GENETIC CONTROL OF THE MOLECULAR SIGNALLING EVENTS INVOLVED IN THE HISTOGENESIS OF UNSYNDROMIC CLEFT LIP AND/OR PALATE

CRISTIAN TUDOSE [1*], IULIANA CSILLA BARA[1]

Key words: growth factors, transcription factors, cleft lip, cleft palate

Abstract: Up to date research based on the most recent techniques of molecular biology lead to the detection of genes, transcription factors, growth factors, other signalling molecules and their receptors involved in the determinism of unsyndromic cleft lip and/or palate. The authors review the most recent discoveries regarding this subject: identification of a major candidate gene located on the short arm of chromosome 6 and, mainly, the modifier role of growth and transformation factor alpha (TGFA). There are discussed the role of growth and transformation factor beta (TGFB 2 and 3), of transcription factors Msx and Lef and of homeobox genes as coordinators of mitosis/apoptosis during the fusion and epithelisation processes of internal nasal and maxillary buds, as well as of palatine processes.

INTRODUCTION

Cleft lip and/or palate are consequence of some genetic and environmental factors that determine defects of confluence and epithelisation between facial buds during the fifth and eight weeks of intrauterine life. Most frequent cleft lip and/or palate appear as unique, isolated malformations referred to as unsyndromic clefts; only in 30 – 40% of cases clefts associate with other malformations resulting in plurimalformative syndromes (Cohen, 1983).

Their etiology is complex and difficult to elucidate; cleft lip and/or palate are mainly due to genetic factors (genic and chromosomal mutations) in 65% of cases, multifactorial in 31% of cases and environmental (theratogenesis – e.g. anticonvulsive drugs) in only 4% of cases (table 1).

Table 1: Etiology of cleft lip and/or palate (adapted from Cohen, 1983 and Wyszynski et al., 1996)

ETIOLOGY		Cleft lip	Cleft lip and palate	Cleft palate		TOTAL
				Opened	Submucosal	
Genetic/mainly genetic	Multifactorial	67%	54%	41%	34%	49,00%
	Monogenic	0%	13%	20%	21%	13,50%
	Chromosomal	4%	3%	1%	2%	2,50%
Environmental/ mainly environmental	Theratogenesis	4%	3%	5%	3%	3,75%
	Disruptions	4%	5%	9%	0%	4,50%
	Deformations	21%	22%	24%	40%	26,75%

In the following chapters, authors review the most recent discoveries regarding this subject: identification of genetic loci involved in the determinism of unsyndromic clefts and the molecular mechanism that generate the coalescence defects of facial buds.

GENETIC DETERMINISM AND HEREDITARY TRANSMISSION PATHWAYS OF UNSYNDROMIC CLEFTS

Many authors report strong evidence of well documented familial observations which support monogenic transmission pathways, autosomal dominant (with low penetrance and variable expressivity) (Jenkins şi Stady, 1980 – cited by Cohen, 1982) or X-linked (Lowry şi Trimble, 1977– cited by Cohen, 1982).

The majority of specialists agree with the *multifactorial (threshold) transmission hypothesis* which involves many genes with small, additive effects (polygenic determinism) and environmental factors (Carinici et al., 2000) which is in accordance with the heterogeneity of observations. The candidate genes exhibiting small and additive effects are in different numbers from person to person and determine a variable predisposition /susceptibility to clefts.

The distribution of these risk genes in a given human population is random (discontinuous) and has a graphic aspect according to the curve of Gauss; the distribution curve exhibits a threshold which, if over passed, generates the genetic predisposition.

The most recent candidate genes involved in this hypothesis are located on the short arm of chromosome 6, the long arm of chromosome 4 and chromosome 11 as well as the gene of TGFA (Chenevix-Trench, 1992; Davies, 1995), TGFB 2 and 3, the gene for retinoic acid receptor (RARA) located on chromosome17 q (Hanson and Murray, 1990), the genes Msx 1 (4p) and BCL3 (19q) (Theslef and Nieminen, 1996).

GROWTH AND TRANSCRIPTION FACTORS GENES CANDIDATE FOR CLEFT LIP AND/OR PALATE

Base on segregation, association and linkage studies a number of candidate genes seem to be involved in the determinism of unsyndromic cleft lip and/or palate; these genes and their location are depicted in table 2.

Table 2: Candidate genes for unsyndromic cleft lip and/or palate and their location (adapted from Wyszynski et al., 1996)

Type of cleft	**Location**	**Locus nomenclature**
CLEFT LIP AND/OR PALATE (multifactorial determinism with threshold or oligogenic)	6p23 –24.3	OFC1
	2p13	OFC2 – TGFA
	6p23 + 2p13	OFC1 + OFC2
	19q13	OFC3 -BCL3
	4q31	D4S192
	17q21.1	RARA
CLEFT PALATE (oligogenic determinism)	2p13	TGFA

Studies based on vast family inquiries proved that a mendelian model of transmission cannot be accepted; in function of the studied population two models of transmission may be appropriate:

- a multifactorial (treshold) model
- an oligogenic model

The most important loci involved in the multifactorial model seem to be the ones located on chromosomes 2 and 6. On chromosome 6, inside the region 6p24.3, studies using YACs proved the existence of a major dominant gene referred to as OFC1, placed closely to HGP22 and AP2 genes involved in the morphogenesis of human face. In other populations was proved the association of clefts with the gene of TGFA located on chromosome 2p13 at the OFC2 locus (some studies are correlating the level of expression of this gene with maternal smoking).

The oligogenic model involves the existence of a major autosomal dominant gene (e.g. the OFC1 gene) and of one or many modifier genes (e.g. OFC2, the protooncogene BCL3 located on chromosome 19q13.2 - locus OFC3, the locus D4S192 on chromosome 4q31.3 and the RARA locus on chromosome 17q21.1.) (Chenevix-Trench, 1992; Davies, 1995).

GENETIC CONTROL OF THE MOLECULAR SIGNALLING EVENTS INVOLVED IN CLEFT LIP AND/OR PALATE HISTOGENESIS

As well as all organs and body segments the morphogenesis of oral cavity is placed under a strict genetic control which determines the shape and position of all composing elements. The main groups of genes involved in the formation of lips and palate are (Jorde et al., 2006):

- divergent homeobox genes;
- transcription factors genes;
- growth factors genes (which are signals in epithelium-mesenchyme interactions)
- genes of the receptors of signal molecules: RARA, GABA, activin βA, etc.

The interactions between all these elements concurring to the lack of coalescence and epithelisation of facial buds which will lead to clefts are depicted in figure 1.

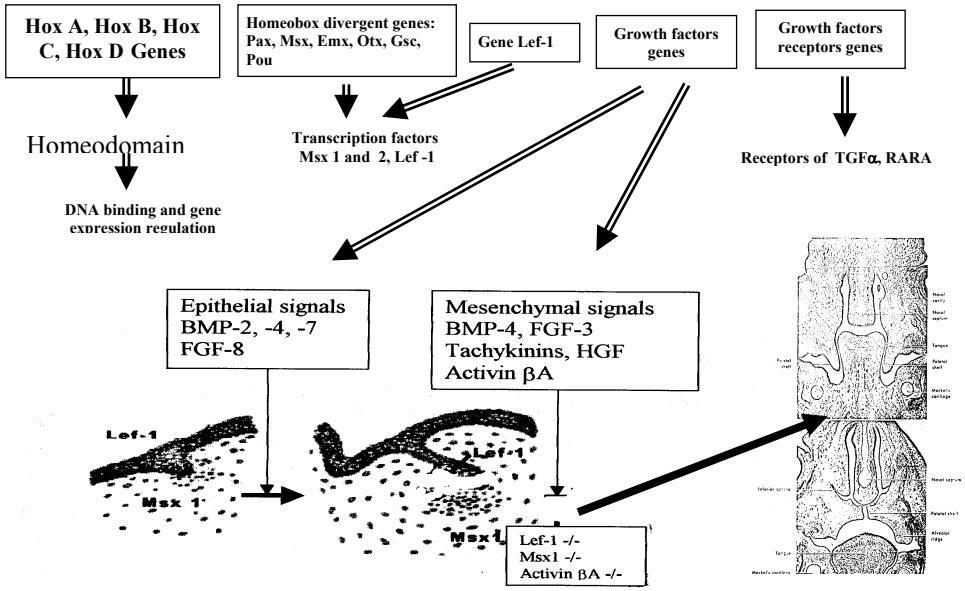

Fig. 1: Genes, transcription factors and signaling molecules which govern the epithelium-mesenchyme interactions leading to the normal/pathological formation of human lips and palate (Tudose et al., 2001).

CONCLUSIONS

Up to date studies based on the most recent techniques of molecular biology lead to the detection of genes, transcription factors, growth factors, other signalling molecules and their receptors involved in the determinism of unsyndromic cleft lip and/or palate.

On chromosome 6, inside the region 6p24.3, studies using YACs proved the existence of a major dominant gene referred to as OFC1, placed closely to HGP22 and AP2 genes involved in the morphogenesis of human face.

In some populations the association of cleft lip and/or palate with mutations of the TGFA gene located on chromosome 2p13 (locus OFC2) was strongly proved.

The role of growth and transformation factor beta (TGFB 2 and 3), of transcription factors Msx and Lef and of homeobox genes as coordinators of mitosis/apoptosis was also proved during the fusion and epithelisation processes of internal nasal and maxillary buds, as well as of palatine processes.

REFERENCES

Ardinger H.H., Buetow K.H. , 1989., *Am J Hum Genet*, 45: 348.
Bixler D., 1981. *Cleft Palate Journal,* 18:10-18.
Carinci F., Pezzetti F.,Sscapoli L. , 2000. *Cleft Palate Craniofacial Journal*, 37, 1:33-40.
Chevenix-Trench G., Jones K., 1992. *Am J Hum Genet*, 51:1377-1385.
Christensen K., Mitchell L.E., 1996. *Am J of Hum Gen,* 58 (1): 182-190.
Cohen M.M.Jr., 1982. *The child with multiple birth defects,* Raven Press, New York.
Davies A.F., Stephens R. J., 1995. *Hum Molecular Genetics*, 4:121-128.
Fraser F.C., 1970. *Am J Hum Genet*, 22:336.
Hanson J.W., Murray J.C., 1990. *Genetic aspects of cleft lip and palate*. In: Bardach J., Morris H.L. (eds.) *"Multidisciplinary cleft lip and palate"*., WB Saunders Company, Philadelphia.
Hibbert S.A., Field J.K. , 1996. *Oral diseases*, 2(3):238-241.
Jorde L., Carey J., Bamshad M., White R., 2006. *Medical genetics,* Mosby Elsevier, St. Louis.
Kelly T. E., 1980. *Clinical Genetics and genetic counselling*. Year Book Med. Publ., Chicago.
Melnick M., Bixler D. , 1980. *Etiology of cleft lip and cleft palate*, A.R. Liss, New York.
Scheidereit C., 1996. *J. Mol. Med*, 74:707-709
Sharpe P.T. , 1995. *Connect Tissue Res*, 32:17-25.
Smith D W, 1988. *Recognizable patterns of human malformation*, WB Saunders, Philadelphia.
Thesleff I., Nieminen P., 1996. *Current Opinion in Cell Biology*, 8:844-850.
Tudose C., Gabriela Halițchi, Monica Dragomir, 2001. *Tehnologii contemporane în clinică şi laborator - Supliment al Revistei de Medicină Stomatologică*, 5,1:63-67.
Wyszynski D.F., Beaty T.H., 1996. *Cleft Palate Craniofacial J.*, 33 (5): 406-417.

1 – University "Al.I.Cuza" Iaşi, Faculty of Biology, Discipline of Genetics
* - cristian.tudose@uaic.ro