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Editorial
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Candidate Gene Analyses of Mandibular Prognathism

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Editorial

Causation of a disease and a symptom generally is classified as genetic inheritance and environmental factors. A disease caused by a single gene disorder is defined as a disease that is attributed to a monogenic factor. A single gene disorder has been reported in more than 3,000 hereditary diseases. On the other hand, a polygenic or multifactorial disease is attributed to some susceptibility genes and their interaction with some environmental factors. Mandibular prognathism (Online Mendelian Inheritance in Man (OMIM) #176700), skeletal Class III malocclusion in orthodontics, occurs in populations throughout the world but with a higher incidence in Asian populations. The prevalence is less than 1% in Caucasians while approximately 10% in Japanese. Mandibular prognathism has been caused by various patterns of genetic inheritance and/or environmental factors in previous studies. In the 20th century, multiple models of inheritance of mandibular prognathism, including monogenic inheritance, autosomal-dominant inheritance, autosomal-recessive inheritance, and polygenic inheritance, have been suggested. A family line of Habsburg, the Spanish and Austrian Royal family, shows an autosomal-dominant inheritance based on multiple generations. However, now it is evident that the majority of mandibular prognathism is a multifactorial phenotype [1,2].

Genome-wide linkage analysis

Recent progress in molecular genetics has enabled us to examine susceptibility genes. Some nonparametric linkage analyses and supplementary association studies for mandibular prognathism have been performed in various races. From the results of genome-wide linkage analysis, chromosomes 1p36, 6q25, and 19p13.2 showed suggestive linkage to mandibular prognathism in Japanese and Korean families. The 1p36 locus harbors positional candidate genes of interest, including *MATN1* (matrilin 1, cartilage matrix protein), *HSPG2* (heparan sulfate proteoglycan 2), and *ALPL* (alkaline phosphatase). Supplementary association studies on 1p36 of the susceptibility locus suggested that *MATN1* (Korean population) and *EPB41* (erythrocyte membrane protein band 4.1) (Han Chinese population) were candidate genes of the phenotype. However, in other linkage analysis of Brazilian families, 1p36, 6q25, and 19p13.2 did not show suggestive linkage to the phenotype.

On the other hand, from results of other genome-wide linkage analysis of Colombian Hispanic families, 5 susceptibility loci: 1p22.1; 3q26.2; 11q22; 12q13.13; and 12q23 showed suggestive linkage to mandibular prognathism. The loci 12q13 and 12q23 correlate with positional candidate genes of interest, including *HOX3* (homeobox region 3), *IGF-1* (insulin-like growth factor 1), and *COL2A1* (collagen alpha-1 (II) chain) genes. Supplementary association study of multiracial patients suggested that *MYO1H* (myosin 1H) located on 12q24.11, close to 12q23, was a candidate gene of mandibular prognathism. Three more linkage analyses on susceptibility loci of the phenotype were reported in Han Chinese families. A few reviews [1,2] showed these results and the results of other association studies on susceptibility loci of mandibular prognathism. However, the loci shown by these linkage analyses for mandibular prognathism are inconsistent.

Genome-wide association study

Genome-wide association study (GWAS) has been proposed as an alternative strategy for linkage analysis. For performing GWAS, single nucleotide polymorphisms (SNPs) and microsatellites have been used as markers on a chromosome map. SNPs are thought to be genetically more stable because of a lower mutation rate, to be biallelic, and to show a low degree of heterozygosity and a short linkage disequilibrium length. On the other hand, microsatellites show a high polymorphic and a high degree of heterozygosity (about 70% on average) and linkage disequilibrium lengths. Microsatellites are not likely to be evenly distributed across the genome, leaving some areas with no or little coverage [3]. A microsatellite-based GWAS, however, can be conducted with a

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small number of markers, and highly polymorphic microsatellites can provide greater power for detection of intermarker linkage disequilibrium than can SNPs [4]. Therefore, loci have been identified in some diseases by association analysis using microsatellite markers.

There has been no report on GWAS of mandibular prognathism. For better understanding the genetic basis of mandibular prognathism, the first GWAS was carried out using microsatellites in Japanese population including 240 individuals with mandibular prognathism (cases) and 360 individuals who were healthy (controls) [5]. The pooled DNA approach was composed of genomic DNA samples that were quantitated accurately from each of the case and control groups. To reduce the number of pseudo-positives resulting from type 1 errors, two steps of screening were performed to sequentially replicate the results in each of the pooled samples. After the first and second typing using independent pooled DNA samples, positive microsatellites were further screened using individual DNA from the pooled DNA set to confirm the significance of allele frequency. The GWAS using microsatellites suggested that six loci (1p22.3, 1q32.2, 3q23, 6q23.2, 7q11.22 and 15q22.22) were susceptibility regions of mandibular prognathism. *SSX2IP* (synovial sarcoma, X breakpoint 2 interacting protein), *PLXNA2* (plexin A2), *RASA2* (Ras p21 protein activator 2), *TCF21* (transcription factor 21), *CALN1* (calneuron 1), and *RORA* (RAR (retinoic acid receptor)-related orphan receptor α) were suggested as candidate genes. The locus 1p22.3 was supported by a previous linkage analysis, and other 5 loci (1q32.2, 3q23, 6q23.2, 7q11.22 and 15q22.22) were novel loci.

Exome sequencing and clinical suggestion

Second-generation methods for targeted sequencing of all protein-coding regions, exomes, have been developed to facilitate discovery of highly penetrant variants. A few exome sequencing has been reported on candidate genes of mandibular prognathism using family subjects. However, inconsistent genes were also shown within the exome sequencing for mandibular prognathism. The differences of genotype for same phenotype, mandibular prognathism, might be due to different races and variation of mandibular prognathism (different degrees and directions of excessive mandibular growth).

Mandibular Growth consists of a periosteal growth of cortical bone and an endochondral growth of the condyle. Active mandibular growth occurs in the condyle. Growth hormone and insulin growth factor-1 regulate endochondral growth of the condylar cartilage. Parathyroid hormone-related peptide, Indian Hedgehog, and Sox9 also regulate differentiation of chondrocyte. It is not understand yet how the proteins, encoded by candidate genes of mandibular prognathism in the nonparametric linkage analyses, GWAS, and exome sequencing, are related to these endochondral growth regulators. From a clinical point of view, if orthodontists could predict whether patients have strong factors and/or regulators for excessive mandibular growth, they would be able to select strategies to treat mandibular prognathism more effectively. Namely, if a growing orthodontic patient with mandibular prognathism has genetic factors such as variants in candidate genes, orthodontists could avoid unnecessary mandibular growth inhibition by long-term use of a chincap appliance and select future orthognathic surgery for the young patient at initial examination.

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