BCL3 GENE POLYMORPHISMS AND NONSYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE

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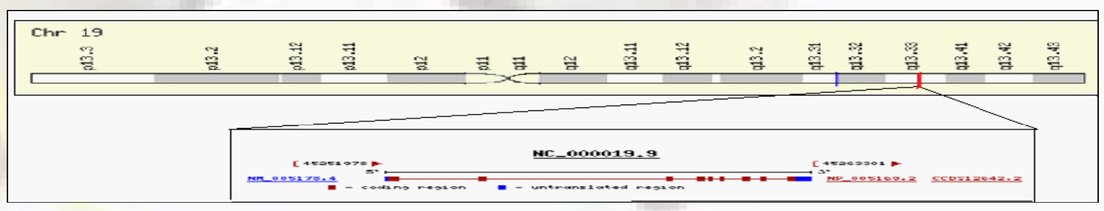
Background

Cleft lip and palate is a congenital malformation that affects the upper lip, alveolar ridge, tooth eruption, and palate fusion to different degrees. Lip and palate formations are the consequence of several processes that involve cell proliferation, cell differentiation, cell adhesion, and apoptosis. Failure anywhere in these processes can lead to clefts.

Orofacial clefts are one of the most common human birth defects, with a prevalence of approximately 1 in 300 - 1 in 2500, the prevalence in Latvia is around 1 in 700. Orofacial clefts form as a result of interaction of environmental and genetic factors but still up to now the exact mechanism or mechanisms of how the clefts form are not known, this is why it is so important to explore and investigate on the genes contributing to this process.

It has been reported that *BCL3* (*B-cell leukemia/lymphoma-3*) gene on chromosome 19q13.1-13.2 (Fig. 1) may play a role in the etiology of nonsyndromic cleft lip with or without cleft palate (NSCLP) based on linkage and association studies in several populations.

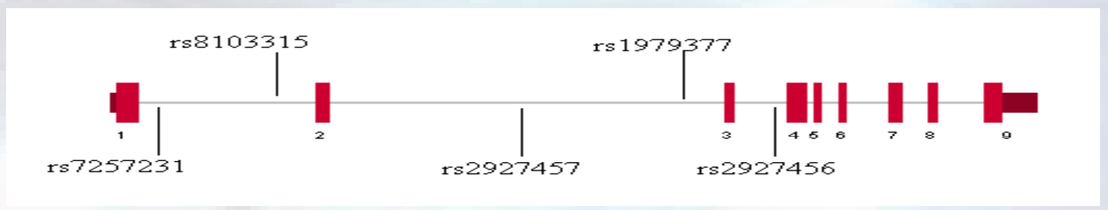
Figure 1. The structure of *BCL3* gene



Subjects and methods

Five SNPs (rs7257231, rs10401176, rs8103315, rs1979377 and rs2927456) in the *BCL3* gene (Fig. 2) were analyzed with MALDI-TOF technique.

Figure 1. Selected markers in *BCL3* gene



Transmission distortion was performed in 102 trios, and case-control analysis was performed in 102 patients and 335 healthy, unrelated and randomly selected individuals from Latvia. NSCLP patients and their parents samples were collected at the Riga Cleft Lip and Palate Centre, Institute of Stomatology, Riga Stradins University and control population samples were collected at the Latvian Biomedical Research and Study Centre within the framework of national project “Genome Database of Latvian Population”. Out of the 102 cleft cases, 73 had CLP and 29 had CL. All cases and their medical records were reviewed by clinical geneticists from Medical Genetics clinic, Children University hospital.

Association analysis of case-control was performed using PLINK software v.1.07 and transmission disequilibrium test (TDT) was performed using FBAT software v.2.0.3 after data cleaning.

The aim of the study was to investigate the possible contribution of BCL3 gene in the development of NSCLP.

Results

Genotype distributions among study groups were in a Hardy-Weinberg equilibrium. An association between the SNP rs7257231 in *BCL3* and nonsyndromic cleft lip with or without cleft palate was found (p=0.003) (Table 1). Haplotype analysis in Latvian families and individuals also showed significant associations with nonsyndromic cleft lip with or without cleft palate (Table 2). No associations were found in the case-control comparisons.

Table 1.
Results of transmission disequilibrium test (TDT)

CHR	SNP	Major allele	MAF	Minor allele	P value
19	rs7257231	T	0.839	A	0.003
19	rs10401176	A	0.897	G	0.371
19	rs8103315	T	0.879	G	1.0
19	rs1979377	G	0.905	T	1.0
19	rs2927456	T	0.954	C	0.414

Table 2.
Most significant results of haplotype analysis

Haplotype			Cases	Controls	P value
rs7257231	rs1040176	rs8103315			
T	A	T	0	0.035	0.002
A	G	T	0.085	0.044	0.014
rs1041176	rs8103315	rs1979377			
A	T	G	0	0.035	0.003
G	G	G	0.065	0.026	0.005
G	T	T	0.085	0.042	0.01
rs8103315	rs1979337	rs2927456			
T	G	T	0.003	0.031	0.013
T	T	C	0.085	0.049	0.035

Conclusions

Our results in the Latvian population continue to support a role for *BCL3* in nonsyndromic cleft lip with or without cleft palate in humans. The results show that there is evidence *BCL3* gene could have involvement in the etiology of NSCLP but additional studies should be made to clarify it.

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