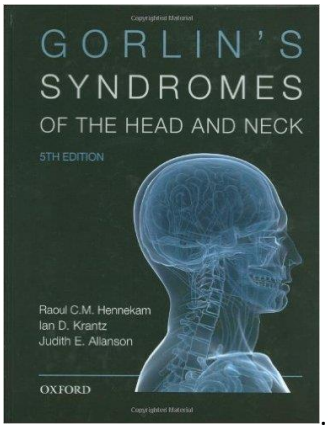
Syndromes of the head and neck, clefts

Syndromes of the head and neck are a numerous group of very rare clinical units. The occurrence of most of them is about one case to tens or hundreds thousands live births. Substantial part of them is monogenic. The best source of information is atlas Gorlin syndromes of the head and neck. This fifth edition is named in honor of its first author Robert J. Gorlin. OMIM web is also a good place to find information.

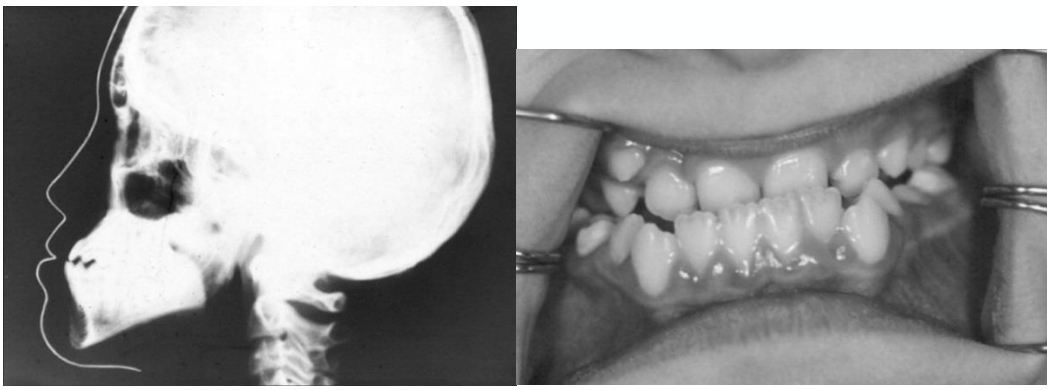


.

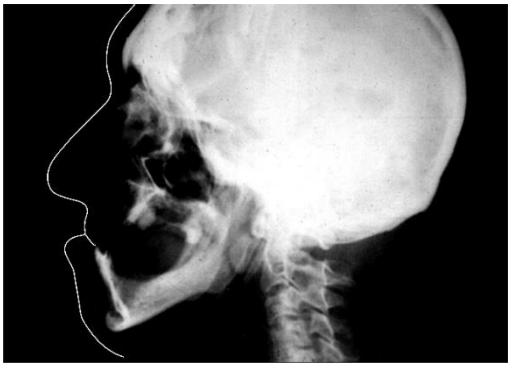
The probability that you meet such patients in you daily practice is very low. So there are only several of them, to remember.

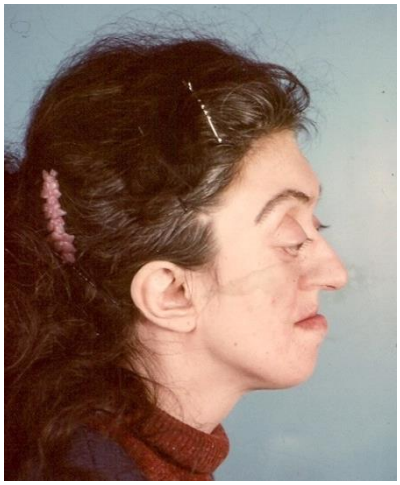
Crouzon syndrome is characterised by craniosynostosis, maxillary hypoplasia, shallow orbits and ocular proptosis. Is transmitted in autosomal dominant manner. Is caused by heterozygous mutation in the gene encoding fibroblast growth factor receptor 2 (*FGFR2*)

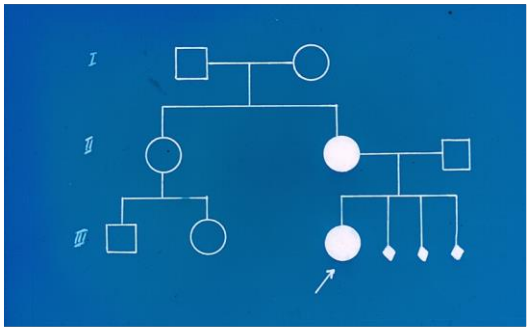
In the next picture is X-ray of a daughter and her teeth. Notice the hypoplastic maxilla and skull deformity (turricephaly).



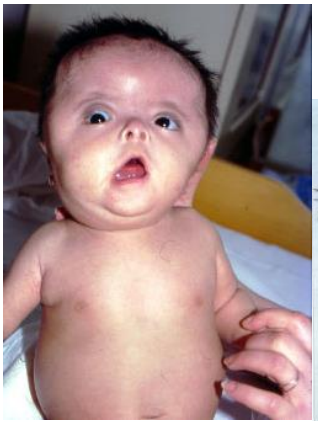
Next pictures show head film and profile of mother with the same condition and pedigree of this family.

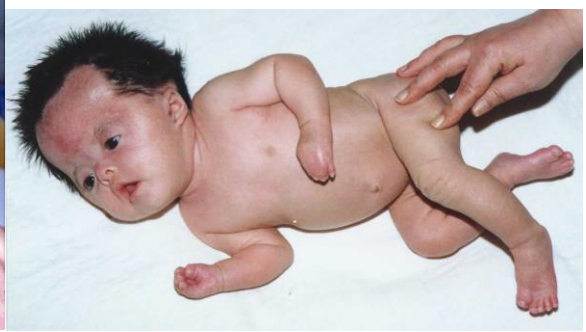




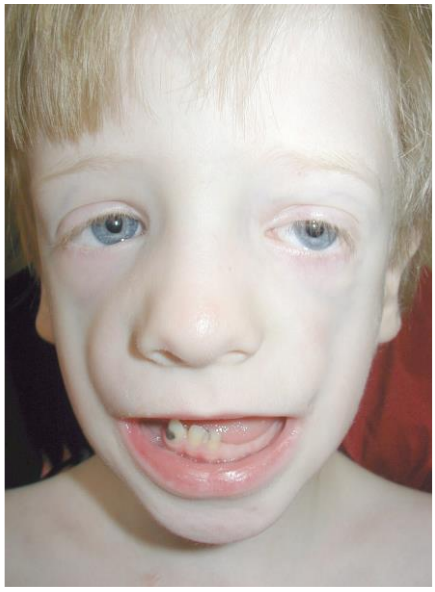


Apert syndrome (acrocephalosyndactyly) is characterised by craniosynostosis, midfacial deformations and symmetric syndactyly minimally involving digits. Many cases are sporadic, but autosomal dominant inheritance has been reported. Mutations in *FGFR2* are responsible.



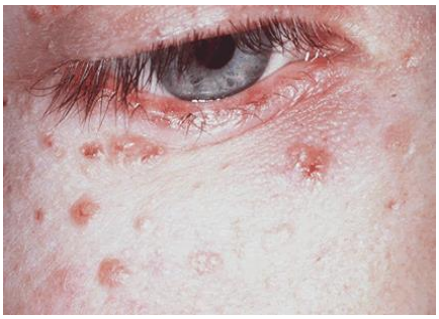


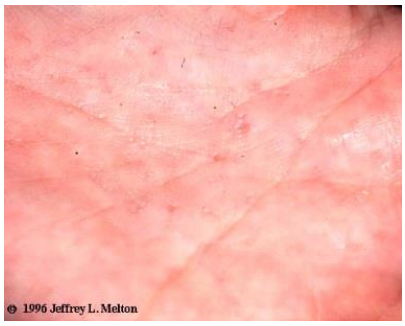
Treacher Collins syndrome – mandibulofacial dysostosis, structures derived from 1. and 2. pharyngeal arch. The features include antimongoloid slant of the eyes, coloboma of the lids, micrognathia, microtia and other deformities of the ears, hypoplastic zygomatic arches and macrostomia. Conductive hearing loss and cleft palate are often present. AD transmission, variable expressivity. Most cases have mutation in *TCOF1* gene. The frequency is 1: 50 000



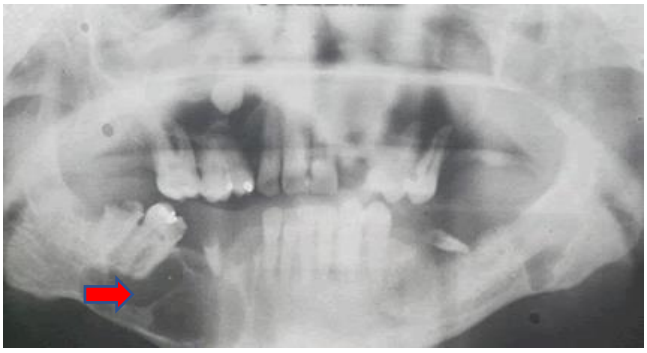
Gorlin syndrome (nevoid basal cell carcinoma syndrome. Is characterised by numerous basal cell cancers and epidermal cysts of the skin, odontogenic keratocysts of the jaws , palmar and plantar pits , calcified dural folds, various neoplasms and hamartomas , rib and vertebral anomalies, cleft lip and or palate.

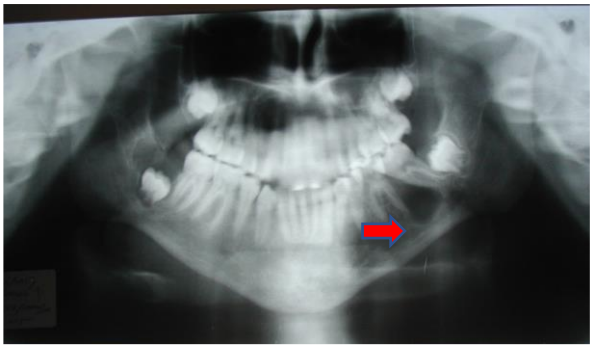
In the next pictures are skin changes – neoplasmatic process (left) and palmar pits (right).



n 

And orthopanthomograms with keratocysts.





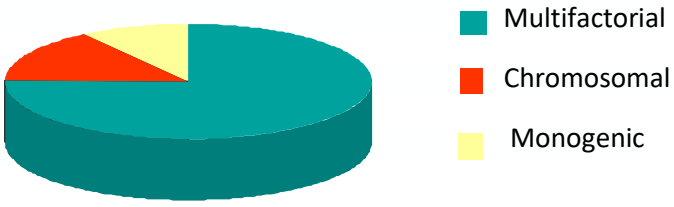
It has autosomal dominant inheritance with complete penetrance and variable expresivity.It is caused by mutations of *PTCH1* gene.

Approximately 350 syndromes are connected with clefts. Some of them will be mentioned in next part.

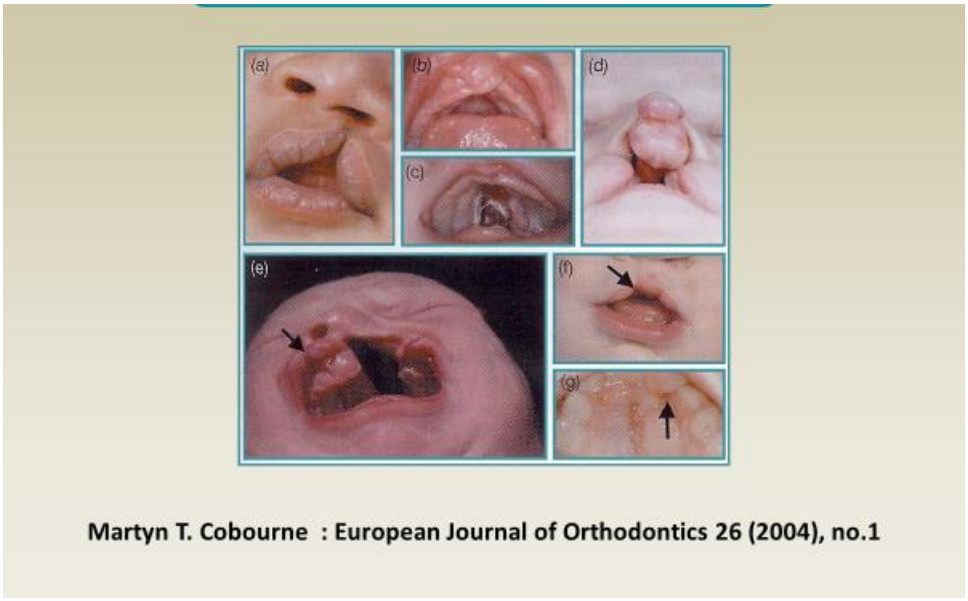
Clefts

Orofacial clefts include cleft lip only (CLO), cleft lip and palate (CLP) and cleft palate only (CPO). They are the most common craniofacial birth defects in humans, affecting approximately 1/800 live births worldwide.

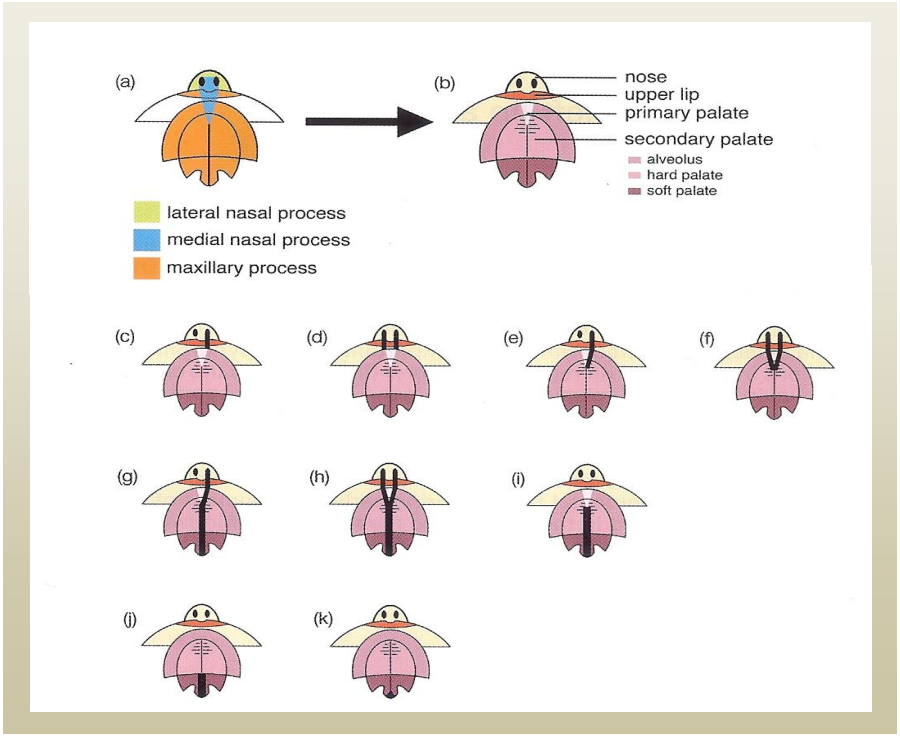
As complex disorders, clefts are thought to result from the interplay of multiple genes and environmental factors. Some clefts are part of syndromes and are caused monogenetically, 9% are part of chromosomal aberrations – next picture.



Following pictures demonstrate large variability of this anomaly, from small lip defect to complete cleft of palate.

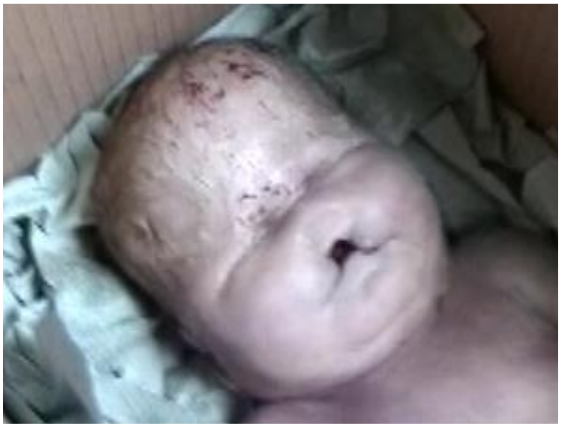


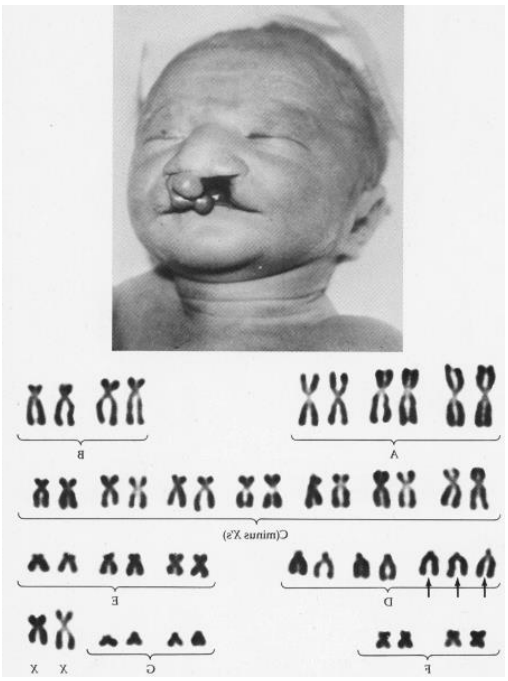
Martyn T. Cobourne : European Journal of Orthodontics 26 (2004), no.1



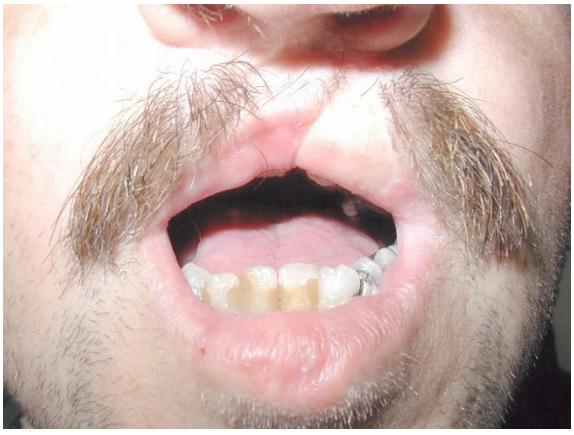
Cleft lip or cleft lip and palate and cleft palate only are genetically and embryologically two different units. The first one originates in the first half of 2nd month and cleft palate only in the beginning of 3rd month.

As a part of a chromosomal aberration cleft occurs e.g. in ***Patau syndrome*** (trisomy of 13th chromosome).

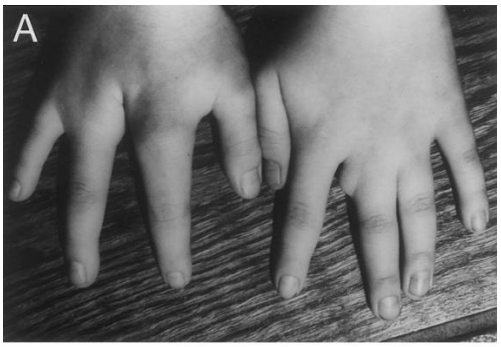




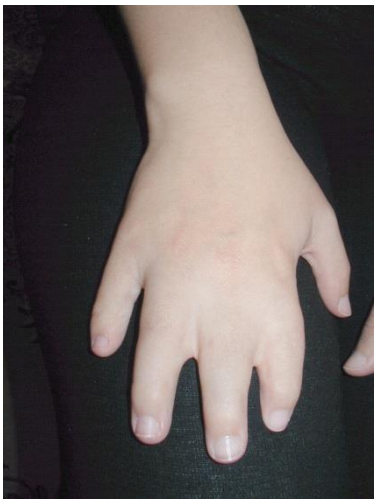
From numerous monogenic cleft syndromes is important ***Van der Woude*** syndrome – the combination of cleft lip- palate and paramedian sinuses of the lower lip. This syndrome occurs in 2% of facial clefts. The syndrome has autosomal dominant inheritance with variable expressivity. Mutations in *IRF6* gene (interferon regulator factor 6) were identified.

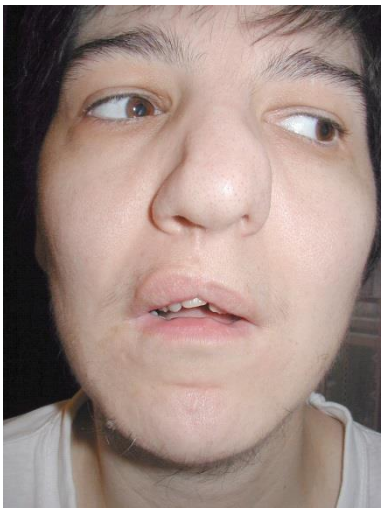


EEC syndrome- ectrodactyly ectodermal dysplasia and cleft lip/ palate syndrome is present in 1 /50000 live births. The syndrome has autosomal dominant inheritance with reduced penetrance and variable expressivity.

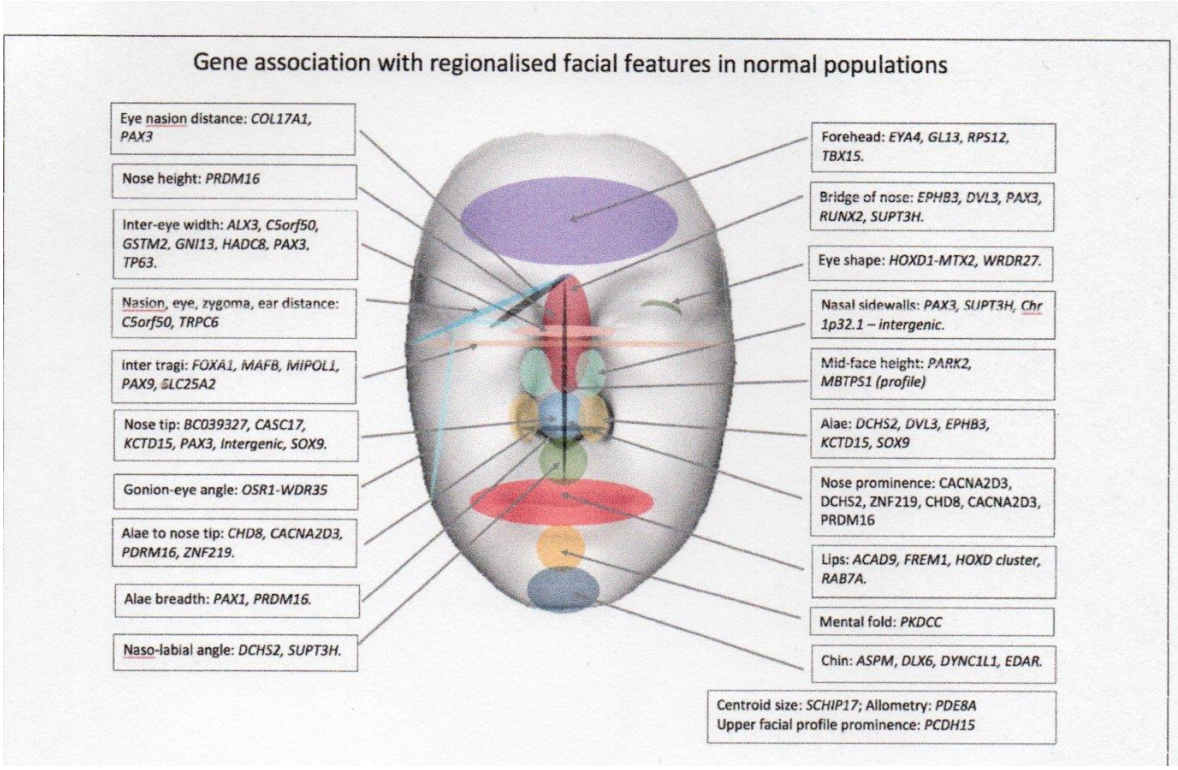


Oral facial digital syndrome (OFD I) dominant X linked, limited to females, lethal in male hemizygotes. Syndrome is characterised by malformation of the face, oral cavity (including clefts) and digits. It is caused by mutation of *OFD1* gene.

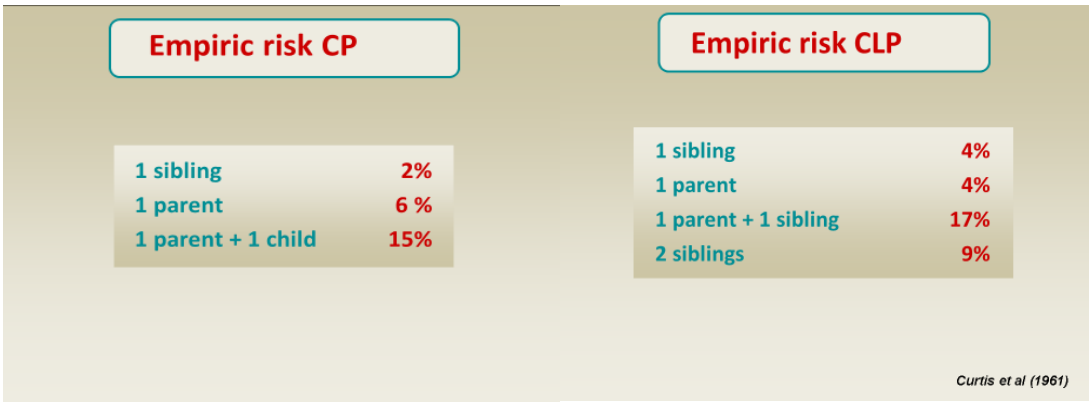




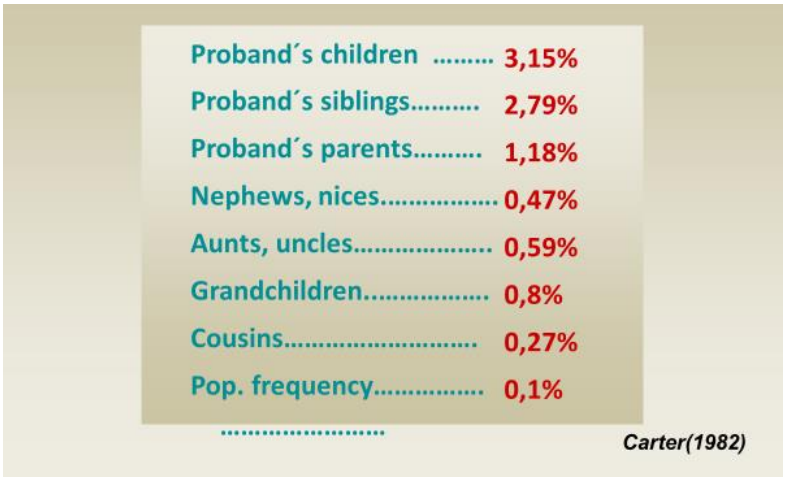
A substantial part of clefts is of multifactorial origin. In the next picture are numerous genes responsible for face development. It is obvious that most of them play role in clefts.



Evaluating large samples of cleft families, empiric risks were calculated. The number of affected relatives and the severity of proband's cleft are factors which increase the risk of recurrence.

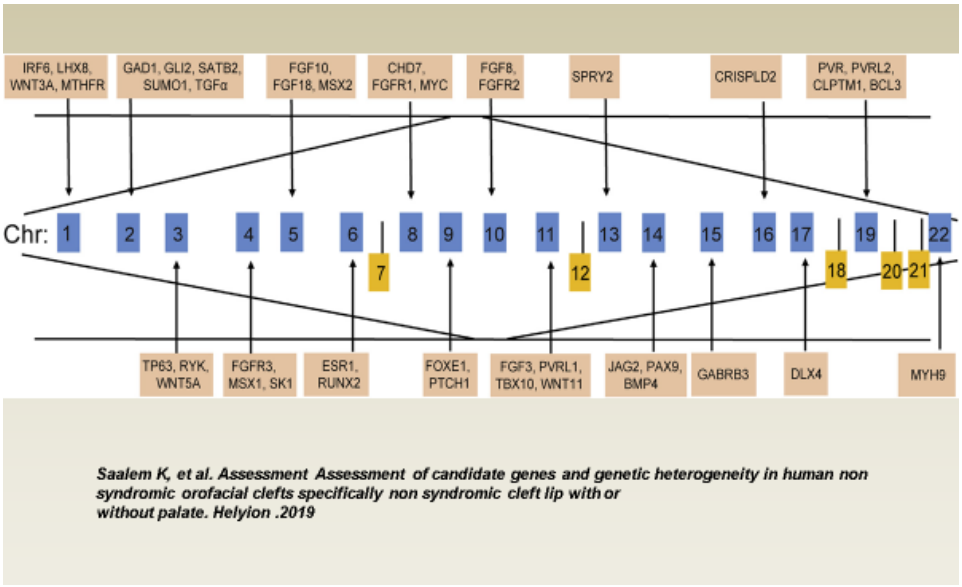


From a large three-generation study it is seen that the risk for remote relatives is not very high.



With development of molecular genetics candidate genes were detected, e.g.*OFC1 – OFC12. OFC5* is in fact *MSX1* gene, whose mutations are also responsible for numeric dental anomalies.

In the last picture there is a recent survey of more than 40 cleft candidate genes.



I would like to thank Dr. Alice Baxová for some pictures of syndromes used in this lecture.