3D atlas of human embryology

New insights in human development

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Link to publication

Citation for published version (APA):

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"The scientific man does not aim at an immediate result. He does not expect that his advanced ideas will be readily taken up. His work is like that of the planter - for the future. His duty is to lay the foundation for those who are to come, and point the way."

*Nikola Tesla, 1934*
The basic human body plan, the arrangement of organs in the body, is laid down during embryonic development. Insight into the formation of this plan informs researchers and clinicians about normal development versus the development of congenital malformations, which have an incidence of 3% in the human population and cause up to one-quarter of all neonatal deaths. Despite modern clinical technologies such as three-dimensional imaging, the intricate morphogenesis of the developing human body is difficult to understand. Textbooks on human development are often based on the works of early embryologists, some published more than 100 years ago. Because of the limited availability of human embryonic specimens, it is difficult or impossible to independently verify the information carried in these textbooks, or even to assess whether this information is derived from studies on human or animal specimen. Present-day textbook morphology is therefore becoming increasingly schematic and deviating from the original substrate. To overcome these issues, we created the 3D Atlas and Database of Human Embryology, that comprises interactive three-dimensional (3D) digital models of human embryos, covering the first two months of development. These models illustrate in an interactive fashion the complex morphological changes that occur during development. With this atlas, we reinstate the link between the original sections of the human embryos in the Carnegie Collection and the interactive 3D models which enables independent verification and further analyses by other researchers.

In chapter 1 the scope of this thesis and a general introduction on embryonic development and growth, from the processes of hatching and implantation to organogenesis, is provided. The 3D Atlas and Database of Human Embryology, is presented in chapter 2. This chapter is divided in three parts. Chapter 2.1 concerns a preliminary report of our experience in creating the 3D Atlas by using serial histological sections of 34 human embryos of the Carnegie Collection between Carnegie stages (CS) 7 (15–17 days) and 23 (56–60 days). Chapter 2.2, the centerpiece of this thesis, covers all aspects of the 3D Atlas, including an extensive materials & methods section, all 3D embryonic models in interactive 3D-PDFs and extensive supplementary data that can serve as reference resources for scientists and clinicians. Chapter 2.3 narrows the focus to only one of the 34 studied embryos from the atlas, known as the Heuser embryo. We compared this embryo with two other specimens to find out whether the Heuser embryo is truly representative for its embryonic stage.

The 3D Atlas presented in chapter 2 shows for the most part stunning resemblance to the work of embryologists from the past century. The following chapters describe a selection of detailed relevant findings in the field of human embryology.
SCOPE OF THIS THESIS

The notochord is a major regulator of embryonic patterning in vertebrates. Abnormal notochordal development is associated with a variety of birth defects. Proper knowledge of the development of the notochord, therefore, is important to understand the pathogenesis of these birth defects. Textbook descriptions vary significantly and the lack of references makes it impossible to verify the presented data. Therefore, a verifiable and comprehensive description of the development of the human notochord is given in chapter 3.1. In chapter 3.2, we argue to revisit the single-site neural tube closure theory in human embryos. Since the multi-site closure theory was first proposed in 1991 as an explanation for the preferential localizations of neural tube defects, the mechanism of closure of the neural tube has been a contentious topic. Although the multi-site closure theory is much cited in clinical literature, single-site closure is most common in embryological literature. Therefore, we decided to re-evaluate both theories of neural tube closure by studying human and mouse embryos.

Contemporary papers and book chapters on nephrology open with the assumption that human kidney development passes through three morphological stages: pronephros, mesonephros and metanephros. Current knowledge of the human pronephros, however, appears to be based on only a handful of human specimen. In chapter 4.1 we provide an overview of literature concerning kidney development, and to clarify the existence of a pronephros in human embryos based on our data. Since both genital and urinary systems are derived from the urogenital ridges, chapter 4.2 focuses on the differentiation of the male and female sex organs from the urogenital ridge.

Chapter 5 provides an overview of the formation and changes in the structure of the hyoid-larynx complex, from its onset of development until adulthood, which are compared with those resulting from traumatic events. Chapter 5.1 focuses on the development of this anatomically intricate region in the neck. A new theory concerning the development of the hyoid-larynx complex from the pharyngeal arch cartilages is proposed in this chapter. Chapter 5.2 concerns the anatomical variations of the hyoid-larynx complex and we explain their etiology based on the proposed developmental theory from chapter 5.1. Furthermore, we emphasize the relevance of these variants to forensic sciences. Discerning a fracture of the hyoid-larynx complex, pointing to a potential cause of unnatural death, from an anatomic variant in this region is of utmost importance in criminal matters.
Congenital muscle diseases, such as myopathies or dystrophies, occur relatively frequent with estimated incidences of up to 4.7 per 100,000 newborns. To diagnose congenital diseases in early stages of pregnancy, and to interpret the results of increasingly advanced in utero imaging techniques, requires a profound knowledge of morphological changes during normal human development of the locomotor and nervous system. The muscular system, however, is an often neglected or only generally described topic in embryology textbooks. As a start to obtain insight into morphological muscle development we present in chapter 6 hitherto undescribed detailed skeletal muscle anatomy in an eight weeks old human embryo, in topographic relation with the skeletal and peripheral nervous systems.

In chapters 7 and 8 the thesis is summarized in English and Dutch, respectively. Chapter 9 provides as addendum two manuscripts demonstrating the value of the 3D Atlas of Human Embryology in both clinic and education. Worldwide, almost one third of neonatal deaths is related to neural tube defects, begging for accurate evaluation of the neural system during early development using ultrasound. In chapter 9.1 new ultrasound rendering software is presented which allows visualization of the entire fetal ventricular system of the brain. Since this new imaging technique presents clinicians highly detailed but complex images of early fetal and embryonic anatomy of the neural system, the 3D Atlas provides a reference resource for topographical anatomy. Not only clinicians, but also students have always been struggling to grasp the intricate morphogenesis of the developing human body by studying textbooks since texts use static, schematic 2D images. To facilitate embryology education on an understandable yet scientific level, we created the 3D Atlas. In chapter 9.2, we validated whether the 3D Atlas actually has an added educational value in the (bio)medical curriculum.