Genetic evidence in planar cell polarity signaling pathway in human neural tube defects

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Abstract  Neural tube defects (NTDs) are a group of birth anomalies having a profound physical, emotional, and financial effects on families and communities. Their etiology is complex, involving environmental and genetic factors that interact to modulate the incidence and severity of the developing phenotype. The planar cell polarity (PCP) pathway controls the process of convergent extension (CE) during gastrulation and neural tube closure and has been implicated in the pathogenesis of NTDs in animal models and human cohorts. This review summarizes the cumulative results of recent studies on PCP signaling pathway and human NTDs. These results demonstrate that PCP gene alterations contribute to the etiology of human NTDs.

Keywords  planar cell polarity; neural tube defects; rare mutations

Introduction

Neural tube defects (NTDs) are the most common and severe malformations of the central nervous system. They result from embryonic failure of neural tube closure that can occur at any level of the embryonic axis. Despite a long history of etiologic studies, the molecular and cellular pathogenic mechanisms underlying NTDs remain poorly understood. Genetic studies in NTDs have focused mainly on folate-related genes and identified a few significant associations between variants in these genes and an increased risk for NTDs [1–5]. The most significant epidemiological finding relevant to NTDs is the protective effect of periconceptional folic acid supplementation, which reduces their incidence by 50%–70% [6]. Despite this, thousands of families are still affected by these devastating conditions each year.

There are few reported associations of NTDs with chromosomal abnormalities and distinct syndromes. Most cases of NTDs are sporadic with a complex etiology involving both environmental and genetic factors [7]. Of the genes that have been associated with NTDs, planar cell polarity (PCP) genes have been implicated as predisposing factors in a fraction of isolated nonsyndromic NTDs [8]. Mutations in PCP genes lead to a wide range of developmental defects, mainly a shortened body axis, a widened neural plate, and NTDs. The PCP signaling pathway, essential for the orientation and coordinated movement of cells during embryonic morphogenesis, is a compelling candidate for investigation in studies of the etiology of human NTDs.

This review will summarize the neural tube formation, human NTDs classification and discuss the major findings of the recent studies of human PCP genes in the variety of NTDs.

Neural tube defects in humans

Neurulation is a fundamental embryonic process that leads to the development of the neural tube, which is the precursor of the brain and spinal cord. Neurulation begins with formation of the neural plate, a thickening of the ectoderm on the dorsal surface of the post-gastrulation embryo. In human beings, neurulation occurs through 2 distinct phases that occur at distinct sites along the rostrocaudal axis of the embryo: primary neurulation and secondary neurulation [9,10]. During the primary neurulation, the neural plate is subject to shaping and folding, with fusion along the midline to form the tube. The secondary neural tube is derived from a population of mesenchymal cells, the tail bud, which undergo proliferation and condensation followed by cavitation and fusion with the primary neural tube [11]. Neurulation is driven by redundant mechanisms both at the tissue and cellular level [12]. Active
processes required for neural tube closure include convergent extension (CE) cell movements, expansion of the cranial mesenchyme, contraction of actin filaments, bending of the neural plate, and adhesion of the neural folds.

In the mouse, closure is initiated at the hindbrain/cervical boundary (closure 1) and then spreads bidirectionally into the hindbrain and along the spinal region. Separate closure initiation sites occur at the midbrain-forebrain boundary (closure 2) and at the rostral extremity of the forebrain (closure 3) [13]. However, Closure 2 found in mice may be absent from human neurulation [14].

Based on a study of the type and frequency of human NTDs, Van Allen et al. [15] proposed a model in which five closure sites exist in human embryos. Although this model was attractive to explain human defects, examination of histological sections of human embryos leads to different models of neural tube closure. In fact, a study by Nakatsu et al. [16] described three sites of apposition, while O’Rahilly and Muller [17] found only two regions of fusion in humans, the first one extending bidirectionally from the rhombencephalic region and the second one that proceeding caudally from the prosencephalic region. The human closure events found by O’Rahilly and Muller have striking resemblance to mouse closures 1 and 3. Therefore, multisite neural tube closure may be a universal phenomenon, although the process appears to be not the same in the human and the other species.

The most common form of NTDs is anencephaly, which results from failure of fusion of the upper and rostral end of the neural tube, and myelomeningocele (commonly called spina bifida), which results from the failure of fusion in the spinal region of the neural tube. All infants with anencephaly are stillborn or die shortly after birth, whereas many infants with myelomeningocele survive, usually as a result of extensive medical and surgical care. Anencephaly and myelomeningocele are referred to as open NTDs where the nervous system and/or meninges are exposed to the environment without normal skin covering. Other open dysraphisms include myeloschisis, hemimyelomeningocele, hemimyelocele, and are sometimes associated with a Chiari II malformation. Another rare form of open NTDs is craniarachiachisis that results from failure of neural tube closure over the entire body axis. There are also a number of closed or skin-covered conditions that involve the neural tube. Closed NTDs are further categorized clinically, depending on the presence or absence of a lower back subcutaneous mass. Closed NTDs with a mass are represented by lipomyeloschisis, lipomyelomeningocele, meningocele, and myelocystocele. Closed NTDs without a mass include simple dysraphic states (intradural lipomas, diastematomyelia, teratoma, dermoid, epidermoid, tight filum terminale, persistent terminal verteicle, and dermal sinus) and complex dysraphic states (dorsal enteric fistula, neurenteric cysts, split cord malformations, caudal regression syndrome, and spinal segmental dysgenesis) [18].

Both genetic and non-genetic factors are involved in the etiology of NTDs. Many non-genetic factors include: parental age [19], parental race [20], parental socioeconomic status [21], hyperthermia during early pregnancy [22], maternal diabetes [23], maternal obesity [24], dietary agents or maternal nutrition (such as the uptake of folate [25], inositol [26]), chemical teratogenic agents (such as valproic acid [27], trichostatin A [28], exposure to pesticides [29] and selective serotonin-reuptake inhibitors [30], and so on).

As for genetic factors, a large repertoire of mouse gene mutations has flagged over 200 genes whose function is required for neural tube closure [31]. These genes are involved in a wide variety of cellular functions, and PCP genes comprise a small subset. The phenotypes of PCP mutants in mice offer a context for interpretation of the findings of studies of PCP gene variants in human NTD cases.

**Planar cell polarity signaling pathway**

PCP, a noncanonical Wnt signaling pathway, is a molecular mechanism that gives cells a coordinated polarized orientation necessary for numerous developmental processes, including their directional movements during vertebrate gastrulation and neurulation, orientation of stereocilia within the hair cells of the inner ear, wound repair, orientation of motile cilia and initiation of left-right asymmetry, and other steps in the development of the kidneys, lungs, and other tissue [32–35].

A role of the PCP pathway in vertebrate cell movements during morphogenesis was first shown in Xenopus and zebrafish [36,37]. In the mouse, Loop-tail (Lp) was the first mutant to implicate a role of PCP pathway and NTDs in mammals [38,39]. Lp heterozygotes are characterized by a “looped” tail appearance, while homozygotes develop a severe NTD resembling human craniarachiachisis. It is caused by independent missense mutations S464N and D255E, localized in the proposed C-terminal cytoplasmic domain of a gene, now referred to as Yangl2.

Genetic and molecular analyses in Drosophila have identified components of the PCP signaling mechanism, and have suggested that they may be divided into three modules [40,41] including a global directional cue that links the direction of polarization to the tissue axes, a core module that amplifies and stabilizes subcellular asymmetry through the activity of a bistable feedback mechanism, and one of several distinct tissue specific effector modules that respond to the upstream modules to produce morphological asymmetry in individual tissue. The global module is comprised of the atypical cadherins Fat (Ft), Dachsous (Ds), and the Golgi resident protein Four-jointed (Fj) [42], whose functions are to translate tissue-wide transcription gradients of two or more components into subcellular gradients. This module is characterized by mutant phenotypes in which cells still polarize and coordinate their polarity with neighboring cells, but often fail to align with the tissue axes. The core module