

Genetics of tooth agenesis: how to move the field forward

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Tooth agenesis is the congenital lack of one or more of the deciduous or permanent teeth. Oligodontia is the agenesis of six or more permanent teeth (excluding third molars), whereas absence of less than six teeth is referred to as hypodontia. Anodontia refers to the absence of all deciduous and permanent teeth.

Tooth agenesis occurs more frequently among a few specific teeth (lateral incisors, second premolars, and third molars), with 10% to 25% of the population affected. Familial tooth agenesis is transmitted as an autosomal-dominant, autosomal-recessive, or X-linked condition, but can also show no clear segregation pattern⁵. Affected members within a family often exhibit significant variability with regard to the location, symmetry, and number of teeth involved. Residual teeth can vary in size, shape, or rate of development. The permanent dentition is more affected than the primary dentition³.

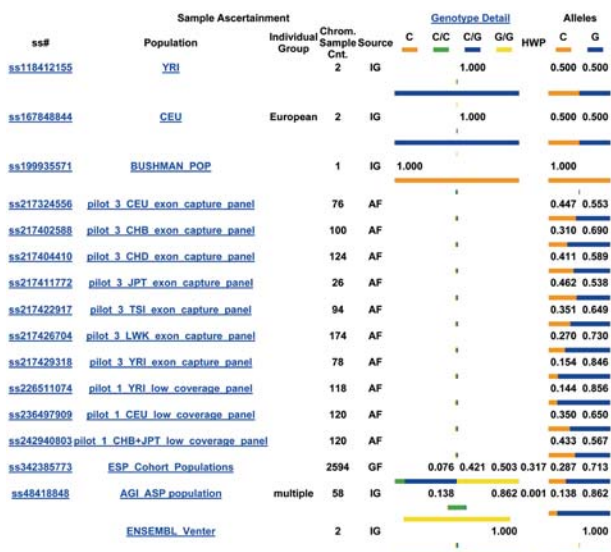
In this issue of the Journal of Applied Oral Science, Wang, et al.⁸ (2013) report a study that combines a case-control analysis of a *PAX9* variant and sporadic isolated tooth agenesis, and a case of anodontia. The case-control analysis probably suffers from low statistical power. The effects of *PAX9* in sporadic cases of tooth agenesis are probably small and may be dependent of interaction with other genes, such as *MSX1*⁷. Effects of *PAX9* have been detected when analysis included cases with preferential third molar agenesis¹. One of the *PAX9* variants studied, rs4904210, is a missense mutation (A240P) that is not considered to have any functional consequences since is highly prevalent in several populations (Figure 1).

The case of anodontia however rings more excitement to this report. The authors failed to find etiological mutations in four genes: *PAX9*, *MSX1*, *AXIN2*, and *EDA*. Sequencing candidate genes is not an unjustified first step, although no reports exist linking these genes with isolated anodontia, even when the whole *PAX9* gene is deleted from one of the chromosomes⁶. The first three genes when mutated cause autosomal dominant forms of oligodontia (with at least one known *MSX1* recessive form)⁶. *EDA* has been linked to isolated X-linked recessive oligodontia, and whereas mutations in this gene cause ectodermal dysplasia, which can lead to anodontia or very severe oligodontia, sequencing *EDA* in a female case is not fully justified, unless the underlying hypothesis includes a chance of skewed X chromosome inactivation.

A very appealing approach to be used for identifying the causal mutation of the anodontia case presented by Wang, et al.⁸ (2013) would be whole exome sequencing². This approach has been used in other craniofacial conditions, such as craniosynostosis⁴. Using this approach, the authors will likely unveil the mutation causing the sporadic anodontia in the case by testing only one or two DNA samples of good quality for a current cost of less than US\$1,000.

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Source: NCBI - National Center for Biotechnology Information. dbSNP Short Genetic Variations. *PAX9*: rs4904210. Bethesda: NCBI; 2013 [cited 2013 June 20]. Available from: http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=4904210

Figure 1- Allele and genotype frequencies of the *PAX9* A240P mutation