It has been reported that dozens of WNT10A variants are associated with human isolated tooth agenesis, however, little is known about the precise phenotypes. In 50 Japanese patients with severe congenital tooth agenesis, we identified 11 patients with WNT10A variants. Comparing phenotypes between the tooth agenesis patients carrying the wild-type and variants of WNT10A, we revealed that the development of lateral incisors is relatively susceptible to insufficiency of WNT/β-catenin signaling.

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Allelic frequency WNT10A variant in Japanese severe tooth agenesis patients

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Figure 1. (a) The ratio of missing teeth in each maxillary and mandibular position of all the 50 patients with tooth agenesis in this study (male, N = 21; female, N = 29). (b) The ratio of missing teeth in each maxillary and mandibular position of the tooth agenesis patients with (dark gray columns; N = 11), and without miss sense variant of WNT10A gene (light gray columns; N = 39). (c) The susceptibility of each tooth to the WNT signal defect. These values are defined as the quotient of the each missing tooth ratio of the patients with WNT10A variant by that without WNT10A variant. Lateral incisors of maxilla and mandible, and maxillary canine are sensitive to WNT signaling. We combined the left and right teeth, since no statistically significant difference between the left and right sides.

dysplasia symptoms. The group of 11 individuals with WNT10A variants consisted of 4 males and 7 females (Table 1). They had a total of 112 missing teeth (92 excluding wisdom tooth) resulting in a mean of 10.2 missing teeth (8.4; excluding wisdom tooth loss). Dentograms on all 11 patients with WNT10A mutations showed a total of 64 absent teeth (55 excluding wisdom tooth loss) in the upper jaw, and 48 (37 excluding wisdom tooth loss) absent teeth in the lower jaw, resulting in a mean of 5.8 and 4.4 (5.0 and 3.4 excluding wisdom tooth loss), respectively (Table 1). The comparison of missing tooth phenotypes with and without WNT10A variants were summarized in the Figure 1b.

Mutations in the WNT10A gene are the most frequently found mutations in patients with nonsyndromic tooth agenesis in several populations studied to date. However, in our current study, the prevalence of WNT10A variants in the Japanese tooth agenesis patients with more than three-tooth loss was lower than that of other reports studying in other ethnic populations.6,7,13,14,16–18

Most of the prevalences of WNT10A variants were ranged about 30–50% in patients among different ethnic groups. In the East Asia, WNT10A variants were detected in 51.6% (16/31) of the Chinese patients with four or more missing teeth, while 15.8% of patients with one-three missing teeth.6 In the current study, we identified 22% (11/50) of patients with missense mutation in WNT10A gene in 50 Japanese patients lacking at least 4 teeth excluding wisdom teeth, and 0% in the healthy 50 Japanese control.

In the Chinese patients with at least 4 missing tooth, the variant c.511C>T (p.R171C) and c.637G>A (p.G213S) WNT10A was frequently detected (22.6%; 7/31 and 25.8%; 8/31).6 In our current Japanese case study, while the variant, c.511C>T was detected only in one patient, the other variant, c.637G>A, was also dominantly present in the tooth agenesis patients with WNT10A gene variants (16%; 8/50). In addition, although the c.511C>T and c.637G>A WNT10A variants were detected in normal Chinese control (2.0% and 2.7%, respectively), none of the healthy Japanese carrying these variants were identified in our control samples. According to the Japanese genetic variation database, HGDV, the population ratios of c.511C>T and c.637G>A variant are 3.1% (72/2340) and 3.0% (70/2318), and the allelic frequencies are 0.0147, and 0.0149, respectively, indicating that the population frequency of p.Gly213Ser variant is concentrated in the tooth agenesis patients (16.0%; 8/50) than general Japanese population (3.0%; 70/2318) as the pervious report with the Chinese population.6 Interestingly, compare to other regions, the frequency of p.Gly213Ser in the East Asia is 373.8 times. Besides these two variants, the p.Arg48His and p.Ala297Thr variants are rare (Supplementary Table S1). The p.Arg48His, p.Arg171Cys and p. Gly213Ser variants, but not p.Ala297Thr variant, are listed in the Japanese genetic variation database HGDV (http://www.hgvd. genome.med.kyoto-u.ac.jp/) and iJGVD (https://ijgvd.megabank. tohoku.ac.jp/about/), however, no information is attached in the database about tooth phenotypes of these individuals with the WNT10A variant. Generally, there is concern that tooth agenesis phenotypes were overlooked in database samples, since nonsyndromic tooth agenesis is rather mild anomaly than other serious congenital disorders.

Though there are minor differences, which may arise from ethnic background, our findings support the notion that the common variants of WNT10A such as c.511C>T (p.Arg171Cys) and c.637G>A (p.Gly213Ser) are predisposing genetic factors for causation,6 and other unknown genetic or environmental factors are needed to express developmental tooth anomaly in human.

The missing teeth species in Japanese severe tooth agenesis patients (at least 4 missing tooth) with WNT10A gene variants varies from those in Chinese patients.6 Especially, the ratio of the missing in the maxillary lateral incisor is higher in Japanese patients (63.6%, Figure 1b) than those in Chinese with severe tooth agenesis (31.3%). By contrast with the missing tooth of Japanese patients with wild-type WNT10A and those with WNT10A variant, lateral incisors of the mandibular and maxilla, and the canine in maxilla are relatively sensitive to insufficiency of WNT/β-catenin signaling (Figure 1c). This finding is partly supported by a previous study on Polish patients with the maxillary lateral incisor agenesis.6 However, the phenotype may...
be swayed by ethnic backgrounds. In addition, it has been demonstrated that about one half of individuals with heterozygous null mutation of WNT10A show a mild ectodermal dysplasia phenotypes with a significantly higher proportion of tooth anomalies in males than in females. However, in the current study, female patients with tooth agenesis were higher proportion than male (63.6%, 7/11). This may arise from difference in biological activity of WNT10A variants. The common variants such as p.R171C and p.G213S are detected in a healthy population, suggesting that these variants may have biological function at least in part.

Finally, it seems to be more direct contribution of the rare variants c.143G>A (p.Arg48His) and c.889G>A (p.Ala297Thr) WNT10A to human tooth agenesis, but biochemical and cell biological studies are needed to elucidate whether these WNT10A variants cause developmental anomaly in human tooth formation.

**HGV DATABASE**

The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.fgshare.hgv.1651; http://dx.doi.org/10.6084/m9.fgshare.hgv.1654; http://dx.doi.org/10.6084/m9.fgshare.hgv.1657; http://dx.doi.org/10.6084/m9.fgshare.hgv.1660.

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**COMPETING INTERESTS**

The authors declare no conflict of interest.

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**Table 1.** Tooth phenotypes of Japanese patients with WNT10A variant (OMIN #150400, STHAG4; tooth agenesis, selective, 4)

| Case ID | Hered. | Gen. # miss. (w. teeth) | Variant ID | Mutation | Base change | Protein alteration | ClinVar | Polyphen 2 | SIFT |
|---------|--------|-------------------------|------------|----------|-------------|-------------------|---------|------------|------|
| 190     | de novo| U L                     | F 6 (5)    | NM_025216.2.c.143G>A | NC_000002.11:g.219746912G>A | 150400   | NA         | 0.102   | dele.     |
| 31      | inherited | L U | M 7 (5) | NM_025216.2.c.511C>T | NC_000002.11:g.219754840C>T | 150400   | Conflict  | 0.999   | dele.     |
| 1       | de novo | U L                     | F 9 (8)    | NM_147680216 | NC_000002.11:g.219754966G>A | 150400   | Conflict  | 1       | dele.     |
| 61      | de novo | U L                     | F 12 (8)   | NM_025216.2.c.637G>A | NC_000002.11:g.219754966G>A | 150400   | Conflict  | 1       | dele.     |
| 79      | inherited | L U | F 12 (12)  | NM_025216.2.c.637G>A | NC_000002.11:g.219754966G>A | 150400   | Conflict  | 1       | dele.     |
| 90      | inherited | L U | F 15 (15)  | NM_025216.2.c.889G>A | NC_000002.11:g.219757628G>A | 150400   | NA         | 1       | dele.     |
| 142     | de novo | U L                     | F 15 (15)  | NM_025216.2.c.889G>A | NC_000002.11:g.219757628G>A | 150400   | NA         | 1       | dele.     |
| 189     | de novo | U L                     | F 15 (15)  | NM_025216.2.c.889G>A | NC_000002.11:g.219757628G>A | 150400   | NA         | 1       | dele.     |
| 195     | inherited | L U | F 15 (15)  | NM_025216.2.c.889G>A | NC_000002.11:g.219757628G>A | 150400   | NA         | 1       | dele.     |

- Missing tooth. Abbreviations: dele, deleterious; F, female; Gen, gender; Hered, hereditary; L, lower jaw; M, male; NA, Not assigned; U, upper jaw; w. teeth, number of missing teeth except for wisdom teeth; # miss., Number of missing teeth.
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Supplementary Information for this article can be found on the Human Genome Variation website (http://www.nature.com/hgv).