



Review

# Specification of the meso-isthmo-cerebellar region: The *Otx2/Gbx2* boundary

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## Abstract

The midbrain/hindbrain (MH) territory containing the mesencephalic and isthmocerebellar primordial is characterized by the expression of several families of regulatory genes including transcription factors (*Otx*, *Gbx*, *En*, and *Pax*) and signaling molecules (*Fgf* and *Wnt*). At earlier stages of avian neural tube, those genes present a dynamic expression pattern and only at HH18–20 onwards, when the mesencephalic/metencephalic constriction is coincident with the *Otx2/Gbx2* boundary, their expression domains become more defined. This review summarizes experimental data concerning the genetic mechanisms involved in the specification of the midbrain/hindbrain territory emphasizing the chick/quail chimeric experiments leading to the discovery of a secondary isthmic organizer. *Otx2* and *Gbx2* co-regulation could determine the precise location of the MH boundary and involved in the inductive events characteristic of the isthmic organizer center. © 2005 Elsevier B.V. All rights reserved.

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## 1. Early development of the central nervous system: the neuromeric theory

The neural tube of developing vertebrates appears subdivided into repeated bulges, named neuromeres by Orr [113], which are separated by transversal constrictions. This transient segmentation, especially evident in the hindbrain, could be responsible for the cellular and molecular events that determine the early specification of the developing central nervous system (CNS) [81,122,148]. In the hindbrain, once they become defined, the limits between these neuromeres (rhombomeres; rh) could define clonal restriction boundaries, preventing the movement of epithelial cells through adjacent segments [45]. Furthermore, differential cell proliferation and specific expression patterns of surface molecules could help to make an initial scaffold for proper hindbrain development [81]. Indeed, Martínez et al. [89] have demonstrated that the cells forming the inter-rhombomere boundaries are linked by gap junctions with a selective reduced permeability when compared with those linking cells in the neuromere walls.

In the last two decades, there has been a major accumulation of evidence that strongly supports the neuromeric theory. The vertebrate homeobox-containing genes of the *Hox* family, whose homologues in *Drosophila* encode parasegment identity, are expressed in restricted portions of the early neural tube with expression usually stopping at the inter-rhombomere boundaries. These genes provide rhombomeres with positional cues along the anterior–posterior axis of the hindbrain [155]. Thus, the differential activation of a combination of regulatory genes in specific neuromeric domains could direct unique developmental pathways in these individual regions, as a result of differential fate specification. In addition, the rhombomere boundaries do not permit the diffusion of inductive signals [90]. In the developing forebrain, the neuromeric model has been confirmed by morphological evidence [123], analysis of movements of labeled cells [42], gene expression patterns [28,122], and experimental results [83,88,91].

The present review summarizes and discusses data concerning the border between the midbrain and the rostral hindbrain, often termed the midbrain/hindbrain (MH) boundary emphasizing the works of Alvarado–Mallart's group. We begin with a brief review of the chick/quail experiments which determined the fate map of the mesencephalic/metencephalic segment and the discovery of a secondary organizing center within this region, the so-called isthmic organizer. Also, we will extensively discuss how several gene families interact to establish the MH boundary and the meso-isthmo-cerebellar specification.

## 2. Location of the cerebellar anlage: the mesencephalic/metencephalic constriction

The chick/quail transplant model introduced by Le Douarin [75] has been a useful approach to the analysis

of several issues in the development of the peripheral nervous system. New markers, in particular the QCPN and the Lance-Jones and Lagenaur [74] anti-quail antibodies, facilitated the analysis of the chimeric embryos. Alvarado-Mallart and Sotelo [9] carried out the pioneering work devoted to studying the development of the mesencephalic/metencephalic region using this elegant experimental approach.

Early anatomical observations suggested that the cerebellar primordium is formed from the first vesicle of the rhombencephalon (the pro-rhombomere RhA1 of Vaage; rh1–2) [148,149], just caudal to the so-called “mesencephalic/metencephalic” (mes/met) constriction. Surprisingly, results of chick/quail transplant experiments using mesencephalic or metencephalic homotopic grafts demonstrated that, in the 10 somites avian embryo (stage 10 of Hamburger and Hamilton) [57], the isthmocerebellar primordium is located more rostrally than previously thought. It lies on both sides of the mes/met (isthmic) constriction. The “mesencephalic” alar plate containing not only the primordium of the mesencephalon but also a portion of the isthmic anlage and the rostromedial portion of the cerebellum (Fig. 1) [11,53,55,86].

The just reported findings raised the possibility that, at stage 10, the mes/met constriction might delimit, within the isthmocerebellar primordium, two different morphogenetic units. Other subregions could be also present within the cerebellar anlage: the external granular layer originates from caudal metencephalon [11,54,55], and rh2 would give rise to the auricula [84], the most caudal–lateral portions of the cerebellum. However, there is no evidence that, at stage 10, the avian mes/met constriction is a clonal restriction limit, or that its cells are linked by low permeability gap junctions, two criteria defining interneuromeric boundaries in the hindbrain [89]. The works of Millet et al. [101] determined that, within the “mesencephalic” vesicle, there is a neuromeric boundary separating the isthmocerebellar and mesencephalic primordia (see below). However, the nature of the constriction observed at stage 10 remains unknown.

## 3. The meso-isthmo-cerebellar region expressing high levels of *En2* is an organizer center

The homeobox-containing gene *En*, a transcription factor homologue to the *engrailed* gene of *Drosophila* (see [65]), was the first gene described in the MH territory of several vertebrates [24,37,39,44,49,69,80,117]. In the chick, the *En2* gene was first detected at stage 9 showing a double decreasing gradient ([49,87]; see also [100]). From the reported data above at stages 10 onwards, the *En2*-positive area includes the cerebellar, isthmic, and mesencephalic primordia (Fig. 2) [9,55,86,87,101].

Mice homozygous for the *En2* mutation are viable and present no major motor control defects: there is only a one-

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