Published in final edited form as:

J Craniomaxillofac Surg. 2017 June ; 45(6): 826–830. doi:10.1016/j.jcms.2017.02.020.

Condylar geometry variation is associated with *ENPP1* variant in a population of patients with dento-facial deformities

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Summary

Purpose—Bone remodeling is essential in maintaining bone health. Considering that *ENPP1* contributes to bone geometry and bone mineralization, the aim of our study was to analyze the association between single-nucleotide polymorphisms (SNPs) of *ENPP1* and condylar remodeling.

Materials and Methods—A total of 156 patients undergoing orthodontic and maxillofacial surgery treatment for correction of malocclusion were included in this prospective study. Saliva samples from all subjects were used for DNA extraction and genotyping. Four *ENPP1* SNPs were selected and tested to determine whether specific allelic variants are correlated with condylar

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Ethics Committee Approvals for the Study: Temple University IRB: Certificate 13438

University of Pittsburgh IRB: Certificate PRO12080373

University of Lille CPP (Committee for Personal Protection): CPP12/44

Disclosures: The authors report no conflicts of interest.

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remodeling. The criteria of condylar remodeling chosen were the ratio between each side of condylar height or surface differences on a dental panoramic of each patient. A diagnostic threshold was set at 15% difference between both sides.

Results—The *ENPP1* SNP rs9373000 showed a statistically significant association with condylar height ratio > 15% ($p=0.012$). The GG genotype was found to be a protective factor against condylar height decrease ($p=0.003$).

Conclusion—This study identifies the genetic variant rs9373000 as a potentially causal variant for mandibular condyle geometry variation for patients presenting with dento-facial deformities.

Keywords

ectonucleotide pyrophosphatase phosphodiesterase 1; mandibular condyle; temporomandibular joint; malocclusion

Introduction

The temporomandibular joint is an adaptive structure that is capable of anatomic modification to ensure morphological, functional, and occlusal stability. This phenomenon is often termed “condylar remodeling,” which occurs in response to genetic, demographic, anthropometric, hormonal, or dysfunctional etiologic influences (Arnett *et al.*, 1996a, 1996b).

Few studies have focused on genes involved in remodeling of the condylar unit, since there is a lack of reproducible diagnostic criteria. The literature identifies several remodeling criteria, including a decrease in condylar head volume, a decrease of condylar unit and mandibular rami height, and changes in mandibular shape and class II malocclusion (Hwang *et al.*, 2004; Huang *et al.*, 1997). These criteria are difficult to identify on standard radiographs, making a phenotypic subclassification of condylar remodeling for genotype associations difficult.

Mineralization of the extracellular matrix is essential for bone growth, bone stability, and bone turnover. The balance between levels of inorganic phosphate and pyrophosphate are essential to the quality of mineralization. During the mineralization process, hydroxyapatite is formed by the crystallization of calcium and inorganic phosphate. *ENPP1* (ectonucleotide pyrophosphatase / phosphodiesterase 1) is a gene encoding a transmembrane ectoenzyme, controlling this process by hydrolysis of inorganic pyrophosphate and therefore inhibiting hydroxyapatite formation. The Framingham cohort study (Cheung *et al.*, 2010) identified associations between single-nucleotide polymorphisms (SNPs) in the *ENPP1* gene with bone morpho-biometrics, such as changes in hip geometry. Subsequent studies identified similar associations in *ENPP1* SNPs with variations in facial bone morpho-biometrics and class III malocclusion (Deeley *et al.*, 2015). Rs858339 (*ENPP1*) has recently been associated with temporomandibular dysfunctions in a population with dento-facial deformities (Nicot *et al.*, 2016). Therefore *ENPP1* is a gene of interest in mandibular condylar bone morphometry. In this study, we investigated the association between SNPs of *ENPP1* and pre-surgical morphometric landmarks associated with condylar remodeling, using measurable diagnostic criteria. Condylar height and surface ratios of the condylar unit were used to evaluate

condylar remodeling, given their reproducibility as biometric measurements on pre-surgical panoramic radiographs.

Materials and Methods

Consecutive subjects undergoing orthodontic and maxillofacial surgery treatment for correction of malocclusion were recruited between February 2013 and June 2014 from the Department of Oral and Maxillofacial Surgery at the University of Lille in France. Patients were adults or non-growing adolescents who had no past history of mandibular trauma, systemic conditions or congenital malformation syndromes that might influence condylar resorption. No patients included showed significant condylar remodeling during presurgical orthodontic treatment. Subjects signed an informed consent form, and the research protocol was validated by the French independent ethical committee, the Temple University and the University of Pittsburgh institutional review boards.

Age, sex, facial biometrics and TMJ symptoms were listed during the preoperative examination. Cephalometric data and classification were obtained applying the Delaire (Delaire *et al.*, 1981) analysis method on presurgical radiographs. Given the lack of repeatable measurable criteria for condylar remodeling in the literature, we have chosen as primary endpoints to measure the ratio between each side of condylar height or surface on presurgical dental panoramic radiographs, carried out according to the same protocol. Two lines were constructed to evaluate condylar height, one drawn tangential to the posterior edge of the mandible passing through the most posterior points of the condyle and mandibular ramus, and the perpendicular line passing through the lower end of the mandibular notch. Condylar height was measured perpendicular to the latter between the mandibular notch and the highest point of the condylar unit (Figure 1A). The surface of the condylar unit was measured using computer software, contouring the lowest point of the mandibular notch to the *lingula mandibulae*, then perpendicular to the rear edge of the mandibular ramus (Figure 1B). Bone remodeling has been determined in this study by a differential measurement of height or condylar surface defined by a percentage in relation to the larger side between right and left sides of presurgical dental panoramic. Diagnosis of remodeling was set at a 15% differential for comparison to data found in the literature.

Saliva samples from all subjects were stored in Oragene kits (DNA Genotek, Ottawa, ON, Canada) and used for DNA extraction and posterior genotyping. Four SNPs of *ENPP1* (rs9373000, rs6569759, rs858339 and rs1409181) were selected for genotyping and tested to determine whether specific allelic variants correlated with condylar biometrics using TaqMan chemistry (Life Technologies, Carlsbad, CA, USA) and end-point analysis in an automatic sequence-detection instrument (ABI Prism 7900HT; Applied Biosystems, Foster City, CA, USA), as described previously (Zuccherro *et al.*, 2004). SNPs chosen to study *ENPP1* had a minor allele frequency (MAF) < 5% and were located in or flanking the gene, with HWE $p < 0.001$ and $r^2 > 0.70$ based on HapMap Phase II, in a northwest European population (Cheung *et al.*, 2010).

The characteristics of the population were presented with the usual rules of descriptive statistics. After ensuring compliance with Hardy-Weinberg equilibrium, the association

between SNPs and condylar height or surface ratios was sought by the Chi-squared test. We divided the analysis population into two groups depending on the surface or height ratios of condylar unit. Considering a threshold of 15% for both primary endpoints, we obtained a qualitative variable in two groups. Patients with condylar surface ratio < 15% (Diff Surf < 15% group) represented the subpopulation without condylar remodeling while patients with condylar surface ratio ≥ 15% (Diff Surf ≥ 15%) were classified in the subpopulation with a potential condylar remodeling. In the same way, patients with condylar height ratio < 15% (Diff Ht < 15% group) represented the subpopulation without condylar remodeling, while patients with condylar height ratio ≥ 15% (Diff Ht ≥ 15%) were classified in the subpopulation with potential condylar remodeling. For each SNP, analysis was performed by considering the three genotypes separately. In case of significance, analysis was completed to compare each genotype to the two others, and odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. The significance level was set at $p = 0.05$. It was recorded in the tables when the Chi-squared test conditions were not met.

Results

A total of 156 were included in the study between February 2013 and June 2014. This sample included a larger proportion of women (68.6%), young people (25.8 ± 11.0 years) and Class II dentofacial deformity patients (68%). Age, sex and biometric characteristics of the population are listed in Table 1. The comparative analysis based on condylar height or surface ratios indicated that there were no significant differences between the two groups for age, sex or biometric characteristics of patients, suggesting that the two populations were similar. We found 112 patients with condylar surface ratio < 15% and 22 patients with condylar surface ratio ≥ 15%. For 22 of 156 patients, the condylar surface ratio was not measurable. A total of 113 patients presented with a condylar height ratio < 15%, and 20 patients had a condylar height ratio ≥ 15%. For 23 patients, the condylar height ratio could not be calculated. No SNP was found to be statistically associated with condylar surface ratio (Table 2). On the other hand, single-nucleotide polymorphism rs9373000 of *ENPP1* presented a statistically significant association with condylar height ratio ($p = 0.012$) (Table 3). In particular, the GG genotype was found to be a protective factor against condylar height decrease (OR = 0.14, 95% C.I. 0.082-0.240, $p = 0.003$) (Table 4).

Discussion

This study highlights the significant association between single nucleotide polymorphism rs9373000 of *ENPP1* and condylar height ratio ($p = 0.012$). The results are consistent with the analysis of the literature pointing out the role of *ENPP1* in bone geometry and bone mineralization.

ENPP1 encodes a transmembrane ecto-enzyme hydrolyzing extracellular molecules having pyrophosphate or phosphodiester bonds. In chondrocytes and osteoblasts, it regulates bone mineralization (Harmey *et al.*, 2004). Specifically, it hydrolyzes inorganic pyrophosphate (PPi), one of the main inhibitors of calcification, which inhibits hydroxyapatite crystal growth (Terkeltaub, 2001). The role of *ENPP1* in inhibiting calcification was initially demonstrated in a murine model of *ttw* / *ttw* phenotype (tiptoe walking), which carries a

nonsense mutation in the *Enpp1* (Hajjawi *et al.*, 2014). The mice *Enpp1*^{-/-} developed a phenotype of hypermineralization, with calcification of tendons and ligaments. These *Enpp1*^{-/-} mice are a particular model for the study of the human disease, which is responsible for the ossification of posterior longitudinal ligament. Phenotypic characteristics of *Enpp1*^{-/-} mice include marked alterations in mineralization of long bones and skull, and the pathological calcification of perispinal soft tissues and medial arterial layer. In human pathology, *ENPP1* gene mutation produces generalized arterial calcification and pseudoxanthoma elasticum in children (Nitschke *et al.*, 2012).

Regarding gene polymorphisms, the SNP rs1974201 has been identified as a potentially causal variant of bone geometry in the Framingham cohort study (Cheung *et al.*, 2010). *ENPP1* has also become a potential gene of interest in the field of craniofacial bone morphometry. In particular, an association has been observed between upper facial height and polymorphisms located near the promoter region and upstream from *ENPP1* (Ermakov *et al.*, 2010a). Deeley *et al.* (Deeley *et al.*, 2015) have also shown an association between rs9373000 and rs6569759 and mandibular prognathism in subjects with dento-facial deformities, suggesting a role of *ENPP1* in facial bone geometry. On the other hand, rs858339 (*ENPP1*) has recently been associated with temporomandibular dysfunctions in a population with dento-facial deformities, which highlights its morpho-functional role (Nicot *et al.*, 2016). Apart from their role in facial bone geometry, several polymorphisms of *ENPP1* were associated with changes in long bone geometry (Cheung *et al.*, 2010; Ermakov *et al.*, 2010b). It has particularly been shown that the association between bone size phenotypes and the distal segment of *ENPP1* imply functional significance of its 3' untranslated region to bone growth (Ermakov *et al.*, 2010b). *ENPP1* polymorphisms also have been associated with radiographic hand osteoarthritis (Suk *et al.*, 2005).

This study identifies the genetic variant rs9373000 in *ENPP1* as a potentially causal variant for mandibular condyle geometry variation in a cohort of patients presenting with dento-facial deformities. Despite not using the Bonferroni correction, the observed association in this study is unlikely to be a spurious finding, since 0.05 divided by four SNP markers would reduce the p-value to 0.0125. Resorption of the mandibular condyle has multifactorial origins (Ferri *et al.*, 2016). The main demographic and biometric factors influencing condylar resorptions are young age, female sex, Class II dentofacial deformity and open-bite malocclusion. These factors are strongly represented in our population. Indeed, the sample included a larger proportion of women (68.6%), young people (25.8 ± 11.0 years) and patients with Class II dentofacial deformity (68%) or open-bite malocclusion (45.5%). Distribution of these factors is, however, similar in both groups, depending on condylar surface ratio or condylar height ratio (patients with condylar surface ratio < 15% and those with condylar surface ratio > 15%, or patients with condylar height ratio < 15% and those with condylar height ratio > 15%). In other words, both study groups were comparable for age, sex and biometric characteristics, limiting the confounders even if we have not performed a multivariate analysis. This is particularly important, given the fact that young age, female sex and some biometric traits such as Class 2 or open-bite malocclusions are factors associated with condylar resorption and condylar remodeling (Wolford and Cardenas, 1999; Papadaki *et al.*, 2007).

The primary endpoints chosen (condylar surface ratio and condylar height ratio) have the benefit of being measurable and therefore reproducible, unlike conventional criteria for condylar resorption found in the literature, which sometimes leaves room for interpretation. Using an orthopantomogram instead of a cone beam for implementing the measures can be considered a limitation of our study. Comparison of the two condyles of a patient on the same radiography limits the measurement bias but poses the problem of the exclusion of bilateral and symmetrical condylar remodeling. Hlawitschka and Eckelt also used panoramic radiographs to compare the two condyles of the same patient with condylar fractures and to measure the loss of condylar height compared with the healthy side (Hlawitschka and Eckelt, 2002). We have chosen a differential of 15 ° in order to limit false-positive results, while Habets *et al.* diagnosed a condylar remodeling when there was a height differential of > 6° (Habets *et al.*, 1987; Habets *et al.*, 1988). Considering the lack of power of our study, these results will have to be verified with a larger sample.

Our results suggest that rs9373000 variant is associated with condylar height ratio ($p = 0.012$). In particular, the GG genotype was identified as a protective factor against condylar height reduction (OR = 0.14, 95% CI 0.082-0.240, $p = 0.003$). How this SNP alters bone metabolism to affect bone formation remains unknown. rs9373000 is an *ENPP1* variant mapped on the 3'UTR (Mignone *et al.*, 2002). Single nucleotide polymorphisms falling specifically in the 3'UTR of genes may interfere with mRNA stability and translation through effects on polyadenylation and regulatory protein-mRNA and miRNA-mRNA interactions (Arnold *et al.*, 2012). For example, previous studies in humans have identified variations in the 3'UTR of genes that appear to affect cancer risk by disrupting normal miRNA binding (Nicoloso *et al.*, 2012). Similarly, with some variations in the 3'UTR of genes affecting cancer risk by disrupting normal miRNA binding, the rs9373000 variant could be another example of polymorphism affecting the 3'UTR of genes by generating a specific modulation of bone geometry. Our results further reinforce those of Ermakov *et al.* regarding the role of the 3'UTR of *ENPP1* in bone geometry (Ermakov *et al.*, 2010b).

These findings are particularly interesting, given the morpho-functional role of the temporomandibular joint. It is clear that a change, even moderate, of mandibular condyle geometry can influence the proper functionality of this joint. In particular, the measurement criteria used are good reflections of the condylar remodeling, emphasizing the morpho-functional role of the variant rs9373000 in the craniofacial field. Bone mineral density and mandibular advancement have been recently identified as contributing factors for postoperative relapse after orthognathic surgery in patients with preoperative idiopathic condylar resorption (Yang and Hwang, 2015). Under these conditions, *ENPP1* could represent a potential gene of interest regarding relapse in orthognathic surgery patients with idiopathic condylar resorption (Hoppenreijns *et al.*, 2013). This study has been performed in a population of patients with dento-facial deformities requiring orthognathic surgery. Therefore, this study design allows us to investigate this potential gene of interest in orthognathic surgery where it could represent a potential gene of interest regarding relapse, in particular in the context of preoperative idiopathic condylar resorption.

Conclusion

In conclusion, we found a significant association between single nucleotide polymorphism rs9373000 of *ENPP1* and condylar height ratio, highlighting its morphofunctional role. The GG genotype was found to be a potential protective factor against condylar height decrease (OR = 0.14, 95% CI 0.082-0.240, $p = 0.003$). This preliminary work leads us to initiate studies of condylar remodeling or resorption and *ENPP1* variants. The next step in this cohort study will be to study the link between *ENPP1* and postoperative condylar resorption after bilateral sagittal split osteotomy.

Acknowledgments

We thank Patrick Gelé and the Centre d'Investigation Clinique de Lille for Data Preservation.

This work is supported by the National Institute of Dental & Craniofacial research through a grant to Dr. Sciote; Musculoskeletal Heritable Influences on Malocclusion - R21DE022427.

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Figure 1. Panoramic landmarks. (A) Condylar height measurement. (B) Condylar surface measurement.

Figure 2.

Implementation of the measures in a patient with a right condylar remodeling. Surface differential measured at 22.22%. Height differential measured at 53.11%.

Table 1
Description of analysis population

Characteristics of analysis population	N=156
Age <i>my</i> (DS)	25,8 (11,0)
Females <i>n</i> (%)	107 (68,6)
Biometrical characteristics:	
Sagittal <i>n</i> (%)	
- Class I	1 (0,6)
- Class II	106 (68,0)
- Class III	49 (31,4)
Vertical <i>n</i> (%)	
- Normal bite	51 (32,7)
- Open bite	71 (45,5)
- Deep bite	34 (21,8)
Mandibular asymmetry <i>n</i> (%)	
- No asymmetry	99 (63,5)
- Mandibular asymmetry > 2mm	57 (36,5)

N : number of observation; my : mean; DS : standard deviation; n (%) : number of observation (percentage)

Table 2
Comparison of SNP genotypes by condylar surface ratio (*Diff Surf*): *Diff Surf* < 15% group vs *Diff Surf* 15%

Gene	SNP	N	Genotype	<i>Diff Surf</i> < 15% n (%)	<i>Diff Surf</i> 15% n (%)	Groups	p
<i>ENPP1</i>	rs9373000	134	AA	59 (52,7)	14 (63,6)	AA vs AG vs GG	0,592 *
			AG	43 (38,4)	7 (31,8)		
			GG	10 (8,9)	1 (4,6)		
	rs6569759	131	GG	26 (23,6)	8 (38,1)	GG vs AG vs AA	0,184 *
			AG	56 (50,9)	11 (52,4)		
			AA	28 (25,5)	2 (9,5)		
	rs858339	113	TT	50 (52,1)	11 (64,7)	TT vs AT vs AA	0,472 *
			AT	41 (42,7)	6 (35,3)		
			AA	5 (5,2)	0 (0)		
rs1409181	134	CC CG GG	CC	20 (17,9)	3 (13,6)	CC vs CG vs GG	0,763 *
			CG	64 (57,1)	12 (54,6)		
			GG	28 (25)	7 (31,8)		

N : number of observation; n (%) : number of observation (percentage);

* Chi-2 test conditions were not met

Table 3
Comparison of SNP genotypes by condylar height ratio (*Diff Ht*) : *Diff Ht* < 15% group vs *Diff Ht* ≥ 15%

Gene	SNP	N	Genotype	Diff Ht < 15%	Diff Ht ≥ 15%	Groups	p
ENPP1	rs9373000	133	AA	64 (56,6)	8 (40)	AA vs AG vs GG	0,012
			AG	43 (38,1)	7 (35)		
			GG	6 (5,3)	5 (25)		
	rs6569759	130	GG	31 (27,9)	2 (10,5)	GG vs AG vs AA	0,270 *
			AG	55 (49,6)	12 (63,2)		
			AA	25 (22,5)	5 (26,3)		
	rs858339	113	TT	52 (54,2)	9 (52,9)	TT vs AT vs AA	0,597 *
			AT	39 (40,6)	8 (47,1)		
			AA	5 (5,2)	0 (0,0)		
rs1409181	133	CC	20 (17,7)	3 (15)	CC vs CG vs GG	0,873 *	
		CG	65 (57,5)	11 (55)			
		GG	28 (24,8)	6 (30)			

N : number of observation; n (%) : number of observation (percentage);

* Chi-2 test conditions were not met

Table 4
Comparison of rs9373000 genotypes of *ENPP1* gene by condylar height ratio (*Diff Ht*); *Diff Ht* < 15% group vs *Diff Ht* ≥ 15%

SNP	N	Génotype	Diff Ht < 15%	Diff Ht ≥ 15%	Groups	p	OR	IC 95%
rs9373000	133	AA	64 (56,6)	8 (40)	AA vs AG vs GG	0,012		
		AG	43 (38,1)	7 (35)				
		GG	6 (5,3)	5 (25)				
					AA vs (AG + GG)		0,169	0,125 0,060 0,261
					AG vs (AA + GG)		0,795	0,186 0,103 0,336
					GG vs (AA + AG)		0,003	0,140 0,082 0,240

SNP : single-nucleotid polymorphism; N : number of observation; n (%) : number of observation (percentage); OR : odds ratio; 95% IC : confidence interval of 95%