Al-Nisour Journal for Medical Sciences

Manuscript 1168

The Ramification of Mutations in Sonic Hedgehog Gene on the Occurrence of Deformities in the Course of the Embryonic Development Stage

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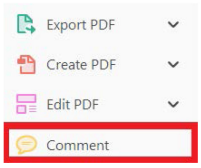

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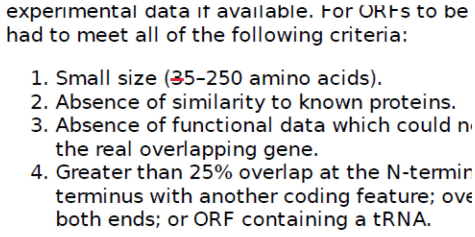

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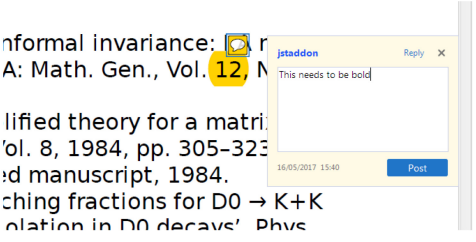

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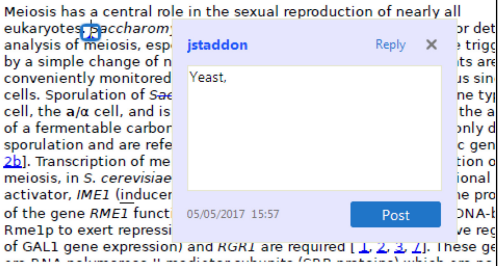

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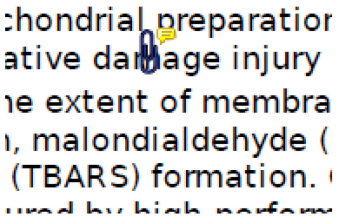

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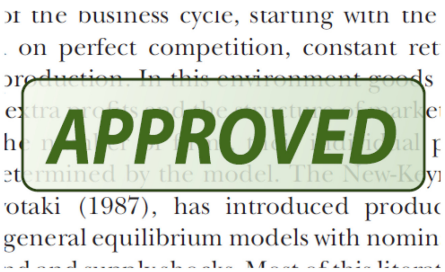

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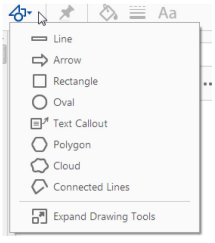

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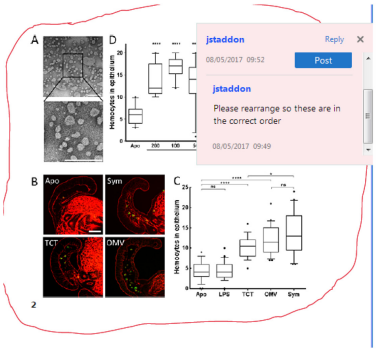
Allows shapes, lines, and freeform annotations to be drawn on proofs and for comments to be made on these marks.



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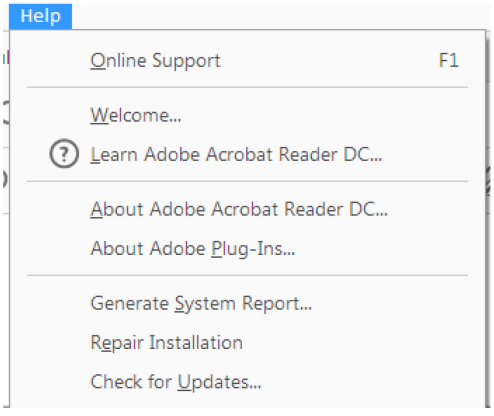

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AL-NISOUR JOURNAL FOR MEDICAL SCIENCE 2026;8:104–109

The Ramification of Mutations in Sonic Hedgehog Gene on the Occurrence of Deformities in the Course of the Embryonic Development Stage

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Abstract

Sonic Hedgehog (SHH) is one of the most significant genes regulating embryonic development in mammals, playing a pivotal role in cell differentiation, tissue fate determination, and regulating lateral symmetry of the embryo. The results of this research show that any mutation whether, a loss of function or a change in the regulation of gene expression in SHH gene leads to severe and highly complex consequences for embryonic development.as a result for that, severe disorders of CNS development SHH is a morphogen essential for germline formation and neuronal differentiation. Mutations in this gene result in failure to develop properly the cerebellum, cerebral cortex, and optic nerve. The holoprosencephaly (HPE) is the most prevalent form where the forebrain doesn't separate to two cerebral hemispheres, which is accompanied by gross deformity of the face and mental retardation. SHH gene controls the axial differentiation of the limbs, SHH gene mutations lead to axial limb deficiencies, also of split hand/ foot malformation, which, among other things, causes the proper placement of organs in the body and the formation of the lungs, intestines and teeth. Conclusion: the study confirms, SHH gene plays one of the major guardian roles in healthy embryonic development. Any impairment in its functioning however insignificant will upset the sensitive homeostasis of the developmental signals, and cause a vast array of malformations of the central nervous system, the skeleton, and internal organs.

Keywords: Sonic hedgehog gen (SHH), Mutation, Holoprosencephaly (HPE)

1. Introduction

SHH signaling cascade represents one of the complicated signal transductions of multicellular organisms that is highly regulated during their development. It also participates in the postembryonic tissue regeneration and repair process besides determining how cells differentiate to form complex organs, the induction of multi-farious neuronal populations in central nervous system, particularly, is part of Shh signaling (Choudhry et al., 2014; Komada, 2012). SHH mediates size, shape, and cell type coordination in the precursor cell (including telencephalon) in the formation of the vertebrate CNS by mediating ventral morphological, reprodection and differentiated capabilities (Ni et al., 2020). SHH dysregulation is a cause of developmental diseases. Early development occurs in SHH gene knock out embryos of mice and late deficits, respectively, in the midline structure and distal limb structure, respectively, in the ciliary eye, and the neural tube, in the ventral cell type,,in spine and the largest part of the ribs respectively (Echevarría-Andino & Allen, 2020). SHH mutations severely impact face and forebrain development in humans such as holoprosencephaly (Monteagudo, 2020). The most typical case is holoprosencephaly, which arises due to a mutation of the SHH gene that leads to left and right brain separating and turning abnormally (de Lussanet & Osse, 2012).

2. The sonic hedgehog gen

SHH gene belongs to hedgehog gene family and it contains five kinds of DNA sequence changes or splices. It is located on chromosome seven and starts producing Sonic Hedgehog protein

Received 22 December 2025; accepted 8 February 2026.
Available online 20 May 2026

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https://doi.org/10.70492/2664-0554.1168

(ENSG00000164690, 2020). This protein conveys both long and short distances to organize the embryonic development (UniprotKB - Q15465, 2020). Robert Ridle, a postdoctoral researcher in the Tabin Lab, the gene was named following his wife returning to home with a magazine that featured an advert to initial issue in the series, SHH (Keen & Tabin, 2004), based on hedgehog species, two of them were called desert and Indian hedgehog and based on video game character Sonic the Hedgehog sonic hedgehog named (Anwood, 2007; Simonite, 2005). SHH controls the growth of the nervous system acting synergistically with most of the factors. An example is that Nurr1 gene can suppress inflammation and cell apoptosis, ultimate neuron protection, and collaborate with SHH to stimulate the proliferation and differentiation of neuron precursor cells (Palma et al., 2005). SHH induced ventral neurons have a pattern of gene expression resembling that of the lateral ganglion eminence, the developmental form of the striatum. The development of the basal telencephalon requires SHH activity in a time-dependent manner. Also, SHH signal is able to control the growth of the cerebellum in different levels (Northcott et al., 2019). the embyroinc morphogesis regulating by this signaling molecule. development and organization of the organs controls via SHH involve the CNS, limbs, digits and the majority of other body parts (Blaess et al., 2015). Moreover, this synergy is capable of successful inducing stem cells of human dental pulp to become nerve cells in vitro diagnostics (Lambrichts et al., 2017). It is a morphogen and function in differentiation of numerous systems- inclusive of anterior pituitary (Herzog et al., 2003) pallium of the brain (Rash & Grove, 2007) spine (Lewis & Eisen, 2001) lungs (Wolpert, 2015) teeth (Dassule et al., 2000) and the thalamus by zona limitans intrathalamica (Scholpp et al., 2006; Rash & Grove, 2011). SHH has been shown as well to play the role of an axonal guidance cue, SHH at ventral midline of the developing spinal cord has been shown to attract commissural axons (Charron et al., 2003). SHH repels and attracts at respective concentrations to retinal ganglion cell (RGC) axons (Kolpak et al., 2005). SHH deletion (non-expression) in cetaceans had been reported to suppress the development of immature hind limbs with the presence of SHH (Thewissen et al., 2006). the SHH indicating path regulates the proliferation of radial glials and intermediate precursor cells to guarantee proliferating capacity, differentiation and maturation of the neurons of the neocortex during the neocortex development process (Komada, 2012). growth of the organ epithelial stem cells during the time of embryonic development regulated by bone morphogenetic protein (BMP) and SHH signaling pathway interaction (Li et al., 2015). SHH dysregulation may cause developmental disorders. The embryos of mice with SHH gene knockout exhibit early developmental deficits in midline structure and late within the structure of the distal limbs, the loss of the ventral cell type of neural tube, the loss of the spine and most of the ribs of central nervous system (Echevarría-Andino & Allen, 2020). Sonic hedgehog has been identified to have important functions in the vertebrate animal central nervous system (CNS) development, with its downstream signal molecule being Gli (Fig. 1) (Yang et al., 2021). cell-fate specification, Pattern formation, proliferation, axon guidance, differentiation and survival of neurons CNS development Shh signalling plays a role in all these processes. SHH has many diseases of the nervous system, which are caused by abnormal signaling pathway of Shh. The SHH signalling is a complicated process that has not

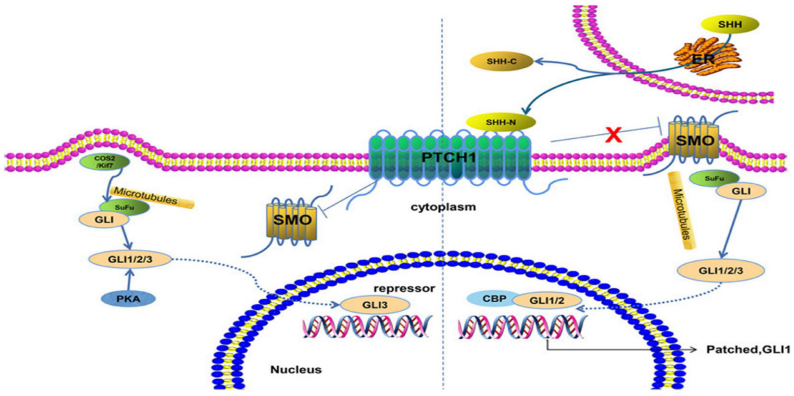

Fig. 1. SHH signal transduction. Two forms are pictorial. Beneath natural condition, Ptch1 suppresses the activity of the SMO protein, hence preventing downstream path. COS2/Kif7 and PKA have a passive regulation. In binding PTCH1 with SHH, SMO release is inhibited and GLI protein and microtubule compound is released to penetrate the nucleus to stimulate the transcription of the downstream target genes (Yang et al., 2021).

yet been fully comprehended. However, it has also been determined that Shh signaling pathway can be divided to canonical and non-canonical courses (Li et al., 2021).

3. Mutation of sonic hedgehog gen

In case of mutation or a lack of SHH gene, the Sonic Hedgehog protein is unable to perform its function. Sonic hedgehog plays a role in the cell development, cell differentiation and cell formation, body plan structuring and organization (Golestaneh & Mishra, 2005). This is a protein that is a signal molecule of importance in morphogenesis., and it has a function in development of numerous organize in embryos developing (SHH gene, 2020). Some of the key organ systems that are influenced by SHH gene include the cardiovascular system, nervous system, musculoskeletal system and respiratory system. (ENSG00000164690, 2020; UniprotKB - Q15465, 2020) SHH gene mutations may lead to defects in the constituents of these systems which may cause serious issues in the growing embryo. Mutations affecting this gene can greatly affect the brain and eyes and, therefore, result in such disorders as Microphthalmia (Fig. 2) (Harding & Moosajee, 2019) and Holoprosencephaly (SHH gene, 2020) in addation to that,The activation of SHH pathway to GLI3R isoform that is translocated to the nucleus is constitutive and neutralizes SHH targets (Lopez-Rios, 2016). SHH provokes the inhibition of GLI3R isoform and formation of GLI3A and GLI2A (GLI activators). As a result, the GLI activators aids in SHH target gene expression. Then, GLI stimulators enhances SHH targeted genes' expression. Other genes that are involved in non-syndromic as well as syndromic CULA are besides ROR2, GLI3. GLI3 gene heterozygous mutations may cause Greig cephalopolysyndactyly syndrome (GCPS; MIM: 175700), Pallister-Hall syndrome (PHS; MIM: 146510), postaxial polydactyly type A1 and B (PAP; MIM:174200) and preaxial polydactyly type IV (PPD; MIM: 174700) (Démurger et al., 2015). GCPAS and PHS are disparate clinical organizations that are allelic syndromes (Johnston et al., 2005).

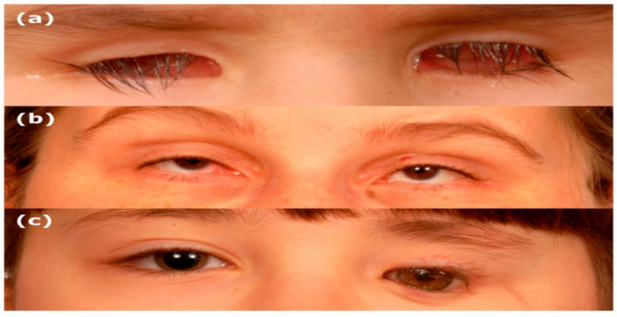

*Fig. 2. Anophthalmia and microphthalmia clinical images. (**a**) Bilateral anophthalmia. (**b**) Bilateral microphthalmia. (**c**) Shell and unilateral anophthalmia (Harding & Moosajee, 2019).*

Holoprosencephaly: is a cephalic defect where prosencephalon (embryo forebrain) does not form two hemispheres, and usually occurs between the 18th and 28th gestation in the embryo. Its estimated to take place about once in every 250 conceptions (Dubourg et al., 2007).

The cause of holoprosencephaly is an undivided midline cleavage of forebrain (i.e., prosencephalon). It encompasses a broad range of intra-cranial and craniofacial midline malformations and a host of clinical phenotypes, comprising neurological and face dysmorphism of face and brain. It has been considered as the most widespread forebrain development defect (Riddle et al., 2021). The symptoms of holoprosencephaly are mild (absence of such defects in face/organs, smell deficiency, or only one central incisor) and severe (cyclopia) (Raam et al., 2011).

4. The holoprosencephaly can be classification into

Alobar: This is the primary and most widespread one (two-thirds of the HPE cases), in which the inability of dividing the forebrain into the left and right hemisphere is complete; this leaves only one, centrally positioned ventricle (Lo et al., 2021). the most severe type of holoprosencephaly, it will involve the development of synophthalmia (single central eye), severe malfunction, and proboscis (Raam et al., 2011).

Semilobar: Partial forebrain cleavage (Lo et al., 2021) may be manifested by a presence of a severely reduced distance between the eyes, eye defects, flattened nose bridge, cleft lip and palate (Fig. 3) (Worley et al., 2018), and severe impairment (Raam et al., 2011).

Lobar: Complete forebrain cleavage (Lo et al., 2021) may be almost complete with a reduction in the distance between the eyes, flattened bridge of the nose, and close-set nostrils. Mental and locomotion delays could be present as well (Raam et al., 2011).

5. HPE phenotype

syntelencephaly: This is an unusual and uncommon type where posterior frontal and parietal lobes form an abnormal midline fusion (Rajalakshmi et al., 2015).

Cyclopia: single centrally located eye, synophthalmia or anophthalmia; proboscis (a tube-like nasal projection with a single nostril above the ocular area) can be single or absent and it can or might not be

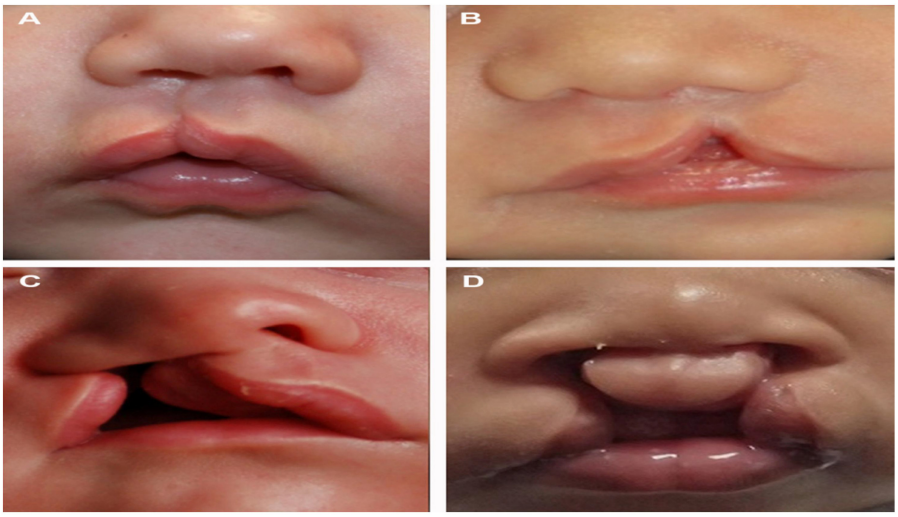

Fig. 3. Cleft lip and palate - Clinics in Perinatology (Worley et al., 2018).

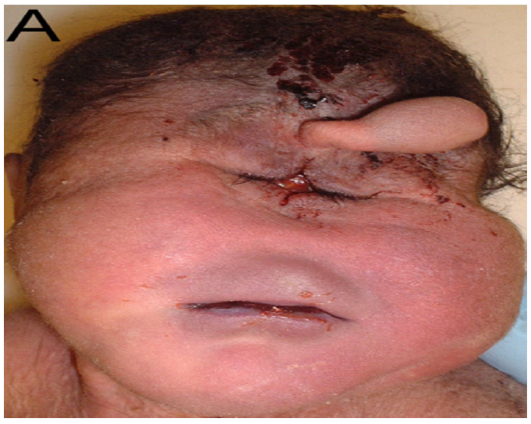

Fig. 4. Proboscis in Patau syndrome, Cyclopia (one median eye) is connected with the lack of nose (arrhinia) and the development of proboscis over the eye (Chan et al., 2007).

Fig. 5. Hydrocephalus with increased circumference of the head in a 3-month-old baby (Rath & Dash, 2012).

accompanied by hypognathism (Fig. 4) (Chan et al., 2007).

Cebocephaly: A unilateral nostril nose and ocular hypotelorism (Aruna et al., 2013).

Ethmocephaly: Proboscis with ocular hypotelorism (Aruna et al., 2013).

Hydrocephalus: is the typical complication of a lobar type of HPE, therefore, it is accompanied by a macrocephaly, instead of microcephaly, which obscures the initial diagnosis (Fig. 5) (Rath & Dash, 2012; Sarica et al., 2018).

6. Effect the mutation in lambs and lung

Bones make up of certain shape and size are placed in very specific patterns in human hands and feet. The digital pattern of limbs of tetrapods (i.e. terrestrial vertebrates) is controlled by the secreted hedgehog (SHH) or conserved hedgehog (Hh) signaling pathway. Analysis of genetic is currently revealing an astonishing array of pathogenetic alteration that modify the Hh pathway. therefore, impairing number and identity of the digits. Some of them are regulatory mutations that are not only more surprising, but also orient the Hh ligands' expression to abnormal locations in growthing limb buds, Other mutations involved another factors also influence a embryonic cell structural property that is very fundamental and which is vital in the Hh signaling (Anderson et al., 2012). Vertebrate limbs development in life of t is a multi-step procedure and this development is regulated through complicated interrelationships between the centers of signaling. In human beings, the differentiation of limb bud starts about the 4th week of embryonic development with the development of a

small bud of lateral body wall (Zeller et al., 2009). glikruppel (GLI) genes encode transcription factors of GLI1,GLI3 and GLI2, which are members of GLI family of SHH signaling pathway, have been associated with various human illnesses like non-syndromic and syndromic CULA. GLI-3 is a regulative or inhibitory modulator of SHH pathway and transcription factor (Démurger et al., 2015).

The protein sonic hedgehog (SHH) secreted has become an essential developmental morphogen in the embryonic lung, and it controls intercellular communication between epithelial and mesenchymal cells in the airways and the alveoli. It is also emerging that SHH pathway is involved in adult pulmonary diseases, like asthma, pulmonary fibrosis, lung cancer, chronic obstructive pulmonary disease (Kugler et al., 2015).

This is as in an experimentation where SHH knockout mice where the mid-line of the forebrain could not form instead forming one telencephalic vesicle hybridized formed Sonic hedgehog yet retained a part in proliferation, preservation and renewal of mature tissues. Signaling SHH has been associated with abnormal activation in adult tissues to cause several cancer types such as breast, skin, brain, liver, and gallbladder among others (Jeng et al., 2020).

7. Conclusion

The study confirms, Sonic Hedgehog gene plays one of the major guardian roles in healthy embryonic development. Any impairment in its functioning however insignificant will upset the sensitive homeostasis of the developmental signals, and cause a vast array of malformations of central nervous system, the skeleton, and internal organs.

Acknowledgments

No.

Ethics approval and consent to participate

Written approval was obtained from the Ethical Approval Committee of the University of Mustansiriyah,Iraq. Study data/information was used for researchpurposes only.

Consent for publication

No personal data are included.

Availability of data and material

The datasets analyzed and producedduring this study can be acquired from the corresponding author on reasonable request.

Competing interests

The authors profess that there is no conflict of interest.

Funding

No funding.

Authors' contributions

All authors have made significant, direct, and mental contributions to the work and have confirmed it for publication.

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