

## Original article

# Evaluation of dental maturity in Muenke syndrome, Saethre-Chotzen syndrome, and *TCF12*-related craniosynostosis

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## Summary

**Objectives:** To determine whether dental maturity (dental development) was delayed in patients with Muenke syndrome, Saethre-Chotzen syndrome, and *TCF12*-related craniosynostosis, compared with a Dutch control group without syndromes.

**Materials and methods:** This study included 60 patients (38 patients with Muenke syndrome, 17 patients with Saethre-Chotzen syndrome, and 5 with *TCF12*-related craniosynostosis), aged 5.8–16.8 years that were treated at the Department of Oral Maxillofacial Surgery, Special Dental Care, and Orthodontics, in Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands. Dental age was calculated according to Demirjian's index of dental maturity. The control group included 451 children without a syndrome.

**Results:** Compared with the control group, dental development was delayed by an average of one year in 5- to 8-year-old patients with Muenke syndrome ( $P = 0.007$ ) and in 8- to 10-year-old patients with Saethre-Chotzen syndrome ( $P = 0.044$ ), but not in patients with *TCF12*-related craniosynostosis.

**Conclusions:** Our results indicated that dental development was delayed by one year, on average, in patients with Muenke syndrome and Saethre-Chotzen syndrome, compared with a Dutch control group without syndromes.

**Implications:** Our findings have improved the understanding of dental development in patients with Muenke and Saethre-Chotzen syndrome. These results can provide guidance on whether the orthodontist needs to consider growth disturbances related to dental development.

## Introduction

Craniosynostosis is the premature fusion of one or more cranial sutures. The prevalence of craniosynostosis ranges from 3.1 to 6.4 in 10 000 live births and is reportedly rising (1–6). It is highly

probable that craniosynostosis is linked to a specific genetic cause (7). Craniosynostosis syndromes with similar mild craniofacial malformations include Muenke syndrome (OMIM #602849), Saethre-Chotzen syndrome (OMIM #101400), and *TCF12*-related craniosynostosis (OMIM #615314) (8–11). The prevalence of

Muenke syndrome is 1:10 000–12 500 among newborns (8). The prevalence of Saethre-Chotzen syndrome is 1:25 000–50 000 among newborns (9, 10). The prevalence of *TCF12*-related craniosynostosis has not been reported in the literature. Patients with syndromic coronal craniosynostosis often have mutation(s) in the following genes: *FGFR2* (MIM #176943), *FGFR3* (MIM #134934), *TWIST1* (MIM #601622), or *TCF12* (MIM #600480) (7, 11). Compared with Apert and Crouzon syndromes, the phenotype is more subtle (12–14). The main features of Muenke syndrome are coronal suture synostosis, carpal and tarsal fusions, and hearing loss (15). The phenotype of Saethre-Chotzen syndrome is characterized by coronal suture synostosis, strabismus, ptosis (16). The phenotype of *TCF12*-related craniosynostosis is characterized by coronal suture synostosis. Because this mutation has been found recently, an extensive description of the phenotype is not yet available (11). All these three craniosynostosis syndromes also have smaller dental arch dimensions (17).

Dental development is delayed in Apert syndrome (OMIM #101200) and Crouzon syndrome (OMIM #123500). This delay might be related to the higher prevalence of tooth agenesis in patients with these syndromes, compared with children without a syndrome (12, 18). Dental development is influenced by environmental and genetic factors. Increasing knowledge of genetic factors that influence the development of teeth and cranial sutures has revealed the relationship between craniofacial and dental development. This relationship includes various mutual growth or transcription factors, such as members of the fibroblast growth factor (*FGF*) family, various FGF receptors (*FGFRs*), and the genes that encode these transcription factors (19–21). Dysfunctions in *FGF*, *FGFRs*, or *TWIST1* can result in craniofacial or dental anomalies, like delayed dental development or craniosynostosis (22, 23). Genetic alterations can also affect dental features. More specifically, *Twist1* is expressed during the early stages of dental development and it is co-expressed with *Fgf3* and *Fgf10*. Furthermore, dental development is regulated by signaling networks that are associated with FGF-3 and FGF-10. The FGF signaling pathway also regulates dental development. (20, 24). In murines, it has been shown that a mutation in *Twist1* delays the development of third molars (21). Knowledge of the genes involved in dental development might broaden our understanding of anomalous dental development (22).

Dental development, also known as dental maturity, is widely determined with Demirjian's index of dental maturity. This index is also considered a superior method for determining biological age in humans, compared with skeletal indicators (25, 26). The dental maturity score provides precise knowledge about general dental development, relative to chronological age, in normal children. The dental maturity score is calculated as the sum of the converted scores of calcification stages of the teeth in the lower left quadrant (25). It is important to determine the specific phases of dental development that occur in patients without (healthy) and with syndromes to create indicators of possibly potentially aberrant craniofacial development. This information is particularly useful for the orthodontist, who can optimize the initiation of an orthodontic treatment for different types of malocclusion. Additionally, knowledge of dental development can facilitate the optimization and management of orofacial interventions that are often performed in craniosynostosis syndromes (18).

This study aimed to compare dental development of patients with Muenke syndrome, Saethre-Chotzen syndrome, or *TCF12*-related

craniosynostosis to dental development in a Dutch control group of healthy children without syndromes.

## Materials and methods

This retrospective cohort study was approved by the Medical Ethics Committee of the Erasmus University Medical Center in Rotterdam, the Netherlands (MEC-2013-536). Panoramic radiographs were part of the orthodontic documentation required in the treatment protocol used by the craniofacial team in the Erasmus University Medical Center Rotterdam, the Netherlands.

### Patient sample

This study included 162 patients that were referred between 1990 and 2019 to the craniofacial team of Erasmus University Medical Center Rotterdam, the Netherlands. The clinical diagnosis was determined by a craniofacial expert (i.e. a clinical geneticist and/or a plastic surgeon). In all patients, the diagnosis was confirmed molecularly. The dental panoramic radiographic documentation started at the age of 6 years, according to the craniofacial team protocol. At the time of the dental panoramic radiographic documentation, all patients were under 18 years old. We searched for available dental panoramic radiographs for all 162 patients (Muenke syndrome,  $n = 84$ ; Saethre-Chotzen syndrome,  $n = 49$ ; *TCF12*-related craniosynostosis,  $n = 29$ ), and we selected radiographs that clearly displayed all teeth. Patients were excluded, when they had no dental panoramic radiographic documentation, when the quality of the dental panoramic radiograph was insufficient, when patients had undergone orthodontic treatment prior to the dental panoramic radiographic documentation, and when they had missing teeth (27) (i.e. agenesis ( $n = 10$ ) or extracted teeth, except for the third molar) or supernumerary teeth. No evidence was found that these patients have a higher prevalence of tooth agenesis. Therefore, patients with tooth agenesis were excluded because the final dental maturity score in children with tooth agenesis is deviant compared with patients without tooth agenesis. Including patients with tooth agenesis would bias the general dental maturity score. Based on these exclusion criteria, we excluded 102 patients (Figure 1).

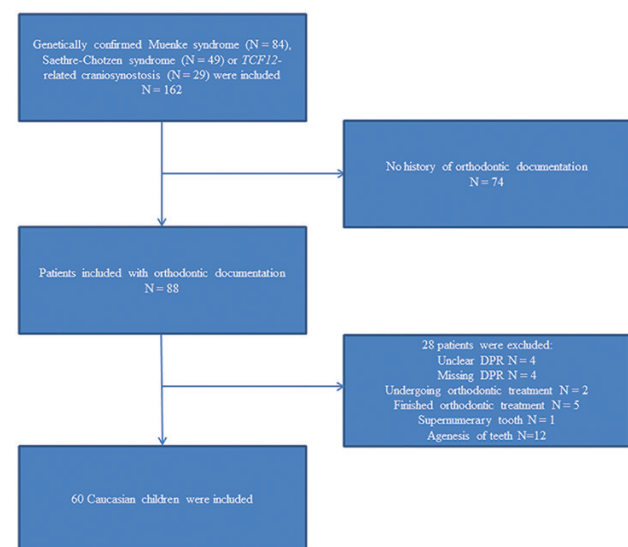


Figure 1. Flowchart displays the patient selection process. DPR, dental panoramic radiograph.

The final study group (syndromic group) consisted of 60 Dutch patients with a mean age of 9.17 years [standard deviation (SD): 2.19]. The group included 36 females (mean age 9.12 years, SD 2.15) and 24 males (mean age 9.24 years, SD 2.28). Of these, 38 patients (18 boys and 20 girls) had Muenke syndrome, with a mean age of 9.66 years (SD 2.12); 17 patients (5 boys and 12 girls) had Saethre-Chotzen syndrome, with a mean age of 8.23 years (SD 2.27); and 5 patients (1 boy and 4 girls) had *TCF12*-related craniosynostosis, with a mean age of 8.61 years (SD 1.39).

The included dental panoramic radiographs were for children between 5.80 and 16.83 years old that were born between 1982 and 2012.

### Control group

The control group consisted of 451 children without a syndrome. The mean age was 8.60 years (SD 3.76), 225 were boys (mean age: 8.27 years, SD 3.63) and 226 were girls (mean age, 8.91 years, SD 3.86). All children had undergone general dentistry at the Academic Centre for Dentistry, Amsterdam, the Netherlands. We included dental panoramic radiographs that were performed in children between 2.9 and 16.9 years old that were born between 1972 and 1993. The dental panoramic radiographs had to be of good quality, with no tooth agenesis or extractions, and no twins were permitted. An effort was made to include solely Caucasian patients by checking the surname of the patients and excluding those that suggested a non-Caucasian background. Thus, the control group was representative of the Dutch population. Further details on the study design and data collection are described elsewhere (28).

### Dental maturity scores

Prior to scoring the twenty dental panoramic radiographs, two raters were trained in the tutorial programme produced by Demirjian, which is available on CD-ROM, (Demirjian, 1993–1994). According to Demirjian (25), the dental maturity score was determined by calculating the cumulative score of the stages of calcification in the teeth in the lower left quadrant on panoramic radiographs (i.e. from the first incisor to the second molar). The scoring procedure for this study was performed by one rater. Subsequently, the dental age was calculated by converting the cumulative dental maturity scores. The scores were calculated separately for boys and girls (29).

### Measurement error

To determine intra-rater reliability, each rater rescored 20 randomly selected radiographs at 2 weeks after the first scores were determined. Inter-rater reliability was determined by having a second investigator rate the same 20 panoramic radiographs. The intra-rater reliability and the inter-rater agreement were calculated with the intraclass correlation coefficient (ICC). A correlation coefficient of at least 0.75 was considered to indicate high reliability (30). For this study, we used the scores from one rater.

### Statistics

For each member of the syndromic group, we analysed the panoramic radiograph that was acquired when the patient's age was closest to the mean age of the control group. We performed descriptive statistics to characterize the study population. Categorical data are expressed as absolute numbers and percentages, and continuous data are expressed as the mean value and standard deviation (SD).

The normality of the data distribution was assessed visually with histograms. We used parametric tests for normally distributed data and non-parametric tests for data that were not normally distributed.

Dental age was calculated, based on the dental maturity score, as described previously (25, 29). We compared the biological ages and dental ages between the three syndromic groups and the control group with ANOVA. We compared the dental maturity score among groups with the Kruskal–Wallis test, and we compared the sex distributions among groups with the chi-square test. The dental maturity scores were compared between groups with the Mann–Whitney *U* test. When we assessed differences in dental maturity scores between the syndromic group and the control group, we stratified age in the following categories: 5–8 years (primary dentition stage to mixed dentition stage), 8–10 years (inter-transitional stage), and 10–15 years (mixed dentition stage to permanent dentition stage). Dental maturity score data were plotted and analysed with logistic curve fitting, as described previously (18, 28).

The difference between the biological age and the dental age (biological-dental age difference) was analysed in each group with a one-sample *t*-test, and among all four groups (Muenke versus Saethre-Chotzen syndrome versus *TCF12*-related craniosynostosis versus control group) with a one-way ANOVA. The biological-dental age difference was compared between two groups with an independent sample *t*-test. The biological-dental age difference was adjusted for age and gender differences between the groups in the linear regression analysis. Outcomes of the linear regression analysis are presented as the unstandardized beta ( $\beta$ ), with the 95% confidence interval (95% CI), and the *P*-value. A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp., Release 2016; Armonk, New York, USA).

## Results

### Rater reliability

The ICC for intra-rater reliability ranged from 0.966 to 0.993. The ICC for inter-rater agreement ranged from 0.858 to 0.978.

### Study population

For all age categories, the syndromic groups were not significantly different in age (5–8 years:  $P = 0.885$ ; 8–10 years:  $P = 0.614$ ; 10–15 years:  $P = 0.134$ ) or gender (5–8 years:  $P = 0.433$ ; 8–10 years:  $P = 0.369$ ; 10–15 years:  $P = 0.275$ ) from the control group. The characteristics of the study population are presented in Table 1, and the age distribution of the patients are presented in Figure 2a–2d.

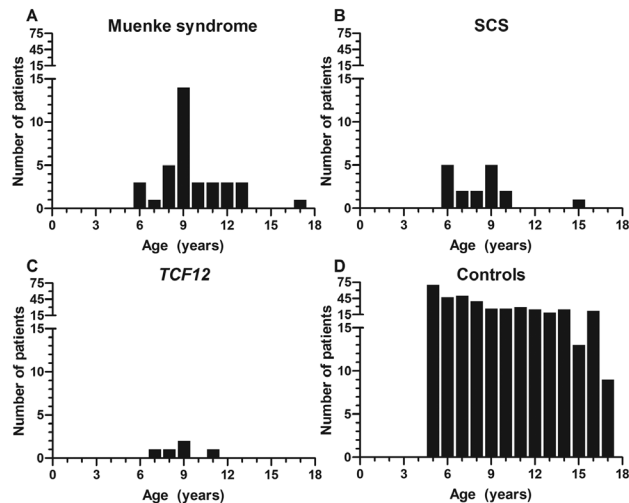
### Difference in dental maturity scores in 5- to 8-year-old age groups

We found that the dental maturity scores were significantly different in patients with Muenke syndrome, Saethre-Chotzen syndrome, and *TCF12*-related craniosynostosis, compared with the control group ( $P = 0.010$ ). A post-hoc analysis showed that the dental maturity score was significantly lower in 5- to 8-year-old patients with Muenke syndrome ( $39.85 \pm 8.98$ ;  $n = 4$ ) compared with individuals in the control group ( $60.36 \pm 14.04$ ;  $P = 0.007$ ;  $n = 156$ ). The dental maturity scores were not significantly different in patients with Saethre-Chotzen syndrome ( $51.06 \pm 12.02$ ;  $n = 8$ ) compared with individuals in the control group, respectively,  $51.06 \pm 12.02$

**Table 1.** Baseline characteristics of children with genetic syndromes and healthy controls.

	Muenke ( <i>n</i> = 38)	SCS ( <i>n</i> = 17)	<i>TCF12</i> ( <i>n</i> = 5)	Controls ( <i>n</i> = 451)	<i>P</i> -value
Age (years)	9.66 ± 2.12	8.23 ± 2.27	8.61 ± 1.39	8.60 ± 3.76	0.356
Female, number (%)	20 (52.6%)	12 (70.6%)	4 (80.0%)	225 (50.0%)	0.212
Dental maturity score	82.66 ± 18.47	65.22 ± 19.43	72.08 ± 21.99	70.67 ± 26.44	0.138
Dental age	10.16 ± 2.71	8.16 ± 2.36	8.90 ± 2.35	9.23 ± 3.84	0.283

Data are presented as the mean ± standard deviation, unless otherwise specified. SCS, Saethre-Chotzen syndrome; *TCF12*, *TCF12*-related craniosynostosis. *P*-values indicate comparisons between the three syndromic groups and the control group. Comparisons of biologic age and dental age were evaluated with ANOVA; comparisons of the number of females was evaluated with the chi-square test; and comparisons of dental maturity scores were evaluated with the Kruskal–Wallis test.



**Figure 2.** Age distributions of patients with Muenke syndrome (a), Saethre-Chotzen syndrome (SCS) (b), or *TCF12*-related craniosynostosis (*TCF12*) (c), and the control group (d).

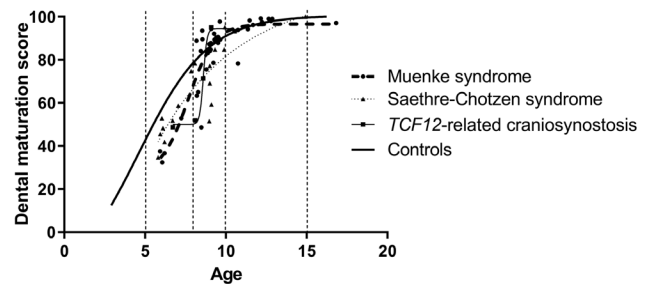
versus ( $60.36 \pm 14.04$ ;  $P = 0.062$ ; **Figures 3** and **4a**). We did not perform this calculation for patients between 5 and 8 years old with *TCF12*-related craniosynostosis, due to the small number of patients in this group.

#### Difference in dental maturity scores in 8- to 10-year-old age groups

The dental maturity score was not significantly different between patients with Muenke syndrome ( $83.95 \pm 11.35$ ;  $n = 23$ ) and individuals in the control group ( $84.72 \pm 8.29$ ;  $P = 0.847$ ;  $n = 58$ ). However, the dental maturity score was significantly lower in patients with Saethre-Chotzen syndrome ( $75.03 \pm 14.37$ ;  $n = 8$ ) compared with individuals in the control group ( $84.72 \pm 8.29$ ;  $P = 0.044$ ; **Figures 3** and **4b**). The dental maturity score was not significantly different in patients with *TCF12*-related craniosynostosis ( $72.80 \pm 21.63$ ;  $n = 3$ ) compared with individuals in the control group ( $84.72 \pm 8.29$ ;  $P = 0.383$ ; **Figures 3** and **4b**).

#### Difference in dental maturity scores in 10- to 15-year-old age groups

The dental maturity score was not significantly different in patients with Muenke syndrome ( $95.36 \pm 6.30$ ;  $n = 10$ ) compared with individuals in the control group ( $96.69 \pm 4.07$ ;  $P = 0.314$ ;  $n = 121$ ). We did not perform this calculation for patients between 10 and 15 years old with Saethre-Chotzen syndrome or *TCF12*-related craniosynostosis (**Figures 3** and **4c**).



**Figure 3.** Dental maturity scores according to age. Logistic curve fit shows that, in most groups, dental maturation occurs before the age of 10 years. Vertical lines indicate the age groups analysed.

#### Difference between biological age and dental age

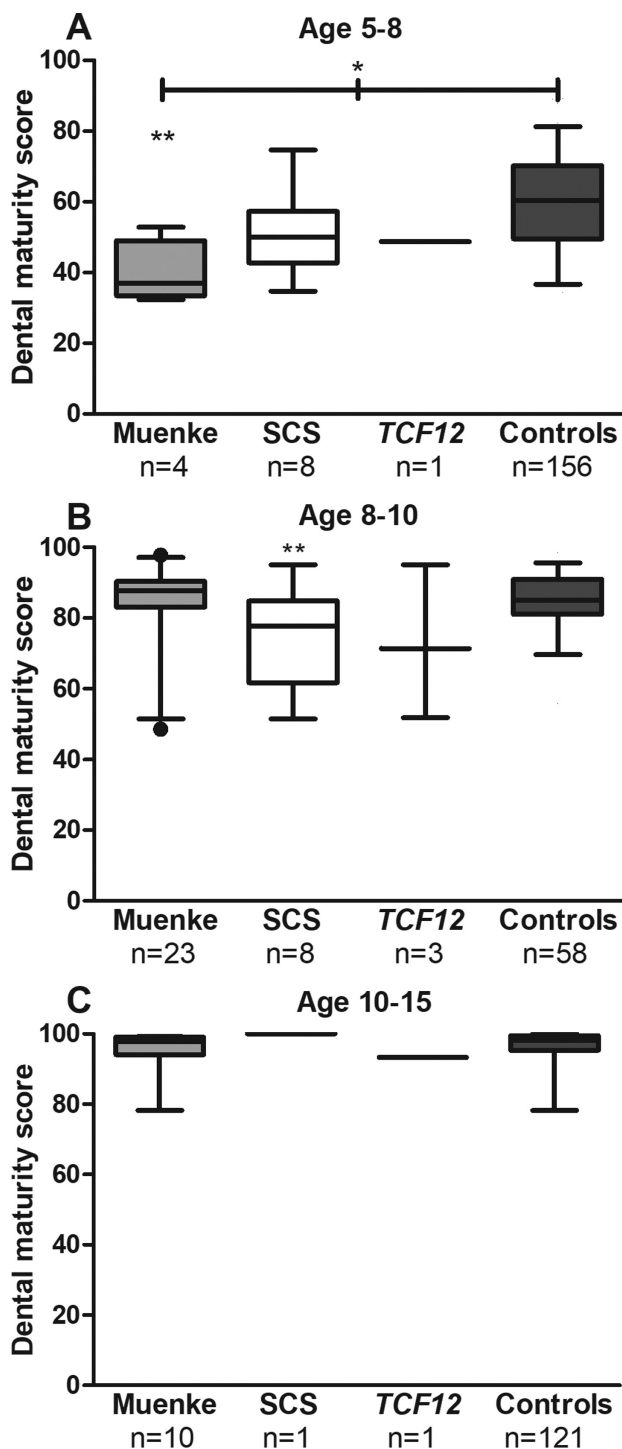
The biological age was significantly different from dental age in patients with Muenke syndrome ( $-0.51 \pm 1.47$ ,  $P = 0.040$ ). The biological age was also different from dental age in controls ( $-0.63 \pm 1.00$ ,  $P < 0.001$ ). In patients with Saethre-Chotzen syndrome ( $0.07 \pm 0.99$ ,  $P = 0.764$ ) and *TCF12*-related craniosynostosis ( $-0.29 \pm 1.38$ ,  $P = 0.666$ ; **Table 2**) the biological age was not different from dental age.

The biological-dental age difference was similar between patients with Muenke syndrome ( $-0.51 \pm 1.47$ ) and the controls ( $-0.63 \pm 1.00$ ;  $P = 0.627$ ). However, the biological-dental age difference was significantly lower in patients with Saethre-Chotzen syndrome ( $0.07 \pm 0.99$ ) compared with the controls ( $-0.63 \pm 1.00$ ;  $P = 0.005$ ). Although the biological-dental age difference was not significantly different between patients with *TCF12*-related craniosynostosis ( $-0.29 \pm 1.38$ ) and the controls ( $-0.63 \pm 1.00$ ) ( $P = 0.450$ ), the effect sizes suggested a difference between these groups.

After adjusting for age and sex, the biological-dental age difference remained higher in patients with Saethre-Chotzen syndrome compared with controls ( $\beta = 0.711$ , 95% CI: 0.224; 1.198;  $P = 0.004$ ). In patients with Muenke syndrome and *TCF12*-related craniosynostosis, the biological-dental age differences were similar to that of controls ( $\beta = 0.110$ , 95% CI:  $-0.237$ ; 0.458,  $P = 0.533$  for Muenke; and  $\beta = 0.339$ , 95% CI:  $-0.550$ ; 1.228,  $P = 0.454$ , for *TCF12*-related craniosynostosis).

#### Discussion

This retrospective cohort study showed that 5- to 8-year-old patients with Muenke syndrome displayed, on average, a one-year delay in dental development compared with control Dutch patients ( $P = 0.007$ ). However, we did not detect significant differences in



**Figure 4.** Dental maturity scores according to different ages and groups. Comparisons of dental maturity are shown for (a) children 5–8 years old; (b) children 8–10 years old; (c) children 10–15 years old. Data are presented as the median and 5–95 percentiles. \*Statistical significantly difference between the four groups  $P < 0.05$ . \*\*Statistical significantly difference in Muenke patients compared with the controls  $P < 0.05$ . SCS, Saethre-Chotzen syndrome; TCF12, TCF12-related craniosynostosis.

dental development between controls and patients with Muenke syndrome at ages 8–10 years ( $P = 0.847$ ) or 10–15 years ( $P = 0.314$ ). We also found that 8- to 10-year-old patients with Saethre-Chotzen

syndrome displayed a one-year delay in dental development compared with the control group ( $P = 0.044$ ). However, we did not detect significant differences in dental development between controls and patients with Saethre-Chotzen syndrome in the other age categories or patients of all ages with TCF12-related craniosynostosis. To our knowledge, no previous studies have assessed dental development in Muenke syndrome, Saethre-Chotzen syndrome, or TCF12-related craniosynostosis. Mutations in the *FGFR3*, *TWIST1*, and *TCF12* genes might cause both craniosynostosis and a delay in dental development (22, 31). However, which mutations in the *FGFR3*, *TWIST1*, and *TCF12* genes might influence dental development remains unknown, due to scarce research in this area. Furthermore, it is known that expression levels of *Fgfr3* is low in sutural osteogenic fronts during calvarial bone development. Also, the timing of expression of *Fgfr3* takes place at a later stage than *Fgfr1* and *Fgfr2*. Because *Fgfr3*, *TWIST1* and *TCF12* are in the same pathway as *Fgfr* but at a later stage, it is possible that dental development can take more alternative routes compared with *Fgfr2* (32). Therefore, more research should be conducted to unravel the relationship between mutations in the *FGFR3*, *TWIST1*, and *TCF12* genes and delayed dental development.

Previous studies found that, among patients with Apert or Crouzon syndromes, dental development was delayed in Caucasian girls compared with Dutch controls. Moreover, dental development was more delayed in Apert syndrome (1.62-year delay) than in Crouzon syndrome (mean 1.08 year delays). This may be due to a higher prevalence of tooth agenesis in these syndromes (21). Our results showed that patients with Muenke syndrome, Saethre-Chotzen syndrome, and TCF12-related craniosynostosis had less delay in dental development compared with patients with Apert or Crouzon syndrome. Also, we did not observe differences in dental development between boys and girls. However, a study in non-syndromic craniosynostosis described that the prevalence of tooth agenesis was not higher compared with normal children (33).

This study had some limitations. First, even before stratification, the small sample size made it difficult to show significant results. The five TCF12-related craniosynostosis patients can only be regarded as case reports, since the number of patients in each age category is too few to perform statistical analysis on. Moreover, the uneven distribution of patients in our study groups might have led to unclear outcomes. For example, we could not detect significant delays in dental development in 8- to 10-year-old ( $P = 0.847$ ) or 10- to 15-year-old ( $P = 0.314$ ) patients with Muenke syndrome. However, our study population was relatively large, when the low prevalences of these syndromes are taken into account. Additionally, we felt that separating patients with Saethre-Chotzen syndrome from those with TCF12-related craniosynostosis was important to maintain data validity and clarity for future researchers interested in these two syndromes.

Another potential limitation was that the children in our syndromic group were born 10–20 years later than the children in our Dutch control group. During that period, there was a positive temporal trend in dental development among Dutch children (34). Consequently, we might expect a difference in dental development between children in the syndromic group and children in the control group that was solely based on the era of birth. Despite this potential bias, we selected the control group because it was the best Dutch growth study conducted that included children within an age range comparable to the age range of patients in our cohort. In the present study, we found no difference

**Table 2.** Difference between biological age and dental age, calculated for all individuals in each group (total population) and for individuals in each group with a DMS below 100.

	Total population ( <i>n</i> = 551)			DMS < 100 ( <i>n</i> = 453)	
	Mean difference ± SD	<i>P</i> -value per group*	<i>P</i> -value compared with controls**	Mean difference ± SD	<i>P</i> -value per group*
Muenke ( <i>n</i> = 38)	-0.51 ± 1.47	0.040	0.627	-0.51 ± 1.47	0.040
SCS ( <i>n</i> = 17)	0.07 ± 0.99	0.764	0.005	0.14 ± 0.97	0.561
TCF12 ( <i>n</i> = 5)	-0.29 ± 1.38	0.666	0.450	-0.29 ± 1.38	0.666
Controls ( <i>n</i> = 451)	-0.63 ± 1.00	<0.001	—	-0.59 ± 0.96	<0.001

DMS, dental maturity score; SD, standard deviation.

\*Outcomes of one-sample *t*-test.

\*\*Outcomes of independent *t*-test.

in dental development between these two groups. However, in theory, our syndromic group might have shown delayed dental development, if we had compared them to a more contemporary Dutch control group.

Despite these limitations, our results provided some guidance for orthodontists in treating patients with these syndromes. From a clinical perspective, it might be advisable to consider growth disturbances in patients with Muenke syndrome or Saethre-Chotzen syndrome. Clinicians should be aware that 5- to 8-year-old children with Muenke syndrome and 8- to 10-year-old children with Saethre-Chotzen syndrome display delayed dental development. This should be taken into account for orthodontic diagnoses and treatment planning and is especially important with a two-phase treatment where facial orthopedics with functional appliances is performed at a young age. The subsequent orthodontic phase with fixed appliances could be different in timing than in non-syndromic patients. In addition, due to the rarity of all these syndromes, we suggest that these patients should be referred to a craniofacial team to provide a multi-disciplinary approach.

## Conclusions

Our findings have improved the understanding of dental development in patients with Muenke and Saethre-Chotzen syndrome. We showed that children between 5 and 8 years old with Muenke syndrome and children between 8 and 10 years old with Saethre-Chotzen syndrome have delayed dental development compared with Dutch children without syndromes. The one-year delay in dental maturity was seen in different age categories in Muenke and Saethre-Chotzen syndromes. In both groups, the catch-up in dental maturity was timely. The timing of the start of potential orthodontic treatment in children with Muenke and Saethre-Chotzen syndrome is delayed in certain dental stages compared with healthy children. This information can provide guidance on whether the orthodontist should consider growth disturbances related to dental development in treatment plans.

## Acknowledgements

We would like to thank Dr. F. Atiq for his contribution to the statistical analysis.

## Conflicts of interest

None to declare.

## Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. Data will be shared on reasonable request to the corresponding author.

## References

- French, L.R., Jackson, I.T. and Melton, L.J., III. (1990) A population-based study of craniosynostosis. *Journal of Clinical Epidemiology*, 43, 69–73.
- Lajeunie, E., Le Merrer, M., Bonaiti-Pellie, C., Marchac, D. and Renier, D. (1995) Genetic study of nonsyndromic coronal craniosynostosis. *American Journal of Medical Genetics*, 55, 500–504.
- Singer, S., Bower, C., Southall, P. and Goldblatt, J. (1999) Craniosynostosis in Western Australia, 1980–1994: a population-based study. *American Journal of Medical Genetics*, 83, 382–387.
- Boulet, S.L., Rasmussen, S.A. and Honein, M.A. (2008) A population-based study of craniosynostosis in metropolitan Atlanta, 1989–2003. *American Journal of Medical Genetics*, 146A, 984–991.
- Kweldam, C.F., van der Vlugt, J.J. and van der Meulen, J.J. (2011) The incidence of craniosynostosis in the Netherlands, 1997–2007. *Journal of Plastic Reconstructive Aesthetic Surgery*, 64, 583–588.
- Cornelissen, M., Ottelander, B.d., Rizopoulos, D., van der Hulst, R., Mink van der Molen, A., van der Horst, C., Delye, H., van Veelen, M.L., Bonsel, G. and Mathijssen, I. (2016) Increase of prevalence of craniosynostosis. *Journal of Cranio-Maxillo-Facial Surgery*, 44, 1273–1279.
- Goos, J.A., et al. (2016) Identification of intragenic exon deletions and duplication of TCF12 by whole genome or targeted sequencing as a cause of TCF12-related craniosynostosis. *Human Mutation*, 37, 732–736.
- Muenke, M., et al. (1997) A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) defines a new craniosynostosis syndrome. *American Journal of Human Genetics*, 60, 555–564.
- Howard, T.D., Paznekas, W.A., Green, E.D., Chiang, L.C., Ma, N., Ortiz de Luna, R.I., Garcia Delgado, C., Gonzalez-Ramos, M., Kline, A.D. and Jabs, E.W. (1997) Mutations in TWIST, a basic helix-loop-helix transcription factor, in Saethre-Chotzen syndrome. *Nature Genetics*, 15, 36–41.
- El Ghouzzi, V., Lajeunie, E., Le Merrer, M., Cormier-Daire, V., Renier, D., Munnich, A. and Bonaventure, J. (1999) Mutations within or upstream of the basic helix-loop-helix domain of the TWIST gene are specific to Saethre-Chotzen syndrome. *European Journal of Human Genetics*, 7, 27–33.
- Sharma, V.P., et al.; 500 Whole-Genome Sequences (WGS500) Consortium. (2013) Mutations in TCF12, encoding a basic helix-loop-helix partner of TWIST1, are a frequent cause of coronal craniosynostosis. *Nature Genetics*, 45, 304–307.
- Reitsma, J.H., Ongkosuwito, E.M., van Wijk, A.J. and Prah-Andersen, B. (2014) Patterns of tooth agenesis in patients with crouzon or apert syndrome. *The Cleft Palate-Craniofacial Journal* 51, 178–183.

13. de Jong, T., Mathijssen, I.M. and Hoogbeem, A.J. (2011) Additional phenotypic features of Muenke syndrome in 2 Dutch families. *The Journal of Craniofacial Surgery*, 22, 571–575.
14. Paumard-Hernández, B., et al. (2015) Expanding the mutation spectrum in 182 Spanish probands with craniosynostosis: identification and characterization of novel TCF12 variants. *European Journal of Human Genetics*, 23, 907–914.
15. Doherty, E.S., et al. (2007) Muenke syndrome (FGFR3-related craniosynostosis): expansion of the phenotype and review of the literature. *American Journal of Medical Genetics. Part A*, 143A, 3204–3215.
16. Gallagher, E.M., Ratisoontorn, C., Cunningham, M.L., Adam, M.P., Ardinger, H.H., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Mirzaa, G. and Amemiya, A. (2003) *Saethre-Chotzen Syndrome*. *GeneReviews*®. University of Washington, Seattle, WA, pp. 1993–2021.
17. Choi, T.M., Kragt, L., Goos, J.A.C., Mathijssen, I.M.J., Wolvius, E.B. and Ongkosuwito, E.M. (2019) Deviating dental arch morphology in mild coronal craniosynostosis syndromes. *Clinical Oral Investigations*, 23, 2995–3003.
18. Reitsma, J.H., Balk-Leurs, I.H., Ongkosuwito, E.M., Wattel, E. and Prah Andersen, B. (2014) Dental maturation in children with the syndrome of crouzon and apert. *The Cleft Palate-Craniofacial Journal*, 51, 639–644.
19. Nie, X., Luukko, K. and Kettunen, P. (2006) FGF signalling in craniofacial development and developmental disorders. *Oral Diseases*, 12, 102–111.
20. Li, C.Y., Prochazka, J., Goodwin, A.F. and Klein, O.D. (2014) Fibroblast growth factor signaling in mammalian tooth development. *Odontology*, 102, 1–13.
21. Meng, T., Huang, Y., Wang, S., Zhang, H., Dechow, P.C., Wang, X., Qin, C., Shi, B., D'Souza, R.N. and Lu, Y. (2015) Twist1 is essential for tooth morphogenesis and odontoblast differentiation. *The Journal of Biological Chemistry*, 290, 29593–29602.
22. De Coster, P.J., Mortier, G., Marks, L.A. and Martens, L.C. (2007) Cranial suture biology and dental development: genetic and clinical perspectives. *Journal of Oral Pathology & Medicine*, 36, 447–455.
23. Parsons, T.E., Weinberg, S.M., Khaksarfard, K., Howie, R.N., Elsalanty, M., Yu, J.C. and Cray, J.J. Jr. (2014) Craniofacial shape variation in Twist1+/- mutant mice. *Anatomical Record (Hoboken, N.J.: 2007)*, 297, 826–833.
24. Kettunen, P., Laurikkala, J., Itäranta, P., Vainio, S., Itoh, N. and Thesleff, I. (2000) Associations of FGF-3 and FGF-10 with signaling networks regulating tooth morphogenesis. *Developmental Dynamics*, 219, 322–332.
25. Demirjian, A., Goldstein, H. and Tanner, J.M. (1973) A new system of dental age assessment. *Human Biology*, 45, 211–227.
26. Patel, P.S., Chaudhary, A.R., Dudhia, B.B., Bhatia, P.V., Soni, N.C. and Jani, Y.V. (2015) Accuracy of two dental and one skeletal age estimation methods in 6–16 year old Gujarati children. *Journal of Forensic Dental Sciences*, 7, 18–27.
27. Lebbe, A., Cadenas de Llano-Pérula, M., Thevissen, P., Verdonck, A., Fieuws, S. and Willems, G. (2017) Dental development in patients with agenesis. *International Journal of Legal Medicine*, 131, 537–546.
28. Leurs, I.H., Wattel, E., Aartman, I.H., Ety, E. and Prah Andersen, B. (2005) Dental age in Dutch children. *European Journal of Orthodontics*, 27, 309–314.
29. Demirjian, A. and Goldstein, H. (1976) New systems for dental maturity based on seven and four teeth. *Annals of Human Biology*, 3, 411–421.
30. Shrout, P.E. and Fleiss, J.L. (1979) Intraclass correlations: uses in assessing rater reliability. *Psychological Bulletin*, 86, 420–428.
31. Wilke, T.A., Gubbels, S., Schwartz, J. and Richman, J.M. (1997) Expression of fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3) in the developing head and face. *Developmental Dynamics*, 210, 41–52.
32. Moosa S. and Wollnik B. (2016) Altered FGF signalling in congenital craniofacial and skeletal disorders. *Seminars in Cell and Developmental Biology*, 53, 115–125.
33. Leinonen, S., Rice, D., Leikola, J. and Heliövaara, A. (2021) Dental age, agenesis, and morphology in patients with operated single-suture Craniosynostoses. *The Cleft Palate-Craniofacial Journal*, 58, 290–298.
34. Vucic, S., de Vries, E., Eilers, P.H., Willemsen, S.P., Kuijpers, M.A., Prah Andersen, B., Jaddoe, V.W., Hofman, A., Wolvius, E.B. and Ongkosuwito, E.M. (2014) Secular trend of dental development in Dutch children. *American Journal of Physical Anthropology*, 155, 91–98.