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Адреса редакції:  
Україна,  
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вул. Галицька, 2  
Івано-Франківський національний  
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Телефон: (0342) 53-79-84  
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*O.V. Tsyhykalo, N.B. Kuzniak, I.S. Popova, I.Yu. Olijnyk, R.R. Dmytrenko, P.P. Perebyinis, Ya.V. Horytskyi*  
**Peculiarities of the Upper Lip Morphogenesis and Its Relation to Facial Development**

Bukovinian State Medical University, Chernivtsi, Ukraine

**Abstract.** An appreciation of the fundamental principles associated with the development of the craniofacial structures is essential for attaining competency within the fields of facial surgery, dentistry and pediatrics.

**The objective** of this literature review was to highlight the main stages and precise time ranges of human upper lip development, as well as to elucidate the fundamental mechanisms of normal morphogenesis and possible congenital malformations.

The structures of the head and neck arise from the lateral portion of the neural tube, which forms five pairs of branchial arches. Recent studies have identified various molecular pathways (including Bmp, Fgf and Shh signaling) and genetic mechanisms in human face development. Primordial structures of the upper lip begin to appear early within the 6<sup>th</sup> week of ontogenesis; their development involves a number of highly coordinated, genetically programmed ontogenetic mechanisms that include growth and expansion of the facial prominences, programmed cell death, active fusion and breakdown of the epithelial seam between the initially freely maxillary, medial nasal, and lateral nasal processes. Defects of epithelial and mesenchymal fusion during upper lip formation result in orofacial cleft. Further research should be directed to studying normal ontogenesis at the molecular and topographical levels with the determination of critical periods, time ranges and developmental stages that are sensitive to teratogens.

**Keywords:** *upper lip; prenatal development; face; morphogenesis*

### Background

Congenital malformations rank first among the causes of infant mortality and disability [4, 11, 17]. Cleft lip and cleft palate being a group of conditions that includes cleft lip (CL), cleft palate (CP), and both together (CLP) is the most common craniofacial birth defect in humans that occurs once in 500–2500 live births worldwide. In Ukraine, from 420 to 450 children with CLP are born annually. Over 300 Mendelian syndromes in humans include CLP as a part of the phenotype [12, 16].

The upper lip (UL) is formed by the fusion of facial processes in which many genetic and environmental factors are involved [7]. Much confusion exists in the literature concerning morphological processes and mechanisms leading to the formation of normal UL, topographic relations between the midfacial structures during ontogenesis, formation of the CLP and other congenital malformations of the oral cavity.

The study of developmental defects can improve the understanding of the mechanisms of normal human development as well as congenital malformations and can help select the most appropriate time for correcting any facial abnormality. An understanding of the fundamental principles associated with the development of the craniofacial structures is essential for attaining competency within the fields of facial surgery, dentistry and pediatrics.

Therefore, **the objective** of this literature review was to highlight the main stages and precise time ranges of human UP development, as well as to elucidate the fundamental mechanisms of normal morphogenesis and possible congenital malformations.

### Main part

The peculiarities of prenatal development of the craniofacial region have always been an acute topic for research and discussion [1, 7, 9, 12]. The formation of the UL and palate is known to be a complicated process which is composed of a series of highly coordinated steps during tissue morphogenesis. Recent studies have clarified various molecular pathways (including Bmp, Fgf and Shh signaling) and genetic mechanisms in human

face development. Genetic variations in TGFBs, RARs, NADH dehydrogenase (an enzyme involved in oxidative metabolism) and cytochrome P-450 (a detoxifying enzyme) have been implicated as contributing genetic factors for CLP development [3, 11].

F. He and Chen Y. (2012) described Wnt signaling as an essential process (I-catenin-dependent (canonical) or I-catenin-independent (non-canonical) Wnt signaling pathway) in UL fusion and, therefore, the formation of the UL as well as the development of the secondary palate; its effect on the pathology of these structures, the determination of cell death, the regulation of cell proliferation, differentiation, and survival [5].

Another method of influence is the fibroblast growth factor (FGF) receptors of which are expressed at specific stages and precise locations during normal formation of the UL and palate regulating cellular processes. Mutations in FGF signaling pathway gene are associated with syndromic forms of CLP with mutations in FGFR1 and FGFR2 [19].

Sonic hedgehog (Shh) is an ectodermal signal that regulates the proliferation of mesenchymal cells in ectoderm and transdifferentiation of epithelial cells to mesenchymal processes of cell death, which is necessary for fusions between palatine processes. In addition, Shh expression in facial ectoderm supports cell survival at the initial stages of ontogenesis and contributes to the proliferation at later stages to control the size of facial protrusion [21].

The structures of the head and neck arise from the cephalic portion of the neural tube, which forms five pairs of branchial arches [13]. Each arch consists of three layers: outer layer of ectoderm, middle layer and inner layer of endoderm. The development of the facial structures starts with the stomodeum which develops into the mouth during the fourth week of ontogenesis. By the fifth week of the prenatal development, the medial (MNP) and lateral nasal (LNP) processes develop on either side of the frontonasal process (FNP). The medial one forms the UL [22].

Tadahiko Iizuka (1973) divided the development of the UL into 5 stages [7]. At the first stage, the fusion between the MNP and the maxillary processes does not involve both sides, while at the second stage, it occurs on more than two-thirds of the total length of the future UL on both sides. The third stage shows that more than two-thirds of the total length of the future UL fuse on both sides, although the boundary grooves between the processes are still deep and can be easily recognized. At the fourth stage, the grooves are less distinct as compared to the previous stage and hardly traceable. The fifth stage is characterized by almost completely developed UL without boundary grooves. The author emphasized that although in several cases, the difference in development of the UL was observed during the initial stages of its formation, there was found no consistency among them.

Relying on fundamental works of human facial embryogenesis it is possible to understand a detailed step-by-step pathway of the UL development using the Carnegie staging system (CSS) for human embryos [1, 7, 9, 12, 17–22]. At stage 11 (the 24<sup>th</sup> day of gestation), according to the CSS, the stomodeum (primitive mouth) is separated rostrally by the developing forebrain and caudally by the developing maxillary arches; the UP is not found yet. An embryo, at this stage, has 19 pairs of somites and 2 pairs of branchial arches. At stage 12 (the 26<sup>th</sup> day of gestation), the facial primordial consists of

prominences surrounding the stomodeum and the FNP is identified on its rostral side. The embryo has three pairs of branchial arches. The stomodeum becomes a transverse slit-like structure that is laterally separated by a pair of the maxillary processes and caudally by mandibular processes [21]. During stages 13-15 (from the fourth to the fifth weeks), the medial ends of the mandibular processes form the lower lip and the jaw. At stage 14 (32 days of gestation), nasal pits are formed. Stage 15 (the 35<sup>th</sup> day of gestation), shows rapid growth of mesenchymal connective tissue in the maxillary processes and ventrolateral growth of the MNP. At this stage, the UP is laterally represented by the maxillary processes, medially – by the MNP with the LNP found between the medial nasal and maxillary processes. Therefore, the LNP and the maxillary process are components of the structure of the UL [9, 11].

At stage 16 (the onset of the 6<sup>th</sup> week), the MNP and maxillary process grow and fuse quickly; damage to this process can result in lateral cleft lip. The type of CLP indicates the inability of MNP fusion with both maxillary processes and the LNP during the development of the UL. This epithelial fusion continues from stage 16 till stage 18 when the groove between the MNP becomes smooth and the nasal pits convert to nose chambers and nasal duct [1]. X.C. Jian, et al. reported on a rare clinical case of massive medial cleft of the UL in a 4-month-old boy with a successful surgical treatment [8].

During stage 16 (the 38<sup>th</sup> day of gestation), three auricular hillocks may be distinguished on the hyoid arch; the cerebral vesicle is prominent and the retinal pigment is observed externally. The cervical sinus disappears totally at stage 17 when the groove between the maxillary process and the LNP becomes visible and the nasal sac is formed. The critical period of UL formation is known to appear between stages 17 and 18. The eyes and nasal pits move to the medial portion of the face at stage 18. At this stage, the maxillary processes constitute more than two-thirds of the UL and both MNP start forming the future nose [3, 7].

At stage 19 (the 48<sup>th</sup> day of gestation), after the breakdown of epithelial seams and mesenchymal fusion between the MNP and the maxillary processes, formation of the UP is completed. The intermaxillary segment derived from the distal part of the MNP forms the central part of the lip. During this period, the anterior part of the primary palate arises from the intermaxillary segment in the oral cavity and, then, connects to the secondary palate derived from the maxillary processes. Since the fusion between the primary and secondary palates occurs much later ontogenetically than the fusion between the maxillary process, the MNP and the LNP during lip formation, damage to the process of lip fusion often affects palatal contact secondarily. As a result, CL is usually accompanied by CP [9]. However, some authors stated that the complete formation of the UL and its surrounding areas is completed only at fetal stage 21 [20]. The early rapid growth of the UL and, accordingly, early maturation are not surprising considering the phylogenetic importance of well-developed lips for breast-feeding.

As mentioned above, the morphogenesis of the craniofacial tissues and structures has a complex basis and is associated with a number of factors, which include the origin of tissues, molecular control of growth disturbances and others [1, 6, 13]. The FNP forms the forehead, the bridge, and dorsum of the nose and the nasal bones. The MNP forms the columella of the nose, the philtrum, the perpendicular plate of the ethmoid bone and the vomer, the cribriform plates, and the primary palate. The LNP forms the sides and alae of the nose. The maxillary processes form the upper cheek region and most of the UL, the maxilla, the zygomatic bone, and the secondary palate. The mandibular processes form the chin, the lower lip, the lower cheek region, and the mandible [2, 10, 18, 22]. B.K. Hall, et al. (2013) noted the importance of the nasal septum as a pacemaker for midfacial growth, and its effect on skeletal and soft tissues [4].

R. Nagaoka, et al. (2012) described the relationship between embryonic hypoxia and UL formation. In hypoxic embryos, the activity of the LNP mesenchymal cell proliferation decreased being accompanied by reduced regulation of the genes being involved in UL formation resulting in insufficient growth of the facial processes [15].

The UL is known to be supplied with blood by two superior labial arteries originating from each facial artery [18]. According to the O. Magden, et al. (2004), about 30% of the labial arteries have a unilateral origin. Therefore, it is recommended to conduct preoperative examination of the vascular system before any microsurgical repair of the lips [12].

The palate develops from the MPP, the LPP, and the nasal septa. The MNP, a part of the intermaxillary segment, is called the primary palate as well; the lateral palatine process is called the secondary palate. When the coordinated development of these processes and the tongue is damaged, a cleft between the processes may develop. The exact time of palatine closure and critical periods of its development are still insufficiently studied [4, 5, 19].

As concerning the prenatal development of the mandibula and the adjacent oral region, T. Humphrey (1971) concluded that more rapid growth of the mandibula is accompanied by change in the position of the tongue and the palatine processes [6]. This acceleration in mandibular growth depends on the presence of the tongue in the floor of the mouth, rather than on change in the position of the palatine processes and the UL.

T. Humphrey [6] noted that the movement of the mandibula during the prenatal development promotes increased growth of blood vessels which affect the accelerated morphogenesis of both the mandibula and the oral cavity (the UL in particular).

The facial muscles arise from the mesenchyme of the second arch and are innervated by the facial nerve. The derivatives of the facial muscles are identified between the 6<sup>th</sup> and 7<sup>th</sup> weeks of ontogenesis [10]. The superficial musculoaponeurotic system (SMAS) is a continuous, organized meshwork connecting the facial muscles to the dermis that is identified since the 8<sup>th</sup> week of ontogenesis. The SMAS is not identifiable in the labial region; however, the SMAS type 1 is clearly visible in the UL and ends postnatally at the nasolabial fold [2].

The Juxtaoral organ (Chievitz organ) is a rudimentary epithelial structure with a neuroendocrine function that appears since the 7<sup>th</sup> week of ontogenesis. It is located deep to the medial pterygoid muscle at the level of the pterygomandibular raphe in close relation to fibers of the buccal nerve and consists of three fibrous strata (the stratum internum, the stratum externum and the stratum nervosum). J. R. Mírida-Velasco, et al. (2005) classified three stages of the Juxtaoral organ development: the blastematic stage, the cavitation stage and the maturation stage [14]. The function of this organ is controversial possibly including secretory, neuroendocrine, masticatory, mechanic and sensory as well as sensory and nervous ones.

CLP is known as orofacial cleft as well. It is generally divided into two groups: isolated CP and CL with or without CP, representing a heterogeneous group of disorders affecting the lips and the oral cavity. CLP can occur in isolation or as a part of broader range of chromosomal, Mendelian or teratogenic syndromes. The effect on speech, hearing, appearance, and psychology can lead to long-lasting adverse outcomes for health and social integration. Although there has been marked some progress in identifying genetic and environmental triggers for developing CLP, the etiology of the isolated forms at the ontogenetic level remains poorly studied [17, 19].

### Conclusions

A detailed study of normal morphogenesis, anatomical peculiarities of the formation of the UL in the prenatal period of human development has both theoretical and practical significance for understanding the mechanisms of the possible

occurrence of congenital diseases, variants and deficiencies, and the development of more effective methods for correcting these anomalies by surgical methods. Further studies of pre- and postnatal developmental features of the UL and adjoining facial structures, in particular, will be useful in planning the reconstruction of congenital lip defects and in-depth knowledge of the mechanisms of ontogenesis and successful treatment of congenital malformations such as CLP.

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### Особливості морфогенезу верхньої губи та їх зв'язок із розвитком лицевої ділянки

ВДНЗ України "Буковинський державний медичний університет", м. Чернівці, Україна

**Резюме.** Розуміння основоположних принципів, пов'язаних з розвитком структур черепно-лицевої ділянки має важливе практичне значення в галузях лицевої хірургії, стоматології та педіатрії. Метою даного огляду літератури є висвітлення основних етапів і та дискусійних питань щодо часових діапазонів ембріогенезу верхньої губи людини для з'ясування основних нормальних морфогенетичних механізмів онтогенезу та можливих вроджених вад розвитку. Структури голови і шиї походять з латеральної частини нервової трубки, яка утворює п'ять пар зябрових дуг. Останні наукові дослідження вказують на різні молекулярні (включаючи *Vmp*, *Fgf* і *Shh* шляхи сигналізації) і генетичні механізми розвитку структур лица. Структури верхньої губи з'являються на початку 6-го тижня онтогенезу, і їх розвиток включає в себе ряд висококоординованих та генетично запрограмованих механізмів росту клітин, розширення лицевих виступів, запрограмовану загибель клітин, активний синтез і розпад епітеліального шва між спочатку вільно розташованими верхньощелепними, медіальними і бічними носовими відростками. Дефекти епітеліального і мезенхімального злиття в процесі формування верхньої губи може призвести до виникнення розтвору верхньої губи і піднебіння. Подальші вивчення слід направити на вивчення нормальних закономірностей нормального онтогенезу на молекулярному і топографічному рівнях з визначенням критичних періодів, часових діапазонів і чутливих стадій для тератогенних впливів на людський ембріон.

**Ключові слова:** верхня губа, пренатальний розвиток, лицева ділянка, морфогенез.

*Цигикало А.В., Кузняк Н.Б., Попова І.С., Олійник І.Ю., Дмитренко Р.Р., Перебийніс П.П., Горицький Я.В.*

### Особенности морфогенеза верхней губы и их взаимосвязь с развитием черепно-лицевой области

ВГУЗ Украины "Буковинский государственный медицинский университет", г. Черновцы, Украина

**Резюме.** Понимание основных принципов, связанных с ростом и развитием структур черепно-лицевой области имеет важное практическое значение в лицевой хирургии, стоматологии и педиатрии. Целью данного обзора литературы является освещение основных этапов и дискуссионных вопросов связанных с временными диапозонами эмбриогенеза верхней губы человека для выяснения основных нормальных морфогенетических механизмов развития и возможных врожденных аномалий верхней губы. Структуры головы и шеи возникают из латеральной части нервной трубки, которая образует пять пар жаберных дуг. Последние научные исследования указывают на различные молекулярные (включая *Vmp*, *FGF* и *Shh* пути сигнализации) и генетические механизмы развития структур лица. Структуры верхней губы появляются в начале 6-й недели онтогенеза, и их развитие включает в себя ряд высокосоординированных и генетически запрограммированных механизмов роста клеток, расширение лицевых отростков, запрограммированную гибель клеток, активный синтез и распад эпителиального шва между поначалу свободно расположенными верхнечелюстными, медиальными и боковыми носовыми отростками. Дефекты эпителиального и мезенхимального слияния в процессе формирования верхней губы могут привести к возникновению расщелин верхней губы и неба. Дальнейшие исследования следует направить на изучение закономерностей нормального онтогенеза верхней губы на молекулярном и топографическом уровнях с определением критических периодов, временных диапозонов и чувствительных стадий для тератогенных воздействий на человеческий эмбрион.

**Ключевые слова:** верхняя губа, пренатальное развитие, лицо, морфогенез.

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