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Genetic Variation in *Myosin 1H* Contributes to Mandibular Prognathism

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Abstract

Introduction—Several candidate loci have been suggested as influencing mandibular prognathism (1p22.1, 1p22.2, 1p36, 3q26.2, 5p13-p12, 6q25, 11q22.2-q22.3, 12q23, 12q13.13, and 19p13.2). The goal of this study was to replicate these results in a well-characterized homogeneous sample set.

Methods—Thirty-three single nucleotide polymorphisms spanning all candidate regions were studied in 44 prognathic and 35 Class I subjects from the University of Pittsburgh School of Dental Medicine Dental Registry and DNA Repository. The 44 mandibular prognathism subjects had an average age of 18.4 years, 31 were females and 13 males, and 24 were White, 15 African American, two Hispanic, and three Asian. The 35 Class I subjects had an average age of 17.6 years, 27 were females and 9 males, and 27 were White, six African Americans, one Hispanic, and two Asian. Skeletal mandibular prognathism diagnosis included cephalometric values indicative of Class III such as ANB smaller than two degrees, negative Witts appraisal, and positive A–B plane. Additional mandibular prognathism criteria included negative OJ and visually prognathic (concave) profile as determined by the subject's clinical evaluation. Orthognathic subjects without jaw deformations were used as a comparison group. Mandibular prognathism and orthognathic subjects were matched based on race, sex and age. Genetic markers were tested by polymerase chain reaction using TaqMan chemistry. Chi-square and Fisher exact tests were used to determine overrepresentation of marker allele with alpha of 0.05.

Results—An association was unveiled between a marker in *MYO1H* (rs10850110) and the mandibular prognathism phenotype ($p=0.03$). *MYO1H* is a Class-I myosin that is in a different protein group than the myosin isoforms of muscle sarcomeres, which are the basis of skeletal muscle fiber typing. Class I myosins are necessary for cell motility, phagocytosis and vesicle transport.

Conclusions—More strict clinical definitions may increase homogeneity and aid the studies of genetic susceptibility to malocclusions. We provide evidence that *MYO1H* may contribute to mandibular prognathism.

Introduction

In orthodontics, one of the most challenging aspects in treating patients is predicting mandibular growth, especially on patients that show more pronounced characteristics of mandibular development. Through studies predominately conducted within family members and twin siblings, it is well documented that there is a strong link of mandibular prognathism and genetics.^{1,2} More specific, there is evidence that there is an autosomal-dominant inheritance, with incomplete penetrance associated with this phenotype.^{1,3} The expression of the phenotype is a product of genetics and environmental factors.⁴ The multifactorial nature of mandibular prognathism makes it very difficult to study and understand.

Mandibular prognathism has a prevalence of as low as 1% in Caucasians but as high as 15% in Asian populations.^{5,6}

Dohmoto et al.⁷ found that in mice the size of the mandible was controlled by genes located at chromosomes 10 and 11 that correspond to human chromosomal regions 12q21 and 2p13 respectively.

In humans, genome wide linkage analysis provided evidence for linkage to mandibular prognathism at chromosomes 1p36, 6q25, and 19p13.2.⁸ The presence of P561T variant in the growth hormone receptor gene (*GHR*) has been shown to affect mandibular morphology in Chinese and Japanese populations, especially in regards to mandibular height.^{9,10} In a study looking at a Hispanic cohort, Class III (due primarily to maxillary deficiency) was confirmed to be inherited in an autosomal-dominant pattern and linked to five loci: 1p22.1, 3q26.2, 11q22, 12q13.13, 12q23.¹¹ Li et al.¹² detected a specific locus, 14q24.3-31.2, associated with the mandibular prognathism phenotype on a Han Chinese population. In addition to the strong role of heredity there has been evidence suggesting the contribution of certain environmental factors to mandibular prognathism such as enlarged tonsils¹³, endocrine imbalances¹⁴, posture, trauma, and disease.¹⁵

It is well documented that the first studies of complex traits suggest a stronger genetic effect that is found by subsequent studies. Both bias and genuine population diversity might explain why early studies tend to overestimate the disease predisposition conferred by candidate gene polymorphisms.¹⁶ If there is a true effect of any of the previously described loci in mandibular prognathism, the expectation is that those results can be replicated. Therefore, we typed markers in eight loci and measured the association between genetic variation and mandibular prognathism using a population from Pittsburgh, USA.

Materials and Methods

Subjects

The subjects used in this study were active orthodontic patients from the Department of Orthodontics of the School of Dental Medicine at the University of Pittsburgh. Subjects were identified through the Dental Registry and DNA Repository project. In this project, since September of 2006, individuals who seek treatment at the University of Pittsburgh School of Dental Medicine have been invited to be part of the registry. They provide written informed consent authorizing the extraction of information from their dental records. Also, they provide a saliva sample from which DNA can be extracted. Unstimulated saliva samples were obtained from all participants (they were asked to spit) and stored in Oragene DNA Self-Collection kits (DNA Genotek Inc., Ottawa, ON, Canada) at room temperature until being processed. No centrifugation was performed on the saliva samples. DNA was

extracted according to the manufacturer's instructions. This project was approved by the University of Pittsburgh Institutional Review Board.

Clinical Definitions

In September 2009, data from 1,630 individuals were extracted from the registry for this pilot project. The 95 individuals treated at the Orthodontics Department were considered eligible for this study. The assessment of the eligible subjects consisted of a careful review of each subject's clinical and radiographic records. Clinical records consisted of digital orthodontic models (orthoCAD, Cadent, Inc., Carlstadt, NJ, USA), digital tracings of lateral cephalograms (Dolphin, Chatsworth, CA, USA) and digital photographs. The first step in the assessment process were the subject's soft tissue profile photo (concave or straight profile) and certain cephalometric values in order to classify the patients as either orthognathic or prognathic. Specifically we looked at Steiners' ANB, Wits Appraisal and Downs' A–B plane. As described in the Steiner analysis, ANB angle values of less than 2 degrees indicate that the mandible is located ahead of the maxilla. For this study, subjects with smaller than 2 degrees ANB values were reviewed further to clarify if the discrepancy was attributed to a smaller than average size maxilla, by looking at the SNA values. In that case, the subjects were not representing true prognathism but rather a regular size mandible appearing protrusive due to a small maxilla and therefore were excluded from the true prognathic group. The Wits appraisal was another measurement we reviewed because this value has the advantage of indicating the anteroposterior jaw relationship in the facial complex regardless of intra-cranial references. A negative Wits indicates a Class III skeletal relationship and the more negative the value, the more severe the Class III. Downs' A–B plane angle larger than –4.6 degrees indicates a skeletal Class III diagnosis, although this measurement may appear more severe in cases that present a pronounced bony pogonion. Additional Class III criteria included dental classification, such as Class III molar/canine relationships and negative OJ based on the digital models and clinical examination. We excluded any subjects with facial clefting, abnormal anterior cranial base growth defects such as or similar to achondrodysplasia or midfacial growth deficiencies caused by or other pathologies such as tumors, cysts or trauma which might scar midfacial periosteal surfaces and limit normal growth potentials. After analysis of clinical information, 44 mandibular prognathism and 35 orthognathic subjects were selected for this study. The 44 mandibular prognathism subjects had an average age of 18.4 years, 31 were females and 13 males, and 24 were White, 15 African American, two Hispanic, and three Asian. The 35 Class I subjects had an average age of 17.6 years, 27 were females and 9 males, and 27 were White, six African Americans, one Hispanic, and two Asian. Table 1 describes all measurements used in the study. Figure 1 exemplifies the individuals in each comparison group.

Selection of Single Nucleotide Polymorphisms and Genotyping Procedures

We selected 33 single nucleotide polymorphisms covering the eight candidate regions studied (Table 2) from the International HapMap Project database (<http://www.hapmap.org>). We used the function “Download tag SNP data” and selected 26 polymorphisms as representative of the polymorphisms in the region. We selected polymorphisms that maximally represent the linkage disequilibrium structure of a given region to avoid redundant information.¹⁷ Preference was given to polymorphisms with high heterozygosity levels and different minor allele frequencies to avoid intermarker linkage disequilibrium.

Selected SNPs were genotyped using Taqman chemistry¹⁸ on an automatic sequence-detection instrument (ABI Prism 7900HT, Applied Biosystems, Foster City, CA, USA). Assays and reagents were supplied by Applied Biosystems (Applied Biosystems, Foster City, CA, USA).

Statistical Analyses

Chi-square (χ^2) or Fisher's exact calculations were used to assess Hardy-Weinberg equilibrium and significance in all comparisons. The number of copies of each allele and each genotype per marker was compared between mandibular prognathism and Class I subjects (Table 2). Alpha of 0.05 was considered as statistically significant.

Results

Differences in gender and ethnic background between the two groups were not statistically significant. All markers were in Hardy-Weinberg equilibrium in both Class I and mandibular prognathism groups. Markers rs2503243, rs972054, rs1413533, rs1490055, rs2101560, rs1601948, rs1387168, rs2940913, rs7718944, rs3016534, rs9458378, and rs4964541 were not informative and could not be analyzed. The G allele of marker rs10850110 (5' of myosin 1H - *MYO1H*) was over-represented in mandibular prognathism subjects ($p=0.03$; Table 3). In Table 4, details of the samples contributing to the rs10850110 are displayed. The distribution of samples based on ethnic background suggests disproportionate number of samples from a specific subgroup is not influencing the results (among the 27 mandibular prognathism subjects 16 were White, eight were African American, and three belonged to other groups, whereas among Class I subjects, 19 were White, four were African Americans, and three belonged to other groups).

Discussion

This is the first report that independently attempted to replicate the recent results of two genome wide scans for mandibular prognathism and Class III (due primarily to maxillary deficiency).^{8,11} Our findings corroborate the previous suggestive linkage results with 12q23 (LOD score 2.93¹¹). The most common allele of a marker flanking *MYO1H* (rs10850110) was over-represented in mandibular prognathism subjects. The frequency of the less common rs10850110 allele varies from 0.008 in Sub-Saharan Africans, to 0.089 in Japanese, 0.148 in Han Chinese, and 0.275 in Europeans (National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=10850110). *MYO1H* is a class I myosin which is in a different protein grouping than the MHC (myosin heavy chain) isoforms found in the skeletal muscle sarcomere, which are the basis of fiber typing. Class I myosins are necessary for cell motility, phagocytosis and vesicle transport.¹⁹

Since the sample size of our study is modest and some genetic markers were uninformative, we cannot conclude the chromosomal regions studied here do not play a role in mandibular prognathism development. However, the definitions used to select subjects for this study likely increased homogeneity and the evidence of a role of 12q24 in mandibular prognathism is likely to be true. In an interval of 397,305 base pairs in 12q24.11, another four genes flank *MYO1H*. These genes are *ACACB* (acetyl-CoA carboxylase beta), *FOXN4* (forkhead box N4), *KCTD10* (potassium channel tetramerisation domain containing 10), and *UBE3B* (ubiquitin protein ligase E3B). These genes are involved in different aspects of metabolism, and although *MYO1H* is the best candidate for a role in mandibular prognathism, one cannot discard the possibility that these other genes have a role as well.

The cohort selected for this study reflects the ethnic breakdown of the city of Pittsburgh. According to the Pittsburgh Pennsylvania Census of 2000 (<http://www.hellopittsburgh.com/Census.Cfm>), the city was composed by 67.6% of European descent inhabitants and 27.1% of African descent inhabitants. The remaining 5.3% is composed by Hispanics, Asians, and other groups. There was no statistically significant difference between mandibular prognathism and orthognathic subjects in regards to the distribution of age, gender, and ethnic background. However, undetected population substructure could have revealed a

spurious association, even though when this effect is present, we tend to see several positive associations. The small percentage of Asians in our sample likely unable us to detect the reported association between *GHR* (growth hormone receptor) and mandibular height that has been described primarily in Japanese, Chinese, and Koreans.^{9,10,20,21} Future investigations also should expand further the variants studied in the *GHR* locus. One ideal variant to be studied due to its allelic frequency is the *d3/f1-GHR* variant, which minor allele frequencies are 47.9% in African- Americans and 31.3% in European-Americans.²⁰

While concerned about multiple testing, we did not apply the strict Bonferroni correction as it would increase type II errors and a major focus of this study was to replicate putative associations with the previously described contributing loci to mandibular prognathism. For example, under the Bonferroni correction, we would have lowered the alpha to 0.0025 (0.05/20) or 0.00125 (0.05/40) (number of tests in Table 3). Our previous work with other craniofacial defects has shown that true associations will be missed if nominal p-values are not considered as well. One example is the known association between *IRF6* (interferon regulatory factor 6) and isolated cleft lip and palate that would have been missed in a project we performed in which we tested 1,489 genetic markers.²² Therefore we report here results with p-values below 0.05. However, our data must be carefully interpreted since it is expected that some of the p-values below 0.05 can be due to chance.

One of the biological pathways recently identified²³ in contributing to skeletal height in humans is the nicotinic acetylcholine receptor signaling pathway with three associated genes included in the unconventional myosin grouping, *MYOIF*, *MYO6* and *MYO9B*. *MYOIF* is a very similar gene to the *MYOIH* identified as associated with mandibular prognathism in our study and future studies should consider all the genes in the family as candidates for a role in mandibular prognathism development. In summary, we provide further evidence of a role of the 12q24 locus in mandibular prognathism development. The possible role on a type I myosin is intriguing since it would suggest that muscle function may have a more important role than previous thought in the development and deviations of the bone structures of the craniofacial complex. Since the sample size of this study is modest, replication of these findings in independent populations is necessary. We will continue our efforts to expand the population studied to allow the results of our study to be replicated as well as perform these analyses by gender, age groups, and ethnicity.

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Figure 1.
Example of individuals in each study group.

Table 1

Summary of the subject measurements.

Profile	Gender	Age	Ethnicity	Steiner's ANB (degrees)	Wits Appraisal (mm)	Down's A-B plane (degrees)
Prognathic	Female	18	Caucasian	-1.9	-6.5	1.6
	Female	20	Caucasian	-4.9	-6.8	6.6
	Male	17	Caucasian	-8.1	-12	12.7
	Female	23	African-American	-1.2	-8.4	1.3
	Female	20	Caucasian	0.7	-7.6	-0.1
	Female	23	Caucasian	-10.4	-33.4	14.1
	Female	14	Hispanic	-2.7	-6.2	2.7
	Female	22	Caucasian	-6.6	-15.7	4.5
	Female	19	African-American	-3.4	-6.4	-2.8
	Male	19	Caucasian	-1.1	-7.3	1
	Female	30	African-American	-1.2	-12.2	3.7
	Female	15	African-American	2.4	-3.4	-2.4
	Male	15	Caucasian	0.3	-1.3	-1
	Female	16	African-American	-0.9	-5	2.4
	Female	12	Asian	-2.3	-5	2.9
	Female	12	Hispanic	0.6	-8.1	0.7
	Female	21	African-American	-1.9	-4.5	-1.7
	Female	13	African-American	-4	-12	4.9
	Female	21	African-American	-4.8	-4.3	4
	Female	15	Caucasian	-7.5	-13.3	9.1
	Female	28	African-American	-1	-5.9	2.3
	Female	14	Caucasian	-0.3	-4.7	2
	Male	11	Caucasian	-4.4	-7.8	7.3
	Female	18	Caucasian	-4.7	-10.6	4.1
	Male	18	Caucasian	-1.9	-7	0.6
	Female	25	Caucasian	-1.6	-5.5	2.1
	Male	26	Caucasian	-8.8	-12.1	4.3

Profile	Gender	Age	Ethnicity	Steiner's ANB (degrees)	Wits Appraisal (mm)	Down's A-B plane (degrees)
Orthognathic	Female	18	African-American	-6	-10	7
	Female	11	African-American	-2.3	-8.8	2.7
	Female	18	Caucasian	-2.9	-4.4	5.5
	Male	24	Asian	-3.4	-4.1	4.7
	Female	13	Caucasian	-0.9	-5.4	-0.3
	Female	15	Caucasian	-0.7	-4.6	0.4
	Female	15	African-American	-1.2	-7	2.6
	Male	22	Asian	0.3	-6.6	-1.7
	Female	15	Caucasian	-3	-10.6	3
	Male	28	Caucasian	-1.9	-8.3	2
	Male	12	African-American	-3.8	-8.2	4.6
	Male	19	Caucasian	-2.6	-7.7	1.2
	Male	17	African-American	-2.2	-3.6	1.8
	Female	13	African-American	-4.1	-12.5	5.8
	Male	25	Caucasian	-0.3	-4.1	-0.9
	Female	15	Caucasian	-4.7	-10	5.6
	Female	24	Caucasian	-1.1	-3.5	2.1
	Female	14	Caucasian	1.8	-0.2	-3.4
	Female	14	Caucasian	1.7	1.3	-4.5
	Female	13	African-American	2.4	-0.9	-2.7
	Male	14	African-American	2.6	-1.7	-2.7
	Female	17	Caucasian	2	-0.6	-4.1
	Male	36	Caucasian	1.4	-0.7	-3.7
	Male	52	Caucasian	0.8	-1.3	-5.4
	Female	14	Caucasian	2.8	-0.5	-5.3
	Female	13	Caucasian	2.5	1.4	-5
	Female	18	Caucasian	2.6	-1.5	-3.2
	Male	19	Caucasian	2.9	-0.3	-6.8
	Female	14	Caucasian	3.8	1.4	-8.7
	Female	15	Caucasian	1.8	1	-5

Profile	Gender	Age	Ethnicity	Steiner's ANB (degrees)	Wits Appraisal (mm)	Down's A-B plane (degrees)
	Male	11	African-American	2.3	-2.9	-3.4
	Female	24	Caucasian	2.4	-2.7	-3.7
	Female	15	Caucasian	0.1	-2.7	-0.3
	Female	15	Caucasian	2.5	-3.2	-2.5
	Female	15	African-American	2.8	-1.3	-3.9
	Female	12	Caucasian	0.8	-0.1	-1.9
	Female	17	Caucasian	0.7	-0.9	-1.7
	Male	16	Caucasian	1.9	-0.6	-3.6
	Female	13	Caucasian	1.6	-0.2	-4.8
	Female	14	Caucasian	3.3	0.1	-7.4
	Female	12	Caucasian	1.7	0.5	-3.6
	Female	24	Caucasian	3.3	0.5	-7.7
	Male	16	Caucasian	2.1	-1.1	-5.4
	Female	17	Asian	2.2	-0.4	-4.6
	Female	15	Caucasian	1.2	-0.6	-3.1
	Female	15	Caucasian	1	-1.2	-3.5
	Female	11	Hispanic	3.7	0.1	-6
	Female	13	Caucasian	1.7	1.8	-4.5
	Male	28	Asian	3.7	0.9	-5.1
	Female	11	African-American	1.9	-1	-1
	Female	11	Caucasian	3	-0.1	-4.6
	Female	16	African-American	3.8	0.1	-4.8
	Male	22	Caucasian	2.7	-4	-2.6

Table 2

Markers studied.

Marker	Locus	Gene	Original Work Suggesting as a Candidate Region
rs2503243	1p22.2	Intergenic	Frazier-Bowers et al., 2009
rs972054	1p22.2	Intergenic	Frazier-Bowers et al., 2009
rs1413533	1p22.2	Intergenic	Frazier-Bowers et al., 2009
rs4649030	1p36.11	Intergenic	Yamaguchi et al., 2005
rs2101560	3q26.32	Intergenic	Frazier-Bowers et al., 2009
rs1490055	3q26.32	Intergenic	Frazier-Bowers et al., 2009
rs2087312	3q26.32	Intergenic	Frazier-Bowers et al., 2009
rs987526	3q26.32	Intergenic	Frazier-Bowers et al., 2009
rs1601948	3q26.32	Intergenic	Frazier-Bowers et al., 2009
rs1387168	3q26.32	Intergenic	Frazier-Bowers et al., 2009
rs2940913	5p12	Growth Hormone Receptor (<i>GHR</i>)	Yamaguchi et al., 2001; Zhou et al., 2005; Kang et al., 2009; Tomayasu et al., 2009
rs2973015	5p12	Growth Hormone Receptor (<i>GHR</i>)	Yamaguchi et al., 2001; Zhou et al., 2005; Kang et al., 2009; Tomayasu et al., 2009
rs1509460	5p12	Growth Hormone Receptor (<i>GHR</i>)	Yamaguchi et al., 2001; Zhou et al., 2005; Kang et al., 2009; Tomayasu et al., 2009
rs2910875	5p12	Growth Hormone Receptor (<i>GHR</i>)	Yamaguchi et al., 2001; Zhou et al., 2005; Kang et al., 2009; Tomayasu et al., 2009
rs7718944	5p12	Growth Hormone Receptor (<i>GHR</i>)	Yamaguchi et al., 2001; Zhou et al., 2005; Kang et al., 2009; Tomayasu et al., 2009
rs7750085	6q26	Parkinson Juvenile Disease Protein 2 (<i>PARK2</i>)	Yamaguchi et al., 2005
rs3016534	6q26	Parkinson Juvenile Disease Protein 2 (<i>PARK2</i>)	Yamaguchi et al., 2005
rs12207168	6q26	Parkinson Juvenile Disease Protein 2 (<i>PARK2</i>)	Yamaguchi et al., 2005
rs9458378	6q26	Parkinson Juvenile Disease Protein 2 (<i>PARK2</i>)	Yamaguchi et al., 2005
rs1884153	6q26	Parkinson Juvenile Disease Protein 2 (<i>PARK2</i>)	Yamaguchi et al., 2005
rs571407	11q22.3	Caspase 4 Isoform Gamma Precursor (<i>CASP4</i>)	Frazier-Bowers et al., 2009
rs1902768	12q13.13	Keratin 7 (<i>KRT7</i>)	Frazier-Bowers et al., 2009
rs7300317	12q13.13	Keratin 7 (<i>KRT7</i>)	Frazier-Bowers et al., 2009
rs11113231	12q23.3	Intergenic	Frazier-Bowers et al., 2009
rs4964541	12q23.3	Intergenic	Frazier-Bowers et al., 2009
rs10850110	12q24.11 *	Myosin 1H (<i>MYO1H</i>)	Frazier-Bowers et al., 2009
rs10850364	12q24.21 *	T-box 3 (<i>TBX3</i>)	Frazier-Bowers et al., 2009
rs7351083	19p13.2	Fibrilin 3 Precursor (<i>FBN3</i>)	Yamaguchi et al., 2005
rs4804264	19p13.2	Fibrilin 3 Precursor (<i>FBN3</i>)	Yamaguchi et al., 2005
rs8103218	19p13.2	Fibrilin 3 Precursor (<i>FBN3</i>)	Yamaguchi et al., 2005
rs12327845	19p13.2	Fibrilin 3 Precursor (<i>FBN3</i>)	Yamaguchi et al., 2005
rs10411185	19p13.3	Intergenic	Yamaguchi et al., 2005

Note:

* These loci flank the region suggested by Frazier-Bowers et al., 2009 and were included to more comprehensively study this candidate region.

Table 3

Summary of the association results. Values under “Mandibular Prognathism” and “Class I” columns indicate the number of individuals that possess each of the genotypes in each group and the number of alleles found in each group of subjects.

Locus	Marker	Genotype	Allele				
			Mandibular Prognathism	Class I	Mandibular Prognathism		
					Class I		
1p22.2	rs4649030	AA	3	3	A	13	18
		AG	7	12	G	43	46
		GG	18	17		p=0.54	
			p=0.58				
3q26.32	rs2087312	AA	30	26	A	73	61
		AC	13	9	C	13	19
		CC	0	1		p=0.16	
			p=0.41				
	rs987526	CC	1	0	C	7	3
		CT	5	3	T	61	59
		CC	28	28		p=0.24	
			p=0.5				
5p12	rs2973015	AA	9	10	A	27	31
		AG	9	11	G	27	21
		GG	9	5		p=0.32	
			p=0.5				
	rs1509460	GG	5	3	G	35	29
		GT	25	23	T	39	43
		TT	7	10		p=0.4	
			p=0.58				
	rs2910875	AA	4	5	A	18	27
		AG	10	11	G	20	31
		GG	5	10		p=0.94	
			p=0.69				
6q26	rs7750085	AA	8	13	A	35	39
		AT	19	13	T	31	31

Locus	Marker	Genotype	Allele		Class I	Mandibular Prognathism	Class I
			Mandibular Prognathism	Class I			
		TT	6	9		p=0.75	
			p=0.24				
	rs12207168	AA	8	12	A	35	39
		AG	19	15	G	41	33
		GG	11	9		p=0.32	
			p=0.49				
	rs1884153	AA	0	0	A	2	3
		AG	2	3	G	80	67
		GG	39	32		p=0.53	
			p=0.52				
11q22.3	rs571407	CC	1	0	C	7	3
		CT	5	3	T	61	59
		TT	28	28		p=0.24	
			p=0.5				
12q13.13	rs1902768	AA	1	2	A	11	14
		AG	9	10	G	59	50
		GG	25	20		p=0.36	
			p=0.67				
	rs7300317	AA	8	7	A	35	33
		AG	19	19	G	35	37
		GG	8	9		p=0.92	
			p=0.94				
12q23.3	rs11113231	AA	6	5	A	38	30
		AG	26	20	G	42	38
		GG	8	9		p=0.68	
			p=0.8				
12q24.11	rs10850110	AA	1	5	A	8	17
		AG	6	7	G	46	35
		GG	20	14		p=0.03	
			p=0.15				

Locus	Marker	Genotype	Mandibular Prognathism	Class I	Allele	Mandibular Prognathism	Class I
12q24.21	rs10850364	AA	3	7	A	19	30
		AG	13	16	G	29	34
		GG	8	9		p=0.44	
			p=0.66				
19p13.2	rs7351083	AA	6	6	A	34	29
		AG	22	17	G	42	41
		GG	10	12		p=0.69	
			p=0.7				
	rs4804264	CC	9	6	C	33	27
		CT	15	15	T	49	45
		TT	17	15		p=0.73	
			p=0.82				
	rs8103218	CC	6	7	C	25	30
		CT	13	16	T	25	28
		TT	6	6		p=0.86	
			p=0.96				
	rs12327845	CC	25	15	C	63	45
		CT	13	15	T	23	23
		TT	5	4		p=0.34	
			p=0.42				
19p13.3	rs10411185	AA	11	5	A	43	29
		AG	21	19	G	37	39
		GG	8	10		p=0.18	
			p=0.35				

Note: Variations in the number of subjects or the number of alleles are due to PCR failure. These failures are related to the purity of the genomic DNA used and the uniqueness of PCR primer probes. These aspects are hard to be predicted but should not dramatically influence the data.

Table 4

Demographic variables of the samples contributing to the rs10850110 marker analysis.

Ethnicity	Gender	Number of Individuals with genotypes: Mandibular Prognathism			Number of Individuals with genotypes: Class 1		
		AA	AG	GG	AA	AG	GG
White	Male	1	2	4	-	1	2
	Female	-	4	5	5	5	6
African-American	Male	-	-	1	-	-	1
	Female	-	-	7	-	-	3
Other	Male	-	-	-	-	-	1
	Female	-	-	3	1	-	1