Defining Subphenotypes for Tooth Agenesis: Does Side Matter?

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Objectives: *The etiology of tooth agenesis is still poorly understood. The identification of sub-populations with specific types of hypodontia (subphenotypes) would allow testing the specific hypothesis that certain genetic factors contribute to the specific subphenotype. The aim of this work was assessing a large cohort to verify if preferential tooth agenesis subphenotypes could be identified.* ***Method:*** *Panoramic radiographs of 1052 cases were examined and 1034 were used in this study. The presence of tooth agenesis was assessed in the study population.* ***Results:*** *The frequency of tooth agenesis in the studied population was 3.77%. While bilateral cases did not differ in the frequency of agenesis by arch (p = 0.8), unilateral cases presented more commonly agenesis on the mandibular arch (p = 0.03). This result was clearly driven by the frequency of second premolar agenesis, which was the most common absent tooth in the studied population. Unilateral lower second premolar agenesis was found more often than bilateral agenesis (p = 0.047).* ***Conclusions:*** *Our findings that unilateral lower second premolar agenesis is more common than bilateral agenesis, with a trend for unilateral agenesis being more common on the right side may suggest specific genetic factors may be differentially expressed depending on the side.*

Keywords: *Hypodontia; Oligodontia; Fluctuating Asymmetry; PAX9; MSX1; AXIN2; Cleft Lip and Palate*
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INTRODUCTION

Tooth agenesis is the most common congenital anomaly in humans, but just recently the etiology of the condition started to be unveiled. Defects in *PAX9*,[1-12] *MSX1,*[13-19] and *AXIN2*[20] were described in more severe forms of the condition (oligodontia), and in most of the cases segregating in an autosomal dominant fashion. However, these cases account for a very small percentage of the total cases in the population. Tooth agenesis is commonly found in syndromes,[21] and is four to six times more common in cleft lip and palate populations.[22-2]

The majority of tooth agenesis cases are probably caused by a combination of genes and environmental influences. The reported frequency of tooth agenesis varies from 2.6% to 11.3%, second premolars are most frequently recorded absent, and prevalence rates are higher in females compared to males (3:2, respectively).[24]

Although some epidemiologic characteristics of tooth agenesis (frequency, gender distribution, most commonly affected teeth) are well established, the etiology of the disorder remains largely unclear. In this study, we used a cohort of 1,034 pediatric subjects to study tooth agenesis and explore in more detail the clinical presentation of the disorder, investigating if some specific patterns of tooth agenesis (subphenotypes) could be determined.

METHOD

This study was approved by the Clementino Fraga Filho University Hospital Institutional Review Board.

Panoramic radiographs from all 1,052 patients assisted by the Federal University of Rio de Janeiro's Continuing Education Clinical Program in Pediatric Dentistry were examined. All radiographs were taken in the same clinic, by the

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same radiology technician, and developed using the same protocol. All patients, whose ages varied from 6 to 12 years old and were assisted between August of 1997 and December 2004, were included in this study. All radiographs were examined by the same professional using the same protocol. Radiographs were examined in a dark room over a negatoscope that had a frame to avoid light passing on the sides of the radiograph. Tooth agenesis was defined based on the age of the subjects and when initial tooth formation would be visible radiographically.[25] Cases with radiographs of poor quality were excluded (N = 18). No cases were found to have an underlying syndrome.

RESULTS

Among the 1,034 radiographs studied, 515 were from females and 519 from males. Thirty-nine patients (3.77%) had at least one congenitally missing tooth. Twenty-two were females and 17 males defining the ratio female: male at 1.29 to 1. No statistically significant differences in the frequency of tooth agenesis based on gender were found ($p = 0.13$). Also, the distribution of tooth agenesis based on arch (upper versus lower) and laterality (left versus right) was not statistically different ($p = 0.51$ and $p = 0.61$, respectively).

Nineteen cases had one tooth missing, nine cases had two teeth missing, and eleven cases had three or more teeth missing. While bilateral cases did not differ in the frequency of agenesis by arch ($p = 0.8$), unilateral cases presented more commonly agenesis on the mandibular arch ($p = 0.03$). This result was clearly driven by the frequency of second premolar agenesis, which was the most common absent tooth in the studied population. Unilateral lower second premolar agenesis was found more often than bilateral agenesis ($p = 0.047$). Table 1 describes the 39 tooth agenesis cases found in the studied population.

Table 1. Description of the affected cases by gender, age, and teeth missing.

Case Number	Gender	Age (in years)	Absent teeth
1	M	12	35,45
2	M	10	35
3	M	12	15,25
4	F	12	14, 15, 23, 24, 25, 35,45
5	M	12	15
6	M	11	35,45
7	M	11	15, 25, 45
8	F	12	32
9	M	11	45
10	F	7	32, 35, 42, 45
11	F	8	45
12	F	8	45
13	M	10	35, 45
14	F	9	33, 43
15	M	9	35, 45
16	F	9	45
17	M	10	12, 13, 22, 23, 31, 35, 41, 45
18	F	9	15, 25, 45
19	M	7	45
20	F	10	14, 15, 17, 24, 25, 27, 34, 35, 37, 44, 45, 47
21	F	11	14, 15, 24, 25, 34, 35, 45
22	F	8	15, 33, 45
23	F	9	15, 25, 45
24	M	6	31
25	F	7	25
26	M	6	12
27	M	8	45
28	F	10	12, 15, 22, 25
29	F	7	35
30	M	6	35
31	F	8	42
32	F	9	15, 25
33	F	11	15
34	M	12	35, 45
35	F	6	12, 22
36	F	7	45
37	M	9	12
38	M	12	15, 25, 34, 44
39	F	11	35

DISCUSSION

The aim of this study was to identify subphenotypes of tooth agenesis that could be used to study the etiology of the condition. Frequency, sex ratio, and types of teeth affected reported here are similar to previous studies,[24] although the number of females we found affected is slightly decreased compared to previous reports. One additional observation also deserves note. Unilateral tooth agenesis of lower second premolars was more commonly seen than bilateral agenesis. Although not statistically significant, there was a trend for having more mandibular second premolars missing on the right side than on the left side (11 versus 4; $p = 0.13$).

Assuming that genetic information is identical for each side, differences between sides can be interpreted as consequence of environmental factors. On the other hand, one can propose bilateral traits could be influenced by distinctive genes, depending on the particular side. Subtle random deviations from perfect bilateral symmetry is called *fluctuating asymmetry* and is considered an appealing measure of developmental precision because of the apparent ease with which it may be measured and because its developmental origins seem so straightforward.[26] It has been recognized that more *distal* tooth types (second premolars among premolars) have increased size variability between left and right.[27-33] However, true fluctuating asymmetry (the result of real differences between sides) is subject to the influence of a number of methodological variants, and the evaluation of quantitative measures of bilateral variation and their heritability has been interpreted with caution.[26]

Asymmetric lower second premolar agenesis, preferentially on the right side, could be considered directional asymmetry, and its etiology could be related to a particular factor. A number of traits have differences in laterality. Cleft lip is more common on the left side,[34] as well as postaxial polydactyly,[35,36] whereas microtia is more commonly found in the right size.[37] Regarding breast sizes, no significant differences between left and right are described, however

breast asymmetry is greater in healthy women who subsequently developed breast cancer compared to those who remained disease free, suggesting that asymmetrical breasts could prove to be reliable indicators of future breast disease in women.[38]

The fifteen affected individuals with asymmetric agenesis of mandibular second premolars lived in the same metropolitan area of Rio de Janeiro but it is difficult to determine if they were under the influence of a common environmental factor. Although these individuals are not obviously related, one possible explanation is that the same genetic variation could cause these asymmetric differences. There is likely no selective forces acting against these alleles and that is probably the reason tooth agenesis is quite common in humans. No preferential asymmetry can be observed in the families segregating mutations in *AXIN2,*[20] *MSX1*,[13-19] or *PAX9*.[1-12] In contrast with the mutations causing severe forms of tooth agenesis, sporadic tooth agenesis may be due to hypomorphic alleles more frequent in the population.

Our study adds to the bulk of the literature and confirms previously reported characteristics of tooth agenesis. Our observation that unilateral lower second premolar agenesis is more common than bilateral agenesis, with a trend for unilateral agenesis being more common on the right side may suggest specific genetic factors may be differentially expressed depending on the side. A recent study on cleft lip and palate suggested that the genes that contribute to laterality of the cleft may be different, resulting in alternate phenotypes for dental anomalies also.[23] Further studies should take into consideration the types of teeth and if agenesis is bilateral versus unilateral.

REFERENCES

1. Stockton DW, Das P, Goldenberg M, D'Souza RN, Patel PI. Mutation of PAX9 is associated with oligodontia. Nat Genet, 24: 18–19, 2000.
2. Nieminen P, Arte S, Tanner D, Paulin L, Alaluusua S, Thesleff I, Pirinen S. Identification of a nonsense mutation in the PAX9 gene in molar oligodontia. Euro J Hum Genet, 9: 743–746, 2001.
3. Frazier-Bowers SA, Guo DC, Cavender A, Xue L, Evans B, King T, Miliewicz D, D'Souza RN. A novel mutation in human PAX9 causes molar oligodontia. J Dent Res, 81: 129–133, 2002.
4. Das P, Stockton DW, Bauer C, Shaffer LG, D'Souza RN, Wright JT, et al. Haploinsufficiency of PAX9 in associated with autosomal dominant hypodontia. Hum Genet, 110: 371–376, 2002.
5. Das P, Mehreen H, Elcock C, Leal SM, Brown AH, Patel PI. Novel missense nmutations and 288-bp exonic insertion in PAX9 in families with autosomal dominant hypodontia. Am J Med Genet, 118A: 35–42, 2003.
6. Lammi L, Halonen K, Pirinen S, Thesleff I, Arte S, Nieminen P. A missense mutation in PAX9 in a family with distinct phenotype of oligodontia. Eur J Hum Genet, 11: 866–871, 2003.
7. Mostowska A, Kobielak A, Biedziak B, Trzeciack WH. Novel mutation in the paired box sequence of PAX9 gene in a sporadic form of oligodontia. Eur J Oral Sci, 111: 272–276, 2003.
8. Jumlongras D, Lin JY, Chapra A, Seidman CE, Seidman JE, Mass RL, et al. A novel missense mutation in the paired domain of PAX9 cause non-syndromic oligodontia. Hum Genet, 114: 242–249, 2004.
9. Klein ML, Nieminen P, Lammi L, Niebuhr E, Kreiborg S. Novel mutation of the initiation codon of PAX9 causes oligodontia. J Dent Res, 84: 43–47, 2005.
10. Zhao JL, Chen YX, Bao L, Xia QJ, Wu TJ, Zhou L. Novel mutations of PAX9 gene in Chinese patients with oligodontia. Zhonghua Kou Qiang Yi Xue Za Zhi, 40: 266–270, 2005.
11. Mostowska A, Biedziak B, Trzeciack WH. A novel mutation in PAX9 causes familial form of molar oligodontia. Eur J Hum Genet, 14: 173–179, 2006.
12. Hansen L, Kreiborg S, Jarlov H, Niebuhr E, Eiberg H. A novel nonsense mutation in PAX9 is associated with marked variability in number of missing teeth. Eur J Oral Sci, 115: 330–333, 2007.
13. Vastardis H, Karimbux N, Guthua SW, Seidman JG, Seidman CE. A human MSX1 homeodomain missense mutation causes selective tooth agenesis. Nat Genet, 13: 417–421, 1996.
14. van den Boogaard MJH, Dorland M, Beemer FA, van Amstel HKP. MSX1 mutation is associated with orofacial clefting and tooth agenesis in humans. Nat Genet, 24: 342–343, 2000.
15. Jumlongras D, Bei M, Stimson JM, Wang W-F, DePalma SR, Seidman CE, et al. A nonsense mutation in MSX1 causes Witkop Syndrome. Am J Hum Genet, 69: 67–74, 2001.
16. Lidral AC, Reising BC. The role of MSX1 in human tooth agenesis. J Dent Res, 81: 274–278, 2002.
17. Nieminen P, Kotilainen J, Aalto Y, Knuutila S, Pirinen S, Thesleff I. MSX1 gene is deleted in Wolf-Hirschhorn syndrome patients with oligodontia. J Dent Res, 82: 1013–1017, 2003.
18. De Muynck S, Schollen E, Matthijs G, Verdonck A, Devriendt K, Carels C. A novel MSX1 mutation in hyposontia. Am J Med Genet A, 128: 401–403, 2004.
19. Kim JW, Simmer JP, Lin BP, Hu JC. Novel MSX1 frameshift causes autosomal-dominat oligodontia. J Dent Res, 85: 267–271, 2006.
20. Lammi L, Arte S, Somer M, Järvinen H, Lahermo P, Thesleff I, et al. Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer. Am J Hum Genet, 74: 1043–1050, 2004.
21. Vieira AR. Oral clefts and syndromics forms of tooth agenesis as models for genetics of isolated tooth agenesis. J Dent Res, 82: 162–165, 2003.
22. Roth P, Hirschfelder U. Frequency of tooth agenesis in CLP patients with eruption of all four third molars. Dtsch Zahnarztl Z, 46: 734–736, 1991.
23. Letra A, Menezes R, Granjeiro JM, Vieira AR. Defining cleft subphenotypes based on dental development. J Dent Res, 86: 986–991, 2007.
24. Larmour CJ, Mossey PA, Thind BS, Forgie AH, Stirrups DR. Hypodontia—a retrospective review of prevalence and etiology. Part I. Quintessence Int, 36: 263–270, 2005.
25. Moyers RE. Handbook of orthodontics. Year Book Medical Publishers, Chicago; 483, 1988.
26. Palmer AR, Strobeck C. Fluctuating asymmetry and developmental stability: heritability of observable variation vs. heritability of inferred cause. J Evol Biol, 10: 39–49, 1997.
27. Lundström A. Asymmetries in the number and size of the teeth and their aetiological significance. Trans Europ Orthodont Soc, 167–185, 1960.
28. Garn SM, Lewis AB, Kerew-Sky RS. The emaning of bilateral asymmetry in the permanent dentition. Angle Orthod, 36: 55–62, 1966.
29. Garn SM, Lewis AB, Kerew-Sky RS. Buccolingual size asymmetry and its developmental meaning. Angle Orthod, 37: 186–193, 1967.
30. Bailit HL, Workman PL, Niswander JD, MacLean CJ. Dental asymmetry as an indicator of genetic and environmental conditions on human populations. Hum Biol, 42: 626–638, 1970.
31. Perzigian AJ. Fluctuating dental asymmetry: variation among skeletal populations. Am J Phys Anthropol, 47: 81–88, 1977.
32. Harris EF, Nweeia MT. Dental asymmetry as a meausre of environmental stress in the Ticuna Indians of Colombia. Am J Phys Anthropol, 53: 133–142, 1980.
33. Towsend GC, Brown T. Dental asymmetry in Australian Aboriginals. Hum Biol, 52: 661–673, 1980.
34. Fogh-Andersen P. Inheritance of Harelip and Cleft Palate. Arnold Busck, Copenhagen; 1942.

35. Bingle GJ, Niswander JD. Polydactyly in the American Indian. Am J Hum Genet, 27: 91–99, 1975.
36. Rayan GM, Frey B. Ulnar polydactyly. Plast Reconstr Surg, 107: 1449–1454, 2001.
37. Calzolari F, Garani G, Sensi A, Martini A. Clinical and radiological evaluation in children with microtia. Br J Audiol, 33: 303–312, 1999.
38. Scutt D, Lancaster GA, Manning JT. Breast asymmetry and predisposition to breast cancer. Breast Cancer Res, 8: R14, 2006.