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Neurological Disorders Caused by Structural Dysfunction of *VANGL2*

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Abstract

Background: *VANGL2* plays a variety of roles in various cellular processes, including tissue morphogenesis, asymmetric cell division, and nervous system development. There is currently a lack of systematic organization in the development and disease of the nervous system. **Purpose:** To explore the role of *VANGL2* in the development of the nervous system and related diseases. **Methods:** Literature review and analysis of the role of *VANGL2* in the development and disease of the nervous system. **Results:** *VANGL2* defects lead to the development of the nervous system through the misconfiguration of various cells, which affects the development of the cochlea, the conduction of neural signals, and the development of nervous system-related diseases such as Alzheimer's disease, GBM, Bohling-Opitz syndrome, and hydrocephalus. **Conclusions:** The *VANGL2* gene is essential for nervous system development and its deficiency is linked to severe congenital conditions and various disorders, highlighting the need for more research on treatments for related gene defects.

Keywords

VANGL2, Neurological Disorders, Planar Cell Polarity (PCP) Pathway, Neural Tube Defects

1. Introduction

The Planar Cell Polarity (PCP) pathway consists of transmembrane proteins, namely Frizzled and Van Gogh-like (Vangl), as well as cytoplasmic proteins, including Dvl and Prickle (Pk). These proteins play a crucial role in driving planar polarization by localizing asymmetrically to the proximal (Vangl and Pk) and distal (Frizzled and Dvl) of epithelial cells [1]. *VANGL2* is a mammalian protein homologous to the Drosophila core planar cell polar protein Vang/Strabismus.

VANGL2 processes four transmembrane domains, with both the N-terminal and the C-terminus regions located on the cytoplasmic side. The N-terminal region contains two phosphorylated serine/threonine cola, while the C-terminus region contains a coiled-coil domain and a PDZ-binding domain, which can recognize and bind a variety of protein features, such as Dvl (disheveled), Fz (frizzled) and Ror2 (recombinant receptor tyrosine kinase-like orphan receptor 2) [2] [3]. The protein plays a crucial role in various cellular processes such as tissue morphogenesis, asymmetric cell division, localization of epithelial cell appendages, and establishment of asymmetrical cell axes in diverse cell types, including neurons. Its involvement significantly impacts development, proliferation, differentiation, and polarization movements, among other functions [4]. (See **Figure 1**)

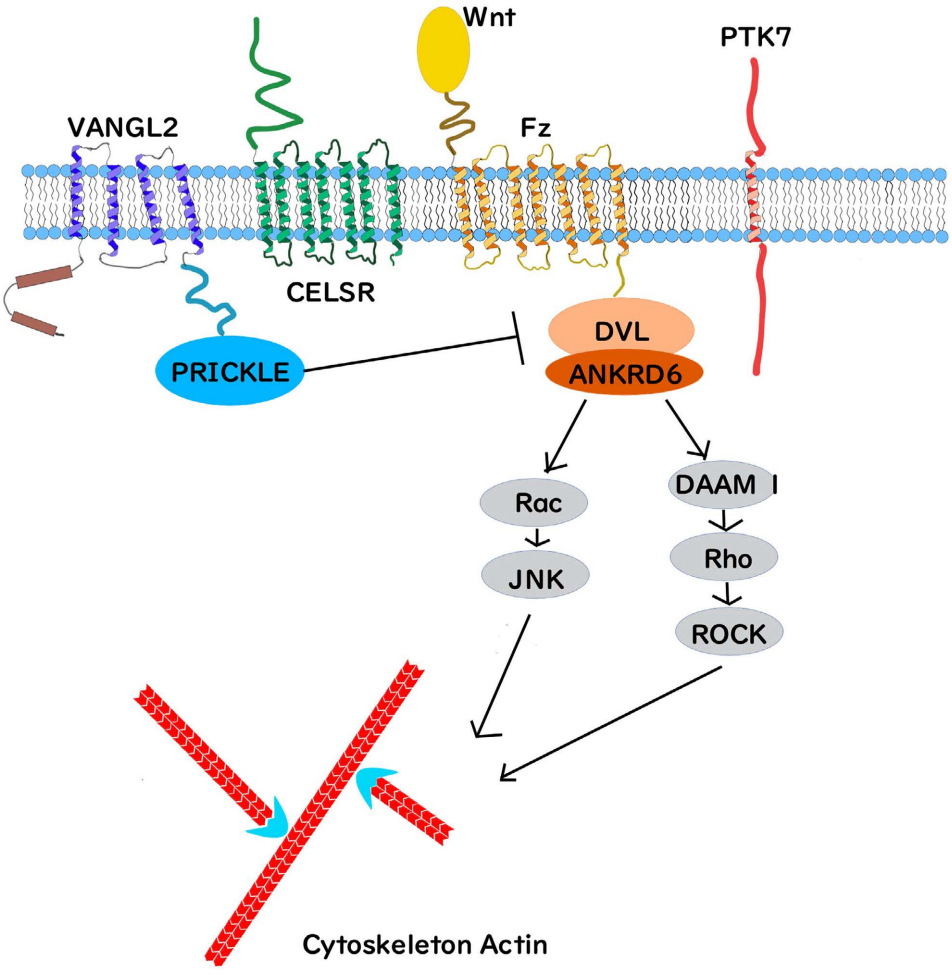

Figure 1. The Wnt/PCP signaling pathways.

Simplistically, the Fz receptor will activate the DVL, and then activate a series of downstream proteins to modulate the cytoskeletal elements, which drive planar polarization. The role of *VANGL2*, a transmembrane protein, localizes the cytosolic protein Prickle and puts it proximally [5]. For another, The Fz receptor will aggregate the cytosolic proteins DVL and ANKRD6 distally [6].

2. Methods

First, we collected all the relevant articles about the *VANGL2* gene and imported them into the ENDnotes document library. We then classified and screened out all the articles related to the nervous system. We further classified these articles into diseases related to nervous system development, diseases related to co-regulation with other genes, diseases related to neural signal transduction, diseases related to cochlear development, Alzheimer's disease, tumors and other diseases. Finally, we sorted out the molecular biological basis of related diseases by reading the literature and conducting a summary discussion (See Figure 2).

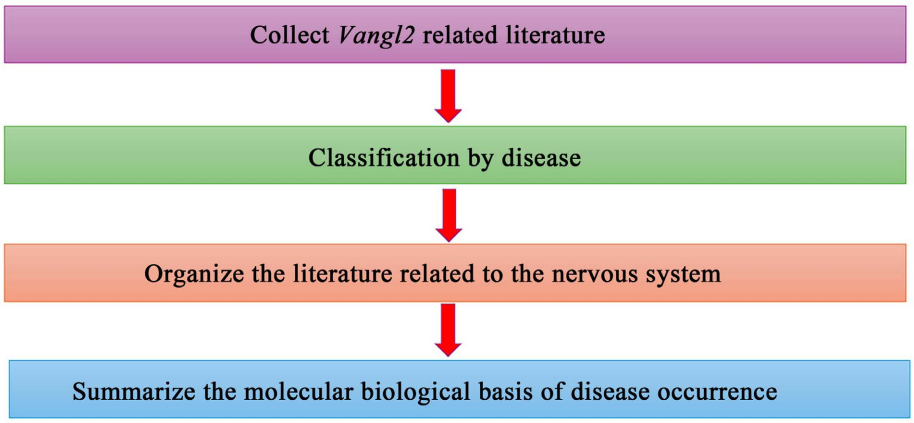

Figure 2. Methodological contents.

2.1. The Role of *VANGL2* in the Nervous System Development and the Occurrence of Related Diseases

VANGL2 plays a crucial role in various aspects of nervous system development, including the embryonic neural tube, the formation of paraganglionic helix at the end of the myelin sheath of the central nervous system, neural crest cell differentiation, brain circuit formation, neurotransmitter release, and the membrane cell cilia and Reissner fiber formation [7] [8] [9] [10]. Neural tube defects (NTDs), also referred to be neural tube malformations, are a group of birth defects resulting from inadequate neural tube formation during the early stages of embryonic development. The primary clinical subtypes of NTDs include anencephaly, spina bifida, and encephalocele [11] [12]. Anencephaly and severe encephalocele frequently result in stillbirths, with only a few cases resulting in live births, albeit with a very limited survival time. Children with spina bifida and mild encephalocele may survive, but unfortunately, there is no cure available, often leading to lifelong disability, manifested as paralysis of the lower limbs, incontinence, and mental retardation, etc, children with spina bifida are also susceptible to hydrocephalus, which often leads to premature mortality. Research conducted on various animal models, including mice, rabbits, zebrafish, and monkeys, have demonstrated a significant correlation between *VANGL2*

gene abnormalities and the occurrence of neural tube defects, specifically cranial fissures and spina bifida [13] [14] [15] [16]. Furthermore, *VANGL2* deficiency can also lead to polarization and morphological disorder of cells within the tail NP (neural plate) and NT (preventing the closure of the neural tube) [17]. As a result, mutations in *VANGL2* cause the embryonic neural tube to not close properly [7]. Furthermore, in *VANGL2* knockout glial cells, the paraganglionic helix loosens and occurs with cytoskeletal disruption and mislocalization of self-typical adhesion molecules between the inner rings of the helix [8]. Deficiencies in *VANGL2* will directly contribute to disorders in neural crest cell differentiation and brain circuit formation. The downregulation of *VANGL2* expression leads to a decline in the release of neurotransmitters secreted by autonomic nerves, thereby interfering with the repair and formation of alveolar tissue [9]. Deletion of *VANGL2* results in defects in ependymal cell cilia and Reissner fiber formation, as well as idiopathic scoliosis [10]. (See **Figure 3**)

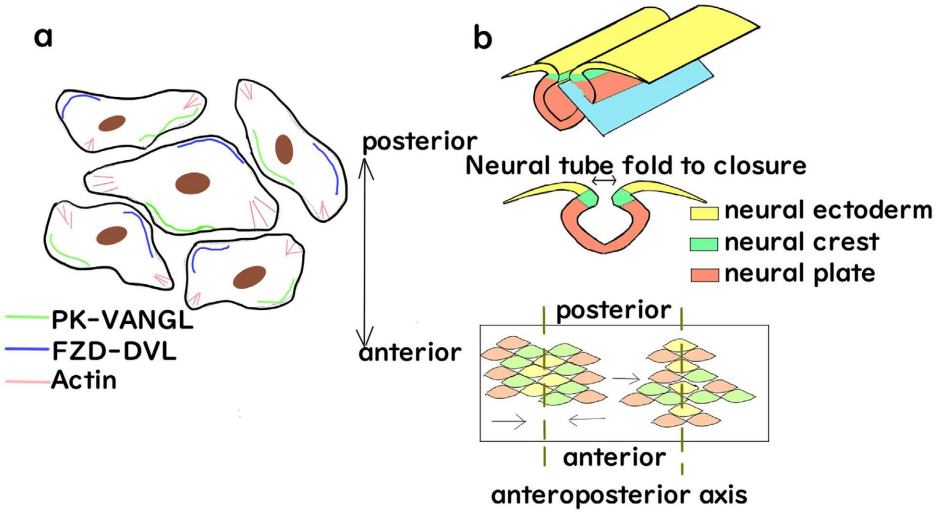

Figure 3. The role of Wnt/planar cell polarity signaling in neural tube closure.

(a) The PCP complex in the process of CE is asymmetric, in which the VANG-PK (green) and FZD-DVL (blue) are localized anteriorly and posteriorly, respectively. (b) Neural tube formation is a complicated process. Neurulation starts with the neural plate, the coiling of the neural plate from outside to inside will form the convergent extension (CE) [18]. Outer layer cell intercalation drives CE movements to narrow and extend tissues along the mediolateral line, respectively. (See **Figure 4**)

*β*1 integrin, Grhl3Cre, Zic3, Ptk7, *VANGL2* exon 1-7 regulate the expression of *VANGL2*, and then affect the occurrence of NP cells, ependymal cell cilium, Reissner fiber, accessory ganglion helix, neural ridge cell differentiation, brain circuits, and finally lead to neural tube defects. hmmr, N-cadherin, Ap2m1, Dvl, Lady1, Zic3, R-Ras, and *VANGL2* work together to establish cell polarity and neuromorphism, ultimately leading to neural tube defects.

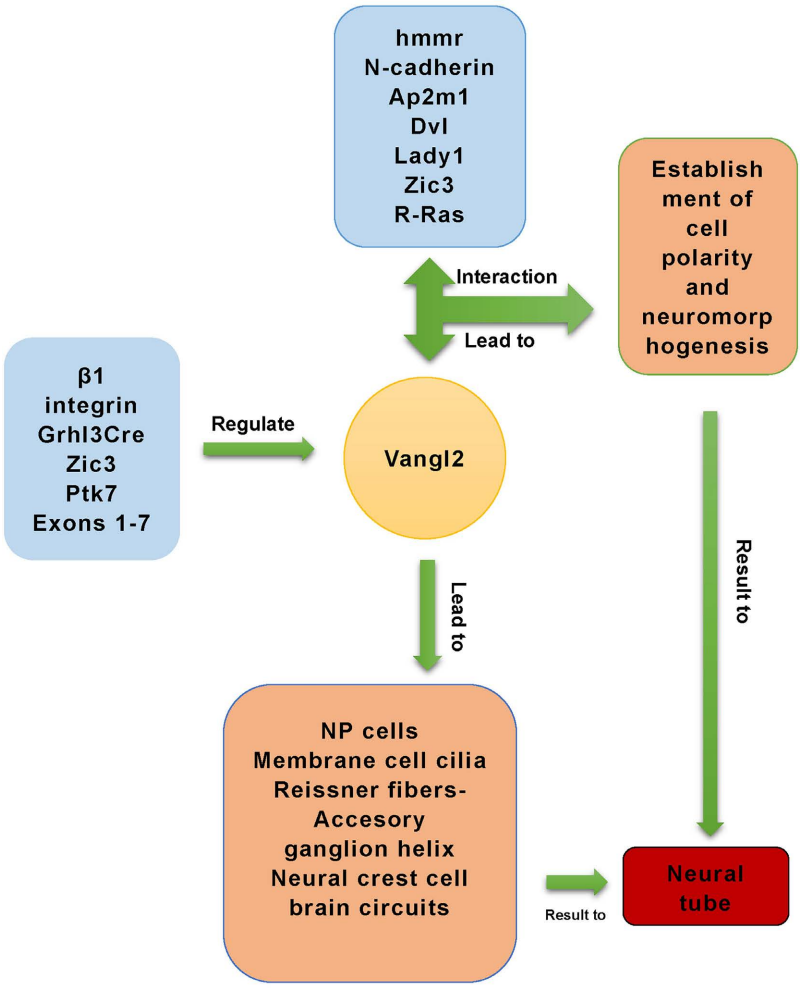

Figure 4. *VANGL2* and other genes co-regulate neural cell mechanisms.

2.2. *VANGL2* and Other Genes Work Together to Regulate Nerve Cells and Their Abnormalities That Lead to the Resulting Diseases

VANGL2 is involved in regulating cell polarity and neuromorphogenesis, alongside a diverse array of other genes. *VANGL2* is associated with HMMR (Hyaluronan-mediated motility receptor), N-cadherin, Ap2m1 (adaptor-related protein complex 2, mu 1 subunit), Dvl, Daam1 (disheveled associated activator of morphogenesis 1), Zic3, R-Ras (Ras-related), which collectively exert a synergistic effect in the establishment of cell polarity and neuromorphogenesis. The interruption and elongation of cell polarization in *VANGL2* and HMMR mutants prevent RI (radial intercalation), a process crucial for proper neuromorphogenesis. Consequently, the neurodevelopment of these mutants is significantly hindered [19]. *VANGL2* and N-cadherin exhibit colocalization and physical interactions within the neural plate, thereby jointly regulating the convergence and expansion of PCP signaling through direct molecular interactions to promote neural tube development [20]. Additionally, *VANGL2* has been identified as a negative regulator of axon outgrowth, modulating the molecular binding strength

between N-cadherin and actin cytoskeleton [21]. Furthermore, *VANGL2* interacts with Ap2m1 in its C-terminal Prickle binding domain, and this interaction mechanism plays a role in neuronal development by inhibiting *VANGL2*, resulting in a reduction in the production of dendritic branches in the cortical neurons during development [20]. Additionally, *VANGL2* inhibits the interaction between Dvl and its downstream effector Daam1, which in turn functionally inhibits the tandemization of Dvl-to-Daam1 genetic information during CE [18] [22]. Moreover, *VANGL2* can function in conjunction with R-Ras to transmit signals that control neural tube formation, and *VANGL2* binds to inactive R-Ras as an initial mechanism to collectively regulate the expression of signaling pathways [23]. The expression of *VANGL2* is various factors, including the regulation of β1 integrins, Grhl3Cre, Zic3, Ptk7, and their genes exons 1-7. The establishment of PCP and the development of β1 integrin play crucial roles in modulating *VANGL2* expression, ensuring the convergent elongation of the notochord, maintaining its structural integrity and localization, and ultimately facilitating the development of the nucleus pulposus and the proper alignment of the vertebral body and intervertebral disc. The downregulation of β1 integrin and *VANGL2* expression has been implicated in the development of congenital spinal deformities in humans [24]. $Grhl3^{Cre}$ reduced the expression of *VANGL2* protein in SE (surface ectoderm) and PNPs (posterior neuropore cells). Reduction in mechanical stress withstood at the main zippering point during the late stage of embryonic closure in $Grhl3^{Cre/+}$ $VANGL2^{Fl/Fl}$, leading to failure of neural tube closure and subsequent spinal bifida [3]. Additionally, it has also been observed that Grhl3 overexpression interacts with the *VANGL2* gene, leading to the development of spina bifida [25]. Furthermore, the deletion of Zic3 disrupts the genetic interaction between the PCP membrane protein *VANGL2* and PCP effector genes Rac1 and Daam1, resulting in an increased frequency and severity of neural tube and heart defects [26]. Embryos exhibiting diheterozygous mutations in the Ptk7 and *VANGL2* genes are associated with the occurrence of spina bifida [27]. Specifically, the deletion of *VANGL2* exon 1-7 has been observed to impact the overall expression of *VANGL2* mRNA and its downstream PCP pathway signaling, resulting in neural tube closure failure [28]. It has been reported in the literature that several combinations of two diheterozygous genes involving the PCP core gene *VANGL2* and other genes (Sec24b, Sfrp1/Sfrp2/Sfrp5, Dvl3, Scrib, Celsr1, Ptk7, Vangl1) may result in open spina bifida, anencephaly or cranial fissure phenotype. However, only the cranial fissure phenotype is observed in cases of homozygous mutations [29]. Contrarily, *VANGL2* serves the dual purpose of inducing the neural tube closure and rescuing NTDs. Additionally, it was found that the core members of Wnt/PCP (RhoA, *VANGL2*, ickle, Wnt11) effectively rescued Gsc-mediated NTDs [30].

2.3. The Manifestation of *VANGL2*-Associated Disorders Is Attributed to Abnormal Neural Signaling

VANGL2 is a key player in the assembly of the molecular core complex at neu-

romuscular synapses, plays an important role in the transmission of Wnt signaling molecules, and acts as a scaffold protein to promote the development of neuromuscular junction (NMJ) [31]. Mutations in this gene result in dysfunction of the motor sensory pathway. Additionally, there exists a genetic interaction between Contactin2 and *VANGL2*, which collaboratively regulates the caudal migration of facial branchiomotor (FBM) neurons [32]. Wnt4 and Wnt11 collaborate in facilitating the formation of NMJ at the mammalian muscle-nerve junction by activating the canonical and *VANGL2*-dependent core PCP pathway [33]. Ryk regulates PCP signaling by asymmetrically modulating the distribution of *VANGL2* in both the cytoplasm and plasma membrane, thereby leading to the rejection of the Wnt gradient by corticospinal tract (CST) axons [34]. Dysfunctions in nerve signaling factors, such as Wnt4, wat11, and Ryk, result in abnormalities in the *VANGL2* protein and cytoskeleton, ultimately leading to the development of neurological disorders.

2.4. The Role of *VANGL2* in Cochlear Development and Its Association with the Pathogenesis of Related Diseases

VANGL2, along with Frizzled3 and Frizzled6, play a crucial role in the development of the cochlea by directing the innervation of type II spiral ganglion neurons [35]. Additionally, *VANGL2*, CELSR1, FZD3, and other core proteins of the PCP pathway collaborate to regulate the polarization organization of the stereociliary tract in auditory and vestibular hair cells, as well as the axonal pathfinding events of these cells. The absence of *VANGL2* results in misorientation of the stereociliary bundles, which in turn leads to abnormal cochlear development [36]. Furthermore, the cochlear defects are also associated with wntless deficiency. Wnts and *VANGL2* interact to ensure the establishment of histiocyte polarity during development. The absence of *VANGL2* significantly exacerbates sensory cell polarization defects [37]. Additionally, genetically heterozygous mice with *VANGL2* and Cdh2 mutants exhibit impairments in neural tube closure and cochlear hair cell orientation [19]. The defect in *VANGL2* leads to abnormal cochlear development due to synergistic failure with Frizzled3, Frizzled6, CELSR1, FZD3, Wnts, and Cdh2.

2.5. The Insufficiency of *VANGL2* Leads to the Emergence of Additional Neurological Disorders

The deficiency of *VANGL2* has been implicated in the pathogenesis of Alzheimer's disease. Additionally, the amyloid precursor protein (APP) interacts physically with the Wnt co-receptors LRP6 and *VANGL2* to activate two arms of Wnt signaling, thereby playing a bidirectional role in the regulation of synaptic stability [38]. Furthermore, defects in the *VANGL2* gene have been identified as the cause of Glioblastoma multiforme (GBM). Nrdp1 interacts with *VANGL2* protein to mediate k63-linked polyubiquitination of the Dishevelled, Egl-10, and Pleckstrin (DEP) domains of the Wnt pathway protein Dvl, thereby hindering the binding of Dvl to phosphatidic acid. The deletion of Nrdp1 in GBM can lead

to abnormal activation of vangl-dependent atypical Wnt pathways, thereby facilitating tumor invasion [39]. The *VANGL2*-ITLN1 fusion is implicated in regulatory networks such as MYCN, ALK, and Wnt/planar cell polarity (PCP) pathways, which are key regulators of neuroblastoma outcome [40]. Increased *VANGL2* expression is associated with Bohling-Opitz syndrome, a rare neurodevelopmental disorder characterized by profound intellectual disability, distinct facial features, excessive hair growth, heightened susceptibility to Wilms tumors, and various congenital abnormalities such as cardiac and skeletal defects, leading to the characteristic "BOS posture". Existing evidence demonstrates that ASXL1 mutant cells exhibit widespread activation of the canonical Wnt signaling pathway at the transcriptional and protein levels, with a particularly notable upregulation of *VANGL2* expression [41]. Mutations in the *VANGL2* gene are causative factors for hydrocephalus. NHERF1 assembles a ternary complex with Fzd4 and *VANGL2* and promotes the translocation of *VANGL2* to the plasma membrane, particularly the apical surface of ependymal cells. The formation of this ternary complex disrupts the development of motor cilia, ultimately resulting in hydrocephalus [42].

3. Discussion

Through a comprehensive review and synthesis of the existing literature, we have determined that the *VANGL2* gene is pivotal in the development of the nervous system. This includes the development of the embryonic neural tube, the formation of the paraganglionic spiral at the end of the central nervous system myelin sheath, the differentiation of neural crest cells, the formation of brain circuits, the release of neurotransmitters, and the formation of cilia and Reissner fibers in tubular cells. *VANGL2* deficiency is closely associated with neural tube defects (NTDs), leading to congenital conditions such as anencephaly, spina bifida, and encephalocele, which can result in severe clinical manifestations like stillbirth, lifelong disability, and premature death. Additionally, *VANGL2* deficiency can cause issues such as cell polarization and morphological disorders, glial cell dysfunction, autonomic dysfunction, and scoliosis. *VANGL2* interacts with multiple genes (such as hmmr, N-cadherin, Ap2m1, Dvl, Daam1, Zic3, R-Ras, etc.) to jointly regulate cell polarity and neural morphogenesis, and mutations can lead to disrupted cell polarization and neurodevelopmental disorders. For example, mutations in *VANGL2* and HMMR—hyaluronan mediated motility receptor Gene prevent radial intercalation, *VANGL2* and N-cadherin co-regulate neural tube development, the interaction between *VANGL2* and Ap2m1 reduces dendritic branching, *VANGL2* inhibits the interaction between Dvl and Daam1, and *VANGL2* and R-Ras control neural tube formation. Furthermore, the expression of *VANGL2* is regulated by genes such as β1 integrin, Grhl3Cre, Zic3, and Ptk7, and its defects may lead to conditions such as spina bifida and neural tube closure failure. *VANGL2* not only plays a key role in neural development but also rescues NTDs through the Wnt/PCP signaling

pathway. *VANGL2* is critical in neural signal transmission and neuromuscular synapse formation, and its defects can lead to various nervous system-related diseases. *VANGL2*, along with signaling molecules such as Contactin2, Wnt4, Wnt11, and Ryk, co-regulates neural development, with abnormalities potentially leading to motor sensory pathway disorders and corticospinal tract axon abnormalities. *VANGL2* is also involved in cochlear development, and defects can result in abnormal cochlear and hair cell polarization. Moreover, *VANGL2* defects are associated with diseases such as Alzheimer's disease, glioblastoma multiforme, neuroblastoma, Bohling-Opitz syndrome, and hydrocephalus. It influences the normal function and development of the nervous system through interactions with the Wnt signaling pathway and other molecules. Although the role of *VANGL2* in nervous system development and related diseases has been extensively studied, research on the treatment of diseases caused by gene defects remains insufficient. We hope that future clinical research will focus on addressing these diseases, ultimately benefiting more patients.

4. Conclusions

VANGL2 deficiency results in abnormal development of the nervous system and is implicated in a variety of related pathologies. These include scoliosis, spina bifida, abnormal nerve conduction, cochlear dysplasia, Alzheimer's disease, and tumors, among others. Currently, most global treatments for these conditions focus on addressing the symptoms rather than the underlying genetic causes. Therefore, we aspire to advance medical science by developing therapies that target the genetic defects associated with these diseases, thereby providing more fundamental and effective treatments in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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