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Dental transposition as a disorder of genetic origin

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SUMMARY A sample of 85 dental transpositions in 75 subjects (27 male, 48 female; mean age at diagnosis 12.25 years) involving both maxillary and mandibular arches was analysed using dental panoramic radiographs and clinical records.

Transposition affected the maxillary dentition (76 per cent) more frequently than the mandibular dentition (24 per cent). Unilateral transposition accounted for 88 per cent of cases, with the maxilla being involved more commonly than the mandible. Overall, the most common transposition involved the maxillary canine and first premolar (58 per cent). Considering the jaws in isolation, the canine and first premolar were the most commonly affected teeth in the maxilla (83 per cent) whilst in the mandible, the canine and lateral incisor teeth were most commonly transposed (73 per cent). No significant difference in symmetrical distribution of the unilateral transposition sample occurred. There was evidence of associated hypodontia in 41 per cent of the sample; however, if third molars were excluded, this figure decreased to 25 per cent. Peg-shaped maxillary lateral incisors were judged to be present in 27 per cent of subjects, whilst 41 per cent had retained primary teeth; all of these, except one, were primary canines. Overall, the majority of the sample (76 per cent) demonstrated at least one of the dental anomalies under investigation.

Multivariate analysis showed associations between unilateral transposition, gender, and the presence of peg-shaped maxillary lateral incisors; whilst bilateral transposition was more closely associated with gender and the presence of retained primary teeth. There was a poor association between both unilateral and bilateral transposition and hypodontia. Together, these results suggest a mutifactorial aetiology to this disorder, with both genetic and environmental factors playing an important role.

Introduction

Dental transposition is the positional interchange of two adjacent teeth, or the development or eruption of a tooth in a position normally occupied by a non-adjacent tooth (Peck *et al.*, 1993). In the general population the prevalence of this anomaly varies according to sample, but remains under 1 per cent in most investigations (Ruprecht *et al.*, 1985; Sandham and Harvie, 1985; Burnett, 1999). Dental transposition can affect the maxillary (Peck and Peck, 1995; Chattopadhyay and Srinivas, 1996; Plunkett *et al*., 1998; Shapira and Kuftinec, 2001) or mandibular (Peck *et al.*, 1998; Plunkett *et al.*, 1998) dentition, either unilaterally or bilaterally (Figure 1); however, the canine tooth is almost always affected, with the majority of cases involving the canine/first premolar in the maxilla (Peck *et al.*, 1993) and canine/lateral incisor in the mandible (Peck *et al.*, 1998).

Several theories have been proposed to account for dental transposition, including the interchange of developing tooth buds (Peck *et al.*, 1993, 1998), altered eruption paths (Gholston and Williams, 1984), the presence of retained primary teeth (Laptook and Silling, 1983) and trauma (Dayal *et al.*, 1983). However, many types of transposition have been associated with factors that have a genetic basis, including female predilection (Peck *et al.*, 1993, 1998; Plunkett *et al.*, 1998; Shapira and Kuftinec, 2001), unilateral left-sided dominance (Peck *et al.*, 1993; Shapira and Kuftinec, 2001), hypodontia (Peck *et al.*, 1993, 1998; Plunkett *et al.*, 1998; Shapira and Kuftinec, 2001), peg-shaped maxillary lateral incisor teeth (Peck *et al.*, 1993, 1998; Plunkett *et al.*, 1998; Shapira and Kuftinec, 2001), retained primary teeth (Shapira and Kuftinec, 2001) and Down syndrome (Shapira *et al.*, 2000). On this basis it has been suggested that the fundamental aetiology for dental transposition is genetic, within a model of multifactorial inheritance (Peck *et al.*, 1993, 1998).

To date, there have been few investigations of dental transposition with original samples of over 50 subjects (Peck *et al.*, 1993, 1998; Peck and Peck, 1995; Plunkett *et al.*, 1998; Shapira and Kuftinec, 2001). Although associations have been found between transposition and a variety of dental anomalies, most of these studies have employed relatively simple descriptive statistics (Peck *et al.*, 1993, 1998; Plunkett *et al.*, 1998; Shapira and Kuftinec, 2001). The aim of this study was to investigate the clinical features associated with dental transposition and to evaluate the aetiological basis of this condition using both descriptive and multivariate analysis.

Subjects and methods

A total sample of 75 subjects, each demonstrating either maxillary or mandibular dental transposition, was collected

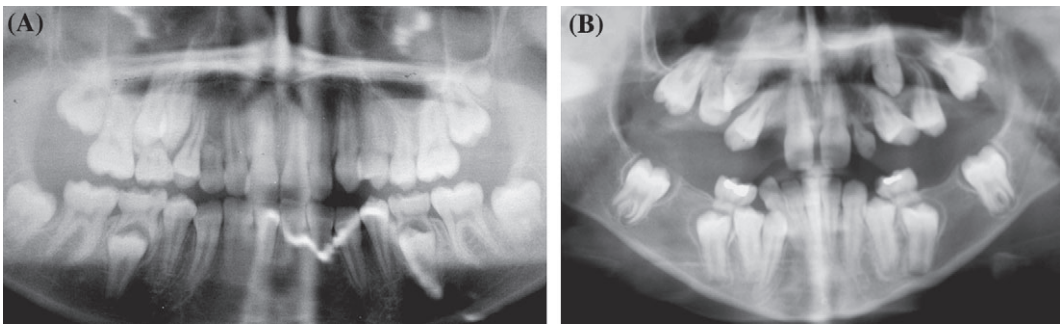

Figure 1 Panoramic radiographs demonstrating (A) right-sided unilateral transposition of the maxillary canine and first premolar teeth, and (B) bilateral transposition of the maxillary canine and first premolar teeth.

from several hospital orthodontic departments and specialist orthodontic practices in London and the south east of England. The following were recorded for each subject:

1. Classification of transposition
2. Age at diagnosis
3. Gender
4. Presence of hypodontia
5. Presence of peg-shaped maxillary lateral incisors
6. Presence of retained primary teeth

The sample consisted of 27 males (36 per cent) and 48 females (64 per cent; Table 1). The mean age at diagnosis was 12.25 years. Panoramic radiographs were available for all subjects included in the study. These were used to confirm the presence of a true transposition, involving both the crown and root of the affected teeth. Associated peg-shaped maxillary lateral incisors, hypodontia and the presence of retained primary teeth were ascertained from both the panoramic radiographs and clinical records. A lateral incisor was defined as peg-shaped when the mesio-distal width was greatest at the cervical margin (Becker *et al.*, 1981).

Statistical analysis

Multivariate analysis was applied to the sample using biplots (Gabriel, 1971). Data were analysed using Stata Statistical Software version 8.2 (StataCorp 2003, College Station, Texas, USA); where appropriate, significance was pre-determined at $\alpha = 0.05$.

Results

Descriptive statistics

Each transposition was considered as a separate entity, which gave a total sample of 85, the distribution of which is shown in Figure 2. Unilateral transposition was by far the most common type, consisting of 66 cases (88 per cent). In contrast, bilateral transposition was only seen in nine cases (12 per cent). Transposition affected the maxillary (76 per cent) far more frequently than the mandibular (24 per cent) dentition. The most common transposition in the sample involved the maxillary canine and first premolar (58 per cent). Considering the jaws in isolation, the canine and first premolar were the most commonly affected teeth in the maxilla (83 per cent), whilst in the mandible, the canine and lateral incisor teeth were most commonly transposed (73 per cent). Overall, there was no significant difference in symmetrical distribution of the unilateral transposition sample. However, in the male sample the majority of unilateral transpositions were left-sided (63 per cent), whilst in females, the majority were right-sided (58 per cent).

Evidence of associated hypodontia was analysed at three levels. Thirty-one subjects (41 per cent) demonstrated some form of hypodontia; however, if isolated third molar hypodontia was excluded from the sample, this figure reduced to 25 per cent. It has been suggested that 85 per cent of third molars are visible radiographically by 12 years of age (Clow, 1984); application of this criterion resulted in 26 cases (35 per cent) being diagnosed with hypodontia. Peg-shaped maxillary lateral incisors were judged to be present in 20 cases (27 per cent). Retained primary teeth were present in 31 subjects (41 per cent) and 84 per cent of these were in the maxilla; all except one were primary canines. In the sample as a whole, 57 cases (76 per cent) exhibited at least one dental anomaly.

Biplot analysis

Biplots allowed a detailed visualization of the relationships between different classifications of dental transposition and certain associated dental features. Firstly, unilateral and bilateral transposition cases were analysed. For cases demonstrating unilateral transposition (Figure 3A) an association was found to exist between the gender of the subject and the presence of peg-shaped maxillary incisors; however, this was not strong. In addition, there was a poor association with the presence of hypodontia or retained primary teeth. In this sample, the presence of hypodontia was, however, closely associated with retention of the primary dentition. In contrast, bilateral transposition was

Table 1 Raw data for the sample under analysis.

Case	Age	Transposition	Gender	Hypodontia	Peg 2/2	Retained primary teeth
1	9	1+2	M	LL5		
2	13	1	M	UL2, UR2		ULC
3	11	1	F	UL2, UR2, UR8, UL8, LL8		ULC
4	14	5	F			
5	10	7	M			
6	9	1+2	M		UR2, UL2	
7	13	8	F			
8	10	7	M			
9	9	1	M	UL2, UR8, UL8, LR8, LL8	UR2	ULB
10	14	1	F	UR2, LR8, LL8	UL2	
11	24	1	M			ULC
12	12	1	M			URC
13	10	2	F		UR2, UL2	
14	12	7	F	UL2, UR8, UL8, LR8, LL8		LRB
15	13	1	F		UR2, UL2	ULC
16	11	6	M		UR2	
17	9	8	F	UL2, UR2, LL8, LR8, UR8		LRB
18	16	2	F			URC
19	13	5	F	UR8, LR8, LR8, LL8	UR2, UL2	
20	13	1+2	F	UR2, UL2, UR8, UL8, LR8, LL8		
21	14	2	F	UR8, LR8, LL8	UL2	URC
22	12	6	F	LR8	UR2	URC
23	14	6	F			
24	7	7+8	F	UR8, UL8, LR8, LL8		
25	14	8	F	UR8, UL8, LR8, LL8, LR5, LL5		
26	14	4	F			
27	12	8	F		UR2, UL2	
28	10	8	M	UR8, UL8, LR8, LL8		
29	17	5	M		UL2	ULC
30	10	2	F			
31	8	1	M	UR8, UL8, LR8, LL8		
32	15	1+2	M			
33	14	4	F	UR8, UL8, UR5, UL5, UR2, UL2, LR8, LL8, LR7, LL7, LR5, LL5		
34	11	5	F			ULC
35	14	1	M			ULC
36	14	6	F			URC
37	12	2	F			
38	14	5	F		UR2, UL2	
39	11	1+2	M			
40	13	2	F	LL8	UR2, UL2	
41	9	2	F	UR8, UL8, LR8, LL8	UR2, UL2	
42	14	1	F	UR8, UL8, LR8, LL8, LL5	UR2, UL2	ULC
43	12	1	F	UR8, UL8	UR2, UL2	ULC
44	12	8	F			
45	12	1	M			ULC
46	12	8	F		UR2, UL2	
47	13	1	F	LL8	UR2, UL2	ULC
48	12	7	F		UR2, UL2	
49	13	2	M			URC
50	12	8	M			LRC
51	14	1	F	UL8		ULC
52	9	3+4	F	UR8, UL8, LR8, LL8		
53	14	2	M			
54	13	2	F			
55	12	1	M			ULC
56	14	6	F			
57	12	2	F			URC
58	12	2	F			URC
59	9	8	M			
60	14	1	F			ULC
61	10	7	F			
62	11	1	M	UR2, UL2, LR2, LL2		
63	12	4	M			ULC, URC
64	9	1	F	UR5, LR5, LL4, LL5		
65	13	4	F			

Table 1 (continued)

Case	Age	Transposition	Gender	Hypodontia	Peg 2/2	Retained primary teeth
66	15	2	F	Supp LR1	UR2, UL2	
67	14	2	M			URC
68	12	1	F	UL2, LR8, LL8		
69	12	2	M	LR5		
70	10	8	F			
71	14	1+3	M			ULC, URC
72	13	1+2	F	UR2, UL2		
73	12	7+8	F	UR5, UL5, LL5		LLB
74	12	1	M	UR2, UL2		
75	9	1	F	UR2, UL2		

Transposition type: (1) UL32; (2) UR34; (3) LL34; (4) LR34; (5) UL23; (6) UR23; (7) LL23; (8) LR23.

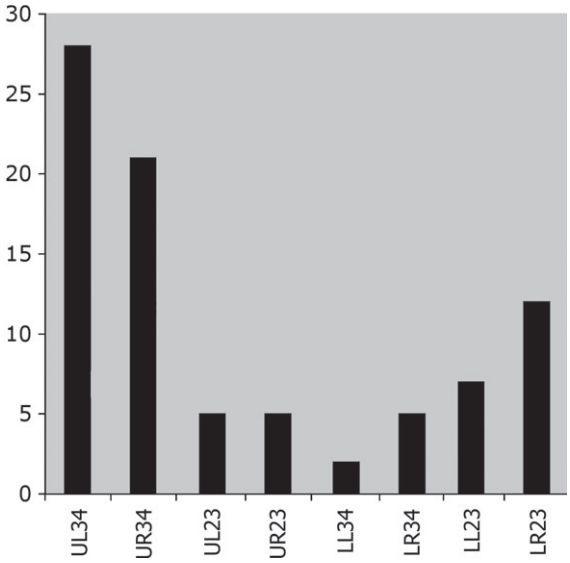

Figure 2 Distribution of transposition type within the sample (UL, upper left; UR, upper right; LL, lower left; LR, lower right).

more strongly associated with the presence of retained primary teeth and gender. The association with peg-shaped maxillary incisors and hypodontia was weak (Figure 3B).

The unilateral transposition group was further analysed for maxillary and mandibular arches in isolation. In the maxilla, a similar pattern emerged; transposition was more closely associated with gender and the presence of peg-shaped maxillary incisors, whilst hypodontia and retained primary teeth were weakly associated (Figure 3C). In the mandible, the pattern was similar, although a closer association existed with peg-shaped maxillary incisors (Figure 3D).

Discussion

This investigation focused upon 85 cases of dental transposition in 75 subjects. Within this group, maxillary transposition accounted for the majority of cases, which is broadly in agreement with previous studies (Peck *et al.*, 1993; Plunkett *et al.*, 1998; Shapira and Kuftinec, 2001) and most commonly involved the canine and first premolar (Peck *et al.*, 1993; Peck and Peck, 1995; Plunkett *et al.*, 1998; Shapira and Kuftinec, 2001). None involved the central incisors or molar teeth, consistent with these forms of transposition being extremely rare (Peck and Peck, 1995). In contrast to the maxilla, mandibular transposition was found to be a less common phenomenon, involving canine and lateral incisor teeth more frequently (Peck *et al.*, 1998; Plunkett *et al.*, 1998). Bilateral transposition was found to be less common than unilateral transposition in both arches (Peck *et al.*, 1993, 1998; Peck and Peck, 1995; Plunkett *et al.*, 1998; Shapira and Kuftinec 2001). In all of the bilateral cases, the same teeth were affected on each side; asymmetrical bilateral transposition is extremely rare (Al-Shawaf, 1988).

The majority of subjects demonstrated at least one of the dental anomalies under consideration. Hypodontia, both including and excluding third molars, peg-shaped maxillary lateral incisors and retained primary teeth were all observed with a prevalence greater than the population norm (Meskin and Gorlin, 1963; Muller *et al.*, 1970; Bot and Salmon, 1977; Mattheeuws *et al.*, 2004). This frequent association between dental anomalies within affected individuals provides a strong argument for a genetic basis to these conditions (Baccetti, 1998). Such findings, in association with dental transposition, have been used as a persuasive argument for a significant genetic basis for this condition in both arches (Peck *et al.*, 1993, 1998). However, studies that have focused upon canine transposition have also found evidence for local rather than genetic factors being the predominant aetiological component (Plunkett *et al.*, 1998; Shapira and Kuftinec, 2001).

The present study has highlighted the complex relationships that exist in the aetiology of dental transposition. The descriptive statistical analysis suggests a clear association between inherited dental anomalies and

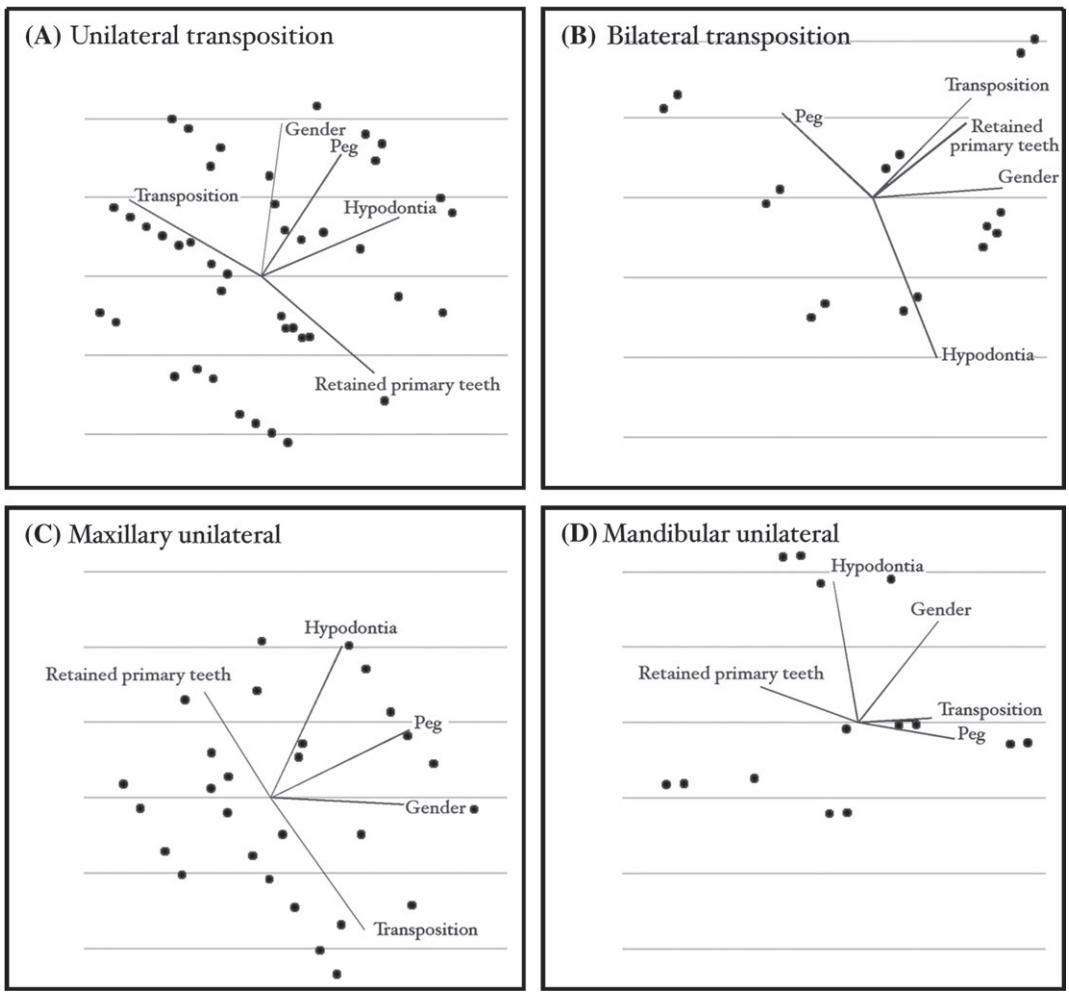

Figure 3 Biplot analysis showing the relationship between (A) unilateral, (B) bilateral, (C) maxillary unilateral, and (D) mandibular unilateral transposition, and gender, presence of retained primary teeth, hypodontia and diminutive peg-shaped maxillary lateral incisor teeth.

transposition; however, this is less clear when multivariate analysis was applied to the sample. Research into dental anomalies and the variable features associated with these conditions generates multivariate data sets where the value of simple tests for pairs of independent variables is limited. This type of analysis can lead to serious and incorrect errors of interpretation due to Simpson's paradox (Simpson, 1951; Everitt, 1995; Agresti and Coull, 1996). The association between two independent variables may be identical within the levels of a single third variable, but can take on a different value when the association measure is calculated from pooled data. To avoid this, the data were analysed using biplots (Gabriel, 1971). Biplots are the multivariate equivalent of the bivariate scatter plot. They are an approximation to the underlying multivariate distribution, typically in two dimensions, and representations of underlying variables are superimposed on the plot. Biplots are useful for the visual inspection of a multivariate data matrix, allowing the identification of patterns, regularities and outliers. Thus they are capable of graphically displaying large multivariate data sets with complex associations and interactions, and are closely related to principal component analysis in that the first dimension explains the highest attributable variance in the data set, the second dimension the second highest, and so on (Gabriel and Odoroff, 1990). The principle observations are plotted as points and the associated variables as vectors from the origin. Points lying close together have similar values and patterns, whilst the vectors represent correlations between variables; the smaller the angle the higher the correlation, and vectorial direction provides the sign of correlation. These plots therefore provide a useful visual description of the relationships within multivariate data sets (Gower and Hand, 1996).

Biplots demonstrated only a weak association between unilateral transposition and one dental anomaly under genetic influence, peg-shaped maxillary lateral incisors; this relationship being even weaker for bilateral transposition. Overall, the most surprising finding was the poor association between transposition and hypodontia, even

though the sample exhibited hypodontia at higher levels than might be expected in a normal population (Mader and Konzelman, 1979; Mattheeuws *et al.*, 2004).

Therefore, a fundamental question with regard to the aetiology of dental transposition is whether this condition has a purely genetic basis or if environmental factors play a role. The most likely explanation, certainly based upon the findings of this study, is that the condition represents a multifactorial disorder, with both genetic and environmental contributions being important. The purest argument for a genetic cause is that transposition arises during development, from a disturbance in the order of developing tooth follicles. In broad support of this is the knowledge that genes play an important role in patterning the dentition (Jernvall and Thesleff, 2000; Cobourne and Sharpe, 2003; Tucker and Sharpe, 2004). Combinatorial expression of homeobox-containing transcription factors pattern the presumptive dental axis prior to dental initiation, and manipulation of these domains can result in the transformation of tooth type (Sharpe, 1995; Tucker *et al.*, 1998). However, no mutations have been identified in any subjects demonstrating transposition. Indeed, mutations in several homeobox genes cause selective tooth agenesis rather than transposition, almost certainly because of the important reiterative role these genes play during the later stages of odontogenesis (Vastardis *et al.*, 1996; Stockton *et al.*, 2000; van den Boogaard *et al.*, 2000; Lammi *et al.*, 2003). Within such a purely genetic model, the canine tooth might be more commonly transposed because it lies at the boundary between the developing incisor and premolar fields of development, a region that is possibly more susceptible to particular thresholds of gene activity for normal patterning to occur (Thesleff, 1996). Indeed, Peck *et al.* (2002) used canine malposition as a model to suggest a molecular basis for this condition. The authors postulated that HOX genes may play a role, although this cannot be true because HOX genes are not expressed in the maxillary and mandibular primordia (Hunt and Krumlauf, 1991). It is not inconceivable, however, that other homeobox-containing transcription factors that are expressed in these regions may also be implicated in the aetiology of ectopic positioning of the canine.

However, the canine tooth has a long path of eruption, is theoretically more susceptible to deflection during its long eruptive descent, and is frequently associated with transposition. Opinions differ as to the relative contribution of genetics and environment in this eruptive process (Peck *et al.*, 1994, 1995; Becker, 1995), but there is currently too little robust statistical or genetic evidence to definitively ascribe malposition of the permanent canine as an isolated disorder of either genetics or environment. Certainly in non-syndromic forms of cleft lip and palate, both genetic mutations and environmental factors seem to play a role in defining thresholds of susceptibility within affected individuals (Cobourne, 2004).

Conclusions

The results of this investigation suggest that dental transposition represents a multifactorial condition. Both genetic and environmental factors seem to be involved in the aetiology of transposition and the relationships are complex. Large-scale population-based studies will be required to further refine our understanding of the genetics of this anomaly.

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