# MSX1 gene in the etiology orofacial deformities

## Gen MSX1 w etiologii wad rozwojowych twarzoczaszki

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## Summary

The muscle segment homeobox (*MSX1*) gene plays a crucial role in epithelial-mesenchymal tissue interactions in craniofacial development. It plays a regulative role in cellular proliferation, differentiation and cell death. The human *MSX1* domain was also found in cow (*Bt 302906*), mouse (*Mm 123311*), rat (*Rn13592001*), chicken (*Gg 170873*) and clawed toad (*Xl 547690*).
Cleft lip and palate is the most common anomaly of the facial part of the skull. The etiology is not fully understood, but it is believed that the key role is played by the genetic factor activated by environmental factors. Among the candidate genes whose mutations could lead to formation of the cleft, the *MSX1* homeobox gene is mentioned. Mutations in the gene *MSX1* can lead to isolated cleft deformities, but also cause other dismorphic changes. Among the most frequently mentioned is loss of permanent tooth buds (mostly of less than 4 teeth – hypodontia, including second premolars).
Mutations of *MSX1* are observed in the Pierre- Robin sequence, which may be one of the features of congenital defects or is observed as an isolated defect. Mutation of the gene can lead to the occurrence of a rare congenital defect Wiktop (dental-nail) syndrome. Deletion of a fragment *MSX1* (4p16.3) located in the WHS critical region, may be a cause of some symptoms of Wolf-Hirschhorn syndrome.

**Key words:**  MSX1 homeobox • cleft lip and/or palate • hypodontia

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*The MSX1* (muscle segment homeobox) gene plays a crucial role in epithelial-mesenchymal tissue interactions in craniofacial development. It plays a regulative role in cellular proliferation, differentiation and cell death – the processes playing a key role in cell growth and morphogenesis [4]. The *MSX1* gene, as well as *PAX9*, *AXIN2*, *EDA* and *EDAR* genes is responsible for tooth hypodontia [35]. The *MSX1* gene is located on chromosome 4p16.1. Its mutation causes autosomally dominant agenesis of second premolars and third molars. The gene causes multiple tooth agenesis, that is a result of a change in nucleotide sequence, where proline substitutes arginine in position 196 [24]. According to Modesto et al. [37], *MSX1* mutation leads to cleft lip and palate formation, when it occurs in parallel with the *PAX9* gene mutation. The mutations within *MSX1* may also lead to rare congenital defects such as Wiktop syndrome and Wolf-Hirschhorn syndrome. It has previously been shown that *MSX1* mutations notably change the quality of dental mesenchyme, but do not have its expression in dental epithelia at the bud, cap or bell stages of dental development [60].

The human *MSX1* domain was also found in cow (*Bt 302906*), mouse (*Mm 123311*), rat (*Rn13592001*), chicken (*Gg 170873*) and clawed toad (*Xl 547690*) [23].

## NONSYNDROMIC CLEFT DEFORMITIES

Cleft deformities are the most common facial malformation and are observed in ca. 10% of all the facial deformities [18]. Clefts of lip, alveolar bone and palate are observed two to three times more frequently in males while as isolated cleft of the palate is more frequent in females [54,56]. The formation of facial clefts takes place within 5-12 week of fetal development, during face formation [38]. The cleft lip and/or palate is a common congenital disorder, observed in 1:700 live births. The full etiology is not known, although a genetic factor is indisputable. There are numerous genes involved in palate formation, which disturbances of which may lead to cleft formation [44].

Observation of cleft's familial occurrence and selective presence in only some of the individuals indicates the genetic basis of the deformity, but also suggests coexistence of other factor. The etiology of clefts is multifactor, the genetics is only a basis "triggered" by environmental causes. The genetic factor is thought to play a crucial role in 20% of cases of clefts [1,43,54]. The genetic factors are divided as follows: genes encoding signaling molecules (Bmp2, Bmp4, Bmp7, Shh, Wnt5a, Smad 2-4), growth factors (Egf, Egfr, Fgf1, Fgf2, Fgf8, Tgfα, Tgfβ1-3) and their receptors (Fgfr1, Fgfr2), transcription factors (Pax9, Tbx22, Msx1, Tbx1, Ap2α, Blx1-6, Lhx6, Gli 2-3, Hoxa2, Irf6, Pitx1, Pitx2, Prx1), cellular adhesion molecules (Pvrl1, cadherin E, connexin 43), and extracellular matrix (fibronexin, Col 1A2, Col2A1, Col11A1 Mmp2, Mmp3, Mmp9, Mmp13, Timp1-3) [46,49]. Beside the multigenetic background, the MSX1 and TGFβ3 genes are found to be the genes most strongly related to cleft anomalies [59]. Many other genes related to the

clefts have their *loci* in different regions of chromosome 6, among them 6p23-24 and 6p24.3 [8].

Probably, most of the cases of isolated clefts are associated with either *MSX1* or *IRF6* mutation – it is assumed that the relation is observed in one third of cases [51]. The other candidate gene for cleft deformity might be *MTHFR* mutation of which lead to disturbances in folic acid transformation and storage [21]. *MSX1* is responsible mainly for secondary palate formation, therefore mutations within that gene is responsible for isolated cleft palate. *MSX1* is responsible for 2% of all non-syndromic clefts. Due to the complex cause of cleft deformities and to gene-to-gene interaction the influence on cleft palate formation is 9.7 times higher, which means it plays role in almost 20% of cases of clefts [29].

An association between *MSX1*-CA marker has been found. The clefts were more frequently observed in the *MSX1* homozygous allele 4 individuals, whose mothers smoked cigarettes or with both parents smoking. Similar results were obtained in children of mothers without daily folic supplementation during the periconceptional period [5].

The strongest association between nonsyndromic clefts and gene mutation is observed for the rs6446693 region in the MSX1 gene [21]. Five variants of MSX1 mutation were found as responsible for cleft palate forming. There were: A34G, G110G, P147Q, M37L and G267A. Among them, the rarest polymorphic variant is G267A mutation [55]. However, the thesis that MSX1 is a factor influencing clefts is not promoted by all the reaearchers. Some claim that MSX1 might not be an etiologic factor responsible for orofacial clefting [12,30,36,37]. Therefore, further genetic analysis of other genes involved in facial development is required.

## WOLF-HIRSCHHORN SYNDROME

Wolf-Hirschhorn syndrome (WHS), also known as chromosome microdeletion 4p syndrome or Dillian syndrome, is a rare congenital disorder observed in 1:50,000 live births. It was first described in 1961 by two independent researchers: Hirschhorn and Cooper. The deformity is more frequently observed in women. Wolf-Hirschhorn syndrome is probably caused by mutation of one of two candidate genes (*WHS1* and *WHS2*). The syndrome is most frequently associated with a deletion within the 4p16.3 chromosome region (165kb), which encodes the *MSX1* gene [17,47,50,61,63,65]. The deletion most probably refers to *HOX7* gene, that maps to 4p16.1 gene [20]. The majority of cases is caused by "pure" *de novo* deletion and the greater the chromosomal material loss, the greater expression of Wolf-Hirschhorn syndrome [48,50].

Children suffer from multiple disorders, which include developmental delay and high mortality range of 30%. The patients suffer from congenital heart defects, muscle hypotonia, urinary tract malformations, cochlear hearing loss and immunodeficiency. The malformations

are so much severe that they may lead to patient's death [11,16,33,47].

The facial features include high forehead with prominent *glabella,* hypertelorism (with "protruding" eyes), high arched eyebrows, broad nasal bridge and short philtrum. A characteristic feature is micrognathia. In some cases they can be associated with facial asymmetry. The head and face take the characteristic look of a "Greek warrior helmet". The mouth has short upper lip and downturned corners [3,41,47].

Multiple tooth agenesis occuring in this syndrome affects premolars and molars mainly. It is associated with *MSX1* mutation and may vary much (from multiple tooth agenesis to oligodontia). Other dental anomalies include taurodontism and late dental development [2,24,25,37,40].

## Pierre Robin syndrome

Pierre-Robin syndrome (or Pierre-Robin Sequence) is known from the triad of symptoms: congenital micrognathia, cleft of secondary palate and *glossoptosis* with upper airway obstruction. In some cases U-shaped palate and obstructive apnea are observed. The occurrence is relatively rare and ranges from 1:8,000 to 1:30,000 births. The sequence might be isolated or be associated with various congenital syndromes, eg. Treacher-Collins syndrome [13,42]. Beside the three characteristics, other defects might be observed. Those include dental anomalies, in particular hypodontia. This anomaly is observed most frequently in mandibular second premolars [31]. Hypodontia in this region accentates mandibular undergrowth, as loss of tooth buds is a factor of bone underdevelopment in this area [53].

The primary anomaly of Pierre Robin syndrome is failure of mandibular growth caused by a failure in dorsal hold of the head in embryonic development. As a consequence, this forces high postion of the tongue in primordia (primary oral cavity). The final result of that is physical obstruction for the posterior palatal shelves to fuse [42]. Micrognathia is found to be connected with deletions within genes 4p16-14, 4q31-35, 6q25-27 and 11q23. Those genes might be associated with Pierre Robin sequence, though its real etiology (and its probable genetic basis) is not known. The most probable genes involved in this syndrome are: the transcription factor *SOX9* (on 17q24.3--q25.1), *GAD67* (on 2q31) and *PVRL1* (on 11q23-q24) [22]. The *SOX9* mutation alters binding of the transcription factor *MSX1* [22,58]. In experiment performed in mice, it had been proved that lacking of *MSX1* function results in cleft of secondary palate, migrognathia and microgenia, which are the most characteristic features of Pierre Robin syndrome as well. Furthermore, the mutation of this transcription factor causes underdevelopment of nasal, frontal and parietal bones, and the malleus. It also disturbs tooth development [45]. In families where *SOX9* mutation is the cause of Pierre Robin syndrome, the sequence is more severely expressed [42].

## Wiktop syndrome

Wiktop syndrome is a rare congenital disease, inherited autosomally dominantly. It is also known as tooth and nail syndrome (TNS) or "nail dysgenesis and hypodontia", and as a type of ectodermal dysplasia. Tooth agenesis is accompanied by nail deformities - the nail plates are defective and thinner [26]. It was firstly described by Wiktop in 1965 [62] and its prevalence is estimated to ca. 1-2:10.000 births [22].

The syndrome is inherited autosomally dominantly [10]. The symptoms are less pronounced than in other types of ectodermal dysplasia, which is why those can be missed by the clinicians [64]. In 2001 it had been proved that the mesenchyme gene MSX1 is responsible for Wiktop syndrome [26]. In 2013 the *3'-UTR* region of this genewas found to be the most predominant locus [14].

In this congenital disorder, nails are dysplastic, thin, spoon-shaped (*koilonychia*) and easy to break (*onychorrhexis*). They grow slowly. Changes are more pronounced in toenails than fingernails. In some cases, nail defects are less pronounced in adulthood and less characteristic [15,19,52,55,64].

The other characteristic feature is hypodontia. There is no pattern of missing teeth – it is dependent on the individuals [19]. The most frequently missing teeth are lower incisors, secondary molars and upper canines [after 10]. The teeth (if present) show deformities such as peg--shape (conical shape). They can also be tapered or pointed [19]. The teeth are narrower and their eruption is disturbed [55].

Due to tooth agenesis, prosthetic appliances to improve chewing function and esthetic appearance might be required. In some cases they can also play a role as space maintainers [55]. Due to the hypodontia, the alveolar bone is hypoplastic and narrowed in its vertical dimension. The jaws are underdeveloped. Loss of occlusion in the vertical dimension may lead to lip eversion [19].

## Dental anomalies

Along with the *PAX9* gene, *MSX1* homeodomain is responsible for tooth agenesis. Both of them are expressed in dental mesenchyme. When homozygously deleted, they result in tooth development delay in an early stage. *MSX1* and *PAX9* mutations lead to disturbances of tooth development in the cap and/or bud stages of dental development, as they are expressed in this period of dental development. In mice, heterozygous deletion of either *PAX9* or *MSX1*, has no expression in dental structure. However, double heterozygous mutation shows arrested tooth development. This could be still rescued by Bmp4-signaling factor expression. Unlike in mice, in humans a heterozygous mutation in either *MSX1* or *PAX9* leads to tooth agenesis, predominantly in the posterior area. The mutation of *MSX1* leads to lack of second premolars and third mo-

lars, while *PAX9* mutation is responsible for lack of "wisdom teeth" [6,28,29,59]. Although MSX1 mutation is the most frequent cause of lack of tooth buds, the mutation in A240P (rs4904210) in the *PAX9* gene results in multiple tooth agenesis, called oligodontia [39].

The nonsense mutation within the *MSX1* gene (eg. c.C565T in exon 2 or intron 1) dramatically reduces mRNA expression, suggesting that it may lead to rapid degradation of the mutated transcript, and cause the tooth agenesis [6,34]. Hypodontia (lack of 4 or fewer tooth buds) may also be a result of heterozygous *R151S* mutation. The allele is mildly deleterious for familial hypodontia. The mutation within this allele itself is insufficient to cause orofacial clefting. When other factors are involved (environmental or other, genetic ones), the cleft might occur [32]. It has also been shown that *MSX1* gene mutation (Ala219Thr, specifically), might be a reason for oligodontia, though due to the fact that lack of more than 4 tooth buds is more characteristic for other genes mutations, further studies of that topic are required [7,12,27]. There are studies, however, indicating that *MSX1* mutation is not a factor causing hypodontia. They point to *WNT10A* as a major cause of isolated congenital lack of teeth [57].

Beside tooth agenesis, underdevelopment of nails (its thinner and defective structure) in *MSX1*-null mice was observed [26]. Eexpression of the gene is unequal in the individuals and families. It takes place not only in mesenchyme structures, but also in the neural crest, cranial sensory placodes and bones [6,9]. Other developmental anomalies could be a result of *MSX1* mutation as well. Those could be deformities such as choanal atresia, anophthalmia, microphthalmia, cataracts, pachygyria, dispigmentation and mental retardation were observed in mice with *MSX1* mutated gene. It might be the main responsibility of *MSX1* gene to modulate the growth and inhibit differentiation. The outgrowth could be reduced by the early differentiation in progress zone of facial processes [1].

Summing up, *MSX1* is an important gene expressing in mesenchyme. Its mutations may lead to developmental disorders such as variety of clefts, tooth and nail anomalies, and many others. The *MSX1* mutation is observed in Pierre-Robin sequence. The mutations may lead to Witkop syndrome or Wolf-Hirschorn syndrome. Further research is required to establish the exact role of this gene.

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