects: the role of transcription factors: HESX1 and beyond. Best Pract Res Clin Endocrinol Metab. ;25(1):115-124
7. Ward RD, Raetzman LT, Suh H, Stone BM, Nasonkin IO, (2005). Camper SA. Role of PROP1 in pituitary gland growth. Mol Endocrinol. ;19(3):698-710
8. Ahmad T, Garcia-Filion P, Borchert M, Kaufman F, Burkett L, Geffner M. (2006). Endocrinological and auxological abnormalities in young children with optic nerve hypoplasia: a prospective study. J Pediatr. ;148(1):78-84.
9. Cerbone M, Guemes M., Wade A, Improda N, Dattani M. (2020). Endocrine morbidity in midline brain defects: Differences between septo-optic dysplasia and related disorders. EClinicalMedicine.; 19:1-17.
10. Skowronska-Krawczyk D, Rosenfield M, eds. (2010). Development of the Pituitary. 6 ed. Philadelphia: Saunders Elsevier. Jameson JL, Groot LD, eds. Endocrinology; No. 1.
11. Newbern K, Natrajan N, Kim HG, Chorich LP, Halvorson LM, (2013). Cameron RS, Layman LC. Identification of HESX1 mutations in Kallmann syndrome. Fertil Steril. ;99(7):1831-1837.
12. Thomas PQ, Dattani MT, Brickman JM, McNay D, Warne G, Zacharin M, Cameron F, Hurst J, Woods K, Dunger D, Stanhope R, Forrest S, Robinson IC, Beddington RS. (2001). Heterozygous HESX1 mutations associated with isolated congenital pituitary hypoplasia and septo-optic dysplasia. Hum Mol Genet. ;10(1):39-45
13. Durmaz B, Cogulu O, Dizdarer C, Stobbe H, Pfaeffle R, Ozkinay F. (2011). A novel homozygous HESX1 mutation

causes panhypopituitarism without midline defects and optic nerve anomalies J Pediatr Endocr Met.;24(9-10):779-782

14. Dattani MT, Martinez-Barbera JP, Thomas PQ, Brickman JM, Gupta R, Martensson IL, Toresson H, Fox M, Wales JK, Hindmarsh PC, Krauss S, Beddington RS, Robinson IC. (1998). Mutations in the homeobox gene HESX1/Hesx1 associated with septo-optic dysplasia in human and mouse. Nat Genet. ;19(2):125-133.
15. Ludwig P, Lopez MJ, Czyz CN. (2021). Embryology, Eye Malformations. StatPearls.
16. Ericson J, Norlin S, Jessell TM, Edlund T. (1198). Integrated FGF and BMP signaling controls the progression of progenitor cell differentiation and the emergence of pattern in the embryonic anterior pituitary. Development. (125):1005-1015.
17. Tsai PS, Moenter SM, Postigo HR, El Majdoubi M, Pak TR, Gill JC, Paruthiyil S, Werner S, Weiner RI. (2005). Targeted expression of a dominant-negative fibroblast growth factor (FGF) receptor in gonadotropin-releasing hormone (GnRH) neurons reduces FGF responsiveness and the size of GnRH neuronal population. Mol Endocrinol. ;19(1):225-236.
18. Fukami M, Iso M, Sato N, Igarashi M, Seo M, Kazukawa I, Kinoshita E, Dateki S, Ogata T. (2013). Submicroscopic deletion involving the fibroblast growth factor receptor 1 gene in a patient with combined pituitary hormone deficiency. Endocr J. ;60(8):1013-1020.
19. Wang Y, Martin JF, Bai CB. (2010). Direct and indirect requirements of Shh/Gli signaling in early pituitary development. Dev Biol. ;348(2):199-209.
20. Haddad-Tóvolli R, Paul F, Zhang Y, Zhou X, Theil T, Puelles L, Blaess S, Alvarez-Bolado G. (2015). Differential requirements for Gli2 and Gli3 in the regional specification of the mouse hypothalamus. Front Neuroanat. :9.
21. Paulo S, Fernandes-Rosa FL, Turatti W, Coeli-Lacchini FB, Martinelli CE, Nakiri GS, Moreira AC, Santos AC. (2015). Castro Md, Antonini SR. Sonic Hedgehog mutations are not a common cause of congenital hypopituitarism in the absence of complex midline cerebral defects. Clinical Endocrinology. ; 82:562–569.
22. Chassaing N., et al. (2013). Molecular findings and clinical data in a cohort of 150 patients with anophthalmia/ microphthalmia. Clin Genet.
23. Gregory LC, Gergics P, Nakaguma M, Bando H, Patti G, McCabe MJ, Fang Q, Ma Q, Ozel AB, Li JZ, Poina MM, Jorge AAL, Benedetti AFF, Lerario AM, Arnhold IJP, Mendonca BB, Maghnie M, Camper SA, Carvalho LRS, Dattani MT. (2021). The phenotypic spectrum associated with OTX2 mutations in humans. Eur J Endocrinol. ;185(1):121-135.
24. Tajima T, Ohtake A, Hoshino M, Amemiya S, Sasaki N, Ishizu K, Fujieda K. (2009). OTX2 loss of function mutation causes anophthalmia and combined pituitary hormone deficiency with a small anterior and ectopic posterior pituitary. J Clin Endocrinol Metab. ;94(1):314-319.
25. Dubourg C, Bendavid C, Pasquier L, Henry C, Odent S, David V. (2007). Holoprosencephaly. Orphanet J Rare Dis. ;2(8):8.
26. Tekendo-Ngongang C, Muenke M, Kruszka P. (1993). Holoprosencephaly Overview. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, eds. GeneReviews((R)). Seattle (WA).
27. Dubourg C, Kim A, Watrin E, de Tayrac M, Odent S, David V, Dupe V. (2018). Recent advances in understanding inheritance of holoprosencephaly. Am J Med Genet C Semin Med Genet. ;178(2):258-269.

DOI:10.31579/2688-7517/224