

# Orthodontics and foetal pathology: a personal view on craniofacial patterning

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**SUMMARY** This article summarizes the essentials of studies on the craniofacial skeleton performed over 17 years. It presents data from research into foetal pathology resulting in new views on craniofacial patterning and/or fields for further discussion.

The fields described cover all areas seen on profile, frontal, and panoramic radiographs. The fields are the theca, frontonasal, maxillary, palatine, and mandibular together with the cerebellar field and cervical spine. Regional fields in the dentition are described according to the pattern of peripheral nerve innervation. Studies on severely malformed fetuses show that the malformation can occur solely within a single field or in several fields. This is the background for these personal views on craniofacial patterning. These new views may assist in the diagnosis and interpretation of malformations in the cranium and dentition.

## Introduction

### *Foetal pathology*

Pathology is the field in medicine dealing with structural and functional changes in tissues and organs which cause or are caused by disease (Taylor, 1988). Foetal pathology is encountered in the foetus aborted either deliberately or spontaneously during the first trimesters of pregnancy (Keeling, 1994). Foetal pathology differs from general pathology in many ways; by focussing on the developmental disorders not compatible with life. The severity of foetal pathological conditions is more extreme than those seen after birth. Though less interest has traditionally been devoted to analysing these rare conditions, some pioneering researchers have been aware of the importance of diagnostics and systematization in the field of foetal pathology. New methods of prenatal diagnosis, particularly ultrasound, amniocentesis, and maternal serum alpha-fetoprotein estimation mean that many more severely malformed fetuses are identified and accordingly the need for exact prenatal diagnostics has significantly increased. Currently, the main textbooks in foetal pathology are Buyse (1990), Keeling (1993, 1994), Gilbert-Barness (1997), Gilbert-Barness and Debich-Spicer (2004), and Schumacher *et al.* (2004).

Even though the discipline of foetal pathology gained more focus during the 1990s, particularly cranial analysis of aborted fetuses is still random and unsystematic. Diagnosing cranial malformations requires a detailed insight into normal embryological development of each cranial bone component. Furthermore, easy and rapid methods for routine cranial autopsy are urgently needed.

Procedures for prenatal cranial analysis, based on faxitron radiography after procedures which were verified by serial sectioning and histological analysis of cranial components, were published by Kjær and Græm (1990) and shortly followed by research on abnormally developed foetal crania

(Kjær *et al.*, 1991). In the following years, a total of 42 studies were published dealing with the patterning of severe cranial malformations observed during foetal autopsy of specimens with known and unknown genotypes. This article presents the essentials of a selection of those studies.

### *Orthodontics*

In orthodontic diagnostics, craniofacial analysis of profile and frontal radiographs is currently based on advanced cephalometric methods. Diagnosis of the dentition and the supporting alveolar bone is based on analyses of panoramic radiographs. There are differences between the goals and possibilities of cranial analyses of children and adults and those performed before birth. When radiographically comparing orthodontics with foetal pathology, it is obvious that orthodontic studies are longitudinal aimed at predicting future growth and morphology for treatment planning, while those in foetal pathology are cross-sectional radiographic or histological studies intended for patho-anatomical diagnostics with a pathogenetic view to previous developmental stages.

The hypothesis initiating this research was that while a malformation in the cranium and dentition can affect all cranial tissue, it can also be limited to a specific region, which secondarily involves the rest of cranial development either by deformation or disruption. This distinction between malformation, deformation, and disruption has been defined by Spranger *et al.* (1982) and is generally used in foetal autopsy.

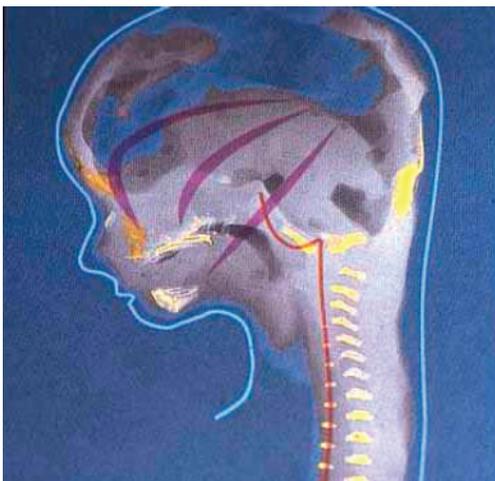
The present article clarifies some important developmental fields diagnosed in foetal pathology in the areas covered by the radiographs analysed daily in an orthodontic clinic. In order to elucidate how these fields can be defined, it is necessary to briefly outline the normal development of the face and cranium.

### Normal embryonic development

On the 28th gestational day, the germ disc closes and forms a neural tube by induction from the notochord. At the cranial end of this neural tube, edges are formed around the so-called, cranial neuropore. These edges are formed by neuroectoderm at the inner aspect and surface ectoderm at the outer aspect. From different areas on these edges, cells migrate anteriorly and form the cranium, face, and dentition. This cell migration was first described by Le Douarin and Teillet (1974). Since then, a number of experimental studies proving this cell migration have been performed. The migrating cells are called the neural crest cells. These cells migrate from different parts of the neural crest to different parts of the cranium and dentition with a well-defined sequence. During migration, the cells move the ectoderm of the face forward like an inflating balloon. The neural crest cells gradually fill up the area anterior to the neural tube. From this first tissue accumulation of neural crest cells, the jawbones and the teeth develop (Figure 1). The neural crest cells have the potency to form nerves, muscle, vessels, cartilage, and bone. For a review of the development of the cranium and dentition, see Kjær (1998a) and Kjær *et al.* (1999b). It is important to differentiate between the various parts or fields of the cranium and those of the dentition because different parts develop from different or similar areas on the neural crest. Thus, the different parts supposedly have different genetic backgrounds.

### Results and discussion

The locations of the six main fields registered in foetal pathology (Figure 2) are as follows:



**Figure 1** Schematic illustration of the midaxial contours and bones in a human foetus, gestational age 16 weeks. The bones are marked in yellow. The notochord is the red line surrounded by the vertebral corpora and the basilar part of the occipital bone. The purple lines exemplify pathways of different neural crest cells towards the jaws.

- Cerebellar and cervical spine (notochordal field)
- Theca (not shown) (induced from notochord and/or from neural crest cells)
- Frontonasal (antero-neural crest field)
- Maxillary (antero-median neural crest field)
- Palatine (postero-median neural crest field)
- Mandibular (posterior neural crest field).

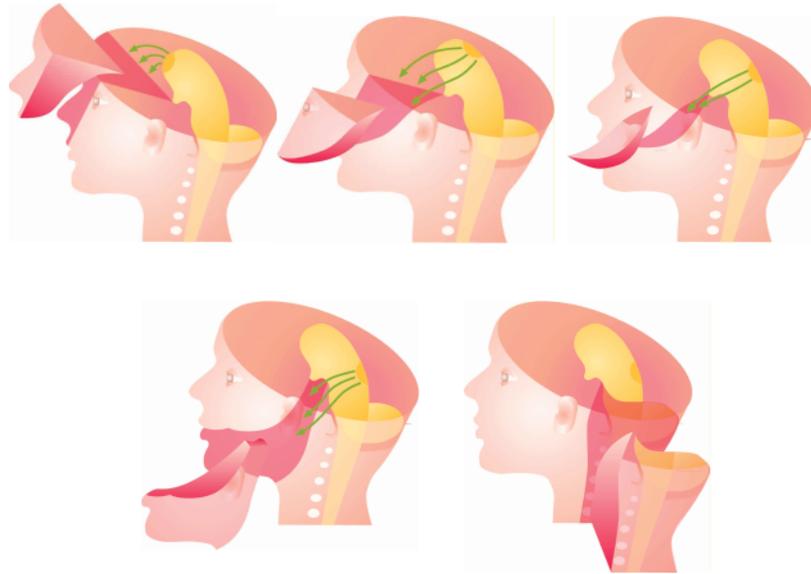
The borders between these embryonic fields have been determined by analysing the extent of malformations in severely malformed fetuses which is exemplified below. Some malformations occur solely within a field and some in more than one field.

### Pathological cranial development fields before birth

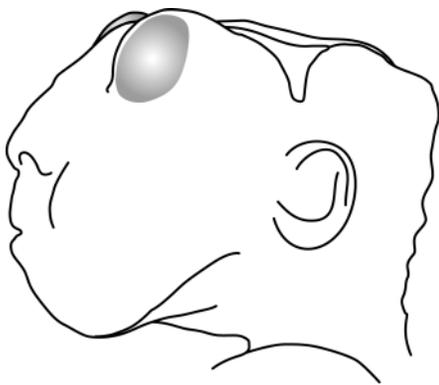
**Cerebellar and cervical spine.** The cerebellar and cervical spine field (Figure 2) has been examined in fetuses with anencephaly (Kjær *et al.*, 1994a; Lomholt *et al.*, 2004), amniotic band sequence (Keeling and Kjær, 1994), cranial encephalocele and myelomeningocele (Kjær *et al.*, 1996a), and Down syndrome (Lomholt *et al.*, 2003). It is characteristic that the cerebellar field is limited anteriorly by the structures originally formed from the notochord. These are the vertebral bodies, the basilar part of the occipital bone, and the post-sphenoid bone (Figure 2). Posteriorly, the cerebellar and cervical spine field are limited by the notochordally induced para-axial components, the cartilaginous part of the occipital bone, and the vertebral arches (Figure 2). The field is shaped like a funnel in which the main part of the brain stem, cerebellum, and cranial part of the spinal cord are located.

The different fields in the spine, i.e. cervical, thoracic lumbar, and coxygeal, have been studied in a series of fetuses with well-known genetic deviations such as trisomy 18 (Kjær *et al.*, 1996b), trisomy 21 (Keeling *et al.*, 1997), trisomy 13 (Kjær *et al.*, 1997a), and triploidy (Nolting *et al.*, 2002). Also spine malformations in several fetuses with unknown genotypes have been published. These studies showed that the malformations in different genetic disorders are more or less located in and limited to genotypically specific segments of the spine. For example, the osseous spine deviations in trisomy 21 are predominantly located in the cervical column and in trisomy 18 predominantly in the thoracic part of the column. Each genotype also has specific types of osseous malformations in the basilar part of the occipital bone and in the spine (Kjær *et al.*, 1994a, 1996b; Kjær, 1998a).

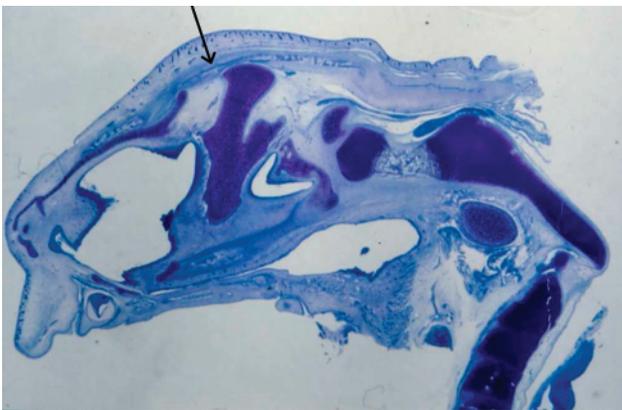
**Theca.** The theca field is in the anterior aspect located above the region of the anterior cranial fossa and in the posterior aspect above the cerebellar field. The borderline between the cerebellar and the theca fields is clearly visible in anencephaly where the hemispheres have not been formed resulting in absence of the theca field (Figure 3). Figure 4 shows a histological section of the foetus shown schematically in Figure 3 illustrating that only the upper part of the frontal bone (not visible) belongs to the theca



**Figure 2** Schematic drawings of the different cranial fields. Top row, from left to right: the frontonasal, maxillary, and palatine fields. Bottom row, left: the mandibular field, right: the cerebellar field.



**Figure 3** Drawing of a human anencephalic foetus, gestational age 16 weeks illustrating the lateral view of the head. Note that the theca field is absent.



**Figure 4** Histological section of the cranial base and maxilla of the anencephalic foetus shown schematically in Figure 3. Arrow marks the lower part of the frontal bone. Other parts of the theca cranii are not shown.

field. The theca field covers the outer aspects of the upper frontal, parietal, and cranial parts of the temporal lobes of the cerebral hemispheres (Silau *et al.*, 1995).

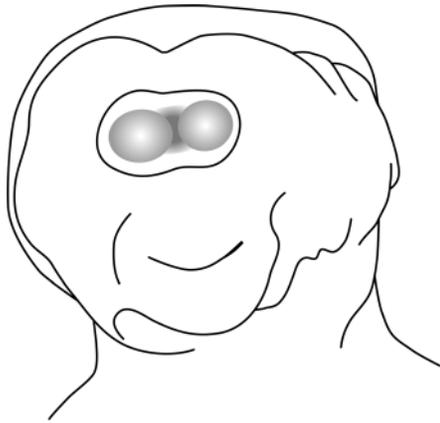
*Mandibular.* The extent of the mandibular field is illustrated in Figure 2. Localized malformations in the mandible are extremely rare. In order to illustrate the mandibular field, 302 normal third trimester anthropological hemi-mandibles were analysed (Chavéz-Lomelí *et al.*, 1996). In that study, three main fields within the mandibular field were demonstrated.

*Frontonasal.* The frontonasal field (Figure 2) was first defined based on eight foetuses with varying degrees of severity of holoprosencephaly (Kjær *et al.*, 1991). A human foetus with the most severe type of holoprosencephaly, cyclopia, is shown in Figure 5. In cyclopia, the frontonasal field has not developed.

*Maxillary and palatine.* The maxillary field forms the cranial part around the eyes and extends laterally to the upper lip, hard palate, sella turcica, and intervening tissue (Figure 2). The palatine field covers external aspects, the posterior bony palate, soft palate, and alveolar bone in the molar region. The two fields have been studied in cleft palate individuals (Lisson and Kjær, 1997; Hansen *et al.*, 2005) and in trisomy 21 (Lauridsen *et al.*, 2001, 2005).

*Transfer of prenatal field malformations to radiographs of children*

In publications based on prenatal material, the main focus has been on diagnosing osseous or dental malformations and



**Figure 5** Drawing of a human foetus, gestational age 13 weeks, with severe holoprosencephaly (cyclopia). Note close-set eyeballs and absence of the nose.

mapping the extent of the malformation in cranial fields. In later follow-ups on children with diagnoses identical to those studied prenatally, bony malformations have been localized in the same fields in children and adults. The actual fields viewed on the radiographs of children are shown in Figure 6.

Some examples of these follow-up studies are as follows:

*The cerebellar and cervical spine field.* Abnormal neural tube closure in myelomeningocele/spina bifida has revealed sella turcica malformations, which are identical pre- and post-natally (Kjær *et al.*, 1998b; Becktor *et al.*, 2000; Sonnesen *et al.*, 2007).

*The mandibular field.* Coordination in eruption times and deviations in eruption and tooth formation occur within subfields of the mandibular field (Kjær, 1997; Parner *et al.*, 2002; Nielsen *et al.*, 2006).

*The frontonasal field.* Short nasal bones have, in several studies, been identified pre- as well as post-natally in individuals with the same diagnoses (Becktor *et al.*, 2001; Kjær *et al.*, 2001a; Hansen and Kjær, 2004; Nielsen *et al.*, 2005a).

*The maxillary and palatine fields.* Deviations in tooth formation and eruption can occur in a single field or in several fields (Bang *et al.*, 1995; Kjær, 1997; Becktor *et al.*, 2002; Nielsen *et al.*, 2005b).

#### *Post-natal manifestations of severe deviations in cranial development*

How the prenatal mapping of fields can influence the understanding of rare deviations in the cranium and dentition in children is exemplified in the single median maxillary central incisor (SMMCI) condition, which can be the mildest type of holoprosencephaly (Kjær *et al.*, 1997b; Becktor *et al.*, 2001; Tabatabaie *et al.*, 2008). In SMMCI, the mildest type of midline deviations are seen in the frontonasal field

(Figure 7) with the most severe form being cyclopia (Figure 5). The midaxial tissue components are absent in SMMCI, and therefore a symmetrical central incisor develops. This central incisor appears to be composed of the two lateral parts of two central incisors (Figure 7). With this condition, midaxial structures such as the intermaxillary suture, incisive papilla, and labial fraenum superior are absent. It has also been demonstrated that the malformed facial region extending to the sella turcica is wedge shaped. The anterior wall of the sella turcica is malformed in this condition (Figure 7). Body height, possibly due to pituitary gland deficiency, can also be affected. The radiographs of a girl with SMMCI, aged 9 years, are shown in Figure 6.

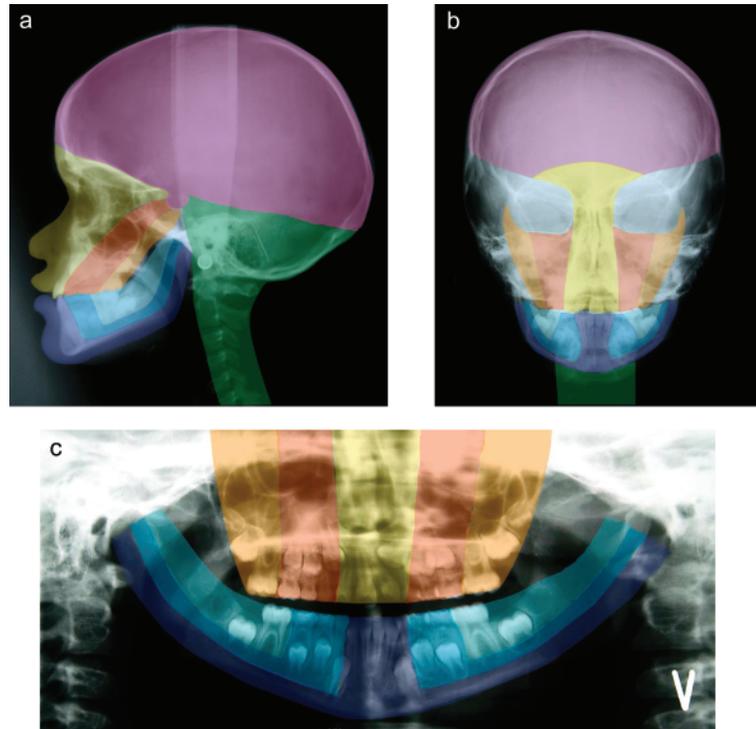
#### *Borderlines between developmental fields*

As the peripheral nervous system develops from the neural crest, the nerves indicate the path of the ectomesenchyme from the neural crest. For example, the naso-palatine nerve and the surrounding tissue, including the maxillary incisors, develop from a neural crest area other than that of the maxillary molars located in the palatine region and innervated by the palatine nerve (Figure 8). This aspect allows for a better understanding of regional differences in the dental arch, e.g. eruption time, eruption arrest, and agenesis (Kjær *et al.*, 1994b; Bang *et al.*, 1995; Kjær, 1998b; Parner *et al.*, 2002; Nielsen *et al.*, 2006). Borderlines between fields in the jaw regions are also borderlines between areas with different peripheral innervation.

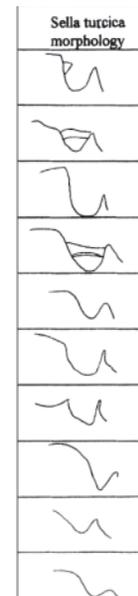
Certain areas or fields are exposed to certain types of malformations. An example of such malformations in the cranium is a cleft lip occurring at the borderlines between the frontonasal and maxillary fields (Figure 9). The most frequent occurrence of agenesis in the dentition seems to be located at the borderline between fields within the maxilla and mandible, e.g. second premolar, lateral incisor, and lower central incisor. The question has also been raised whether the initial so-called bony destruction in juvenile periodontitis in certain locations (borderlines between fields) is not destruction of bone, but rather lack of alveolar bone apposition during continued eruption followed by growth of the alveolar process (Kjær, 1997). In a recent study, it has been shown that alveolar bone growth depends on innervation (Kjær and Nolting, 2008). The exact demarcation in the alveolar process of borderlines between fields is not known.

#### *Sella turcica, a borderline area between many fields*

The sella turcica is formed at the most cranial extent of the notochord (Figure 1). Deviations in all cranial fields described are associated with characteristic developmental deviations in sella turcica and pituitary gland morphology. Moreover, studies have revealed that the same type of malformation in the sella turcica occurs pre- and post-natally in individuals with the same diagnosis. Examples are holoprosencephaly/SMMCI (Kjær and Hansen, 1995; Kjær *et al.*, 1997b; Kjær



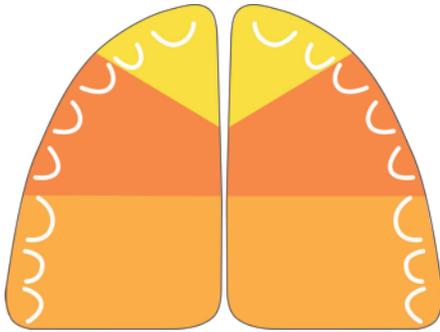
**Figure 6** Profile (a), frontal (b), and panoramic (c) radiographs of a girl aged 9 years with a single median maxillary central incisor. Different developmental fields are marked on the radiographs. Green: cerebellar and cervical spine. Purple: theca. Light and dark blue: mandibular. Yellow: frontonasal. Red: maxillary. Orange: palatine. Note that sella turcica is a borderline region between many fields.



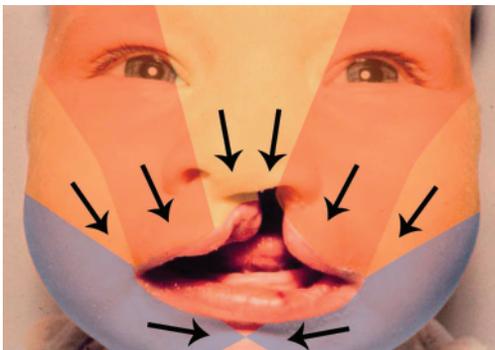
**Figure 7** Left: intra-oral photograph of a patient with a single median maxillary central incisor (SMMCI). Note the symmetrical SMMCI and absence of superior labial fraenum. Right: drawings of abnormal sella turcica contours in 10 children with SMMCI (Kjær *et al.*, 2001a; published with permission of Oxford University Press).

and Hansen, 2000); cleft lip and palate (Mølsted *et al.*, 1993, 1995; Kjær *et al.*, 1997c; Nielsen *et al.*, 2005b); Down syndrome and trisomy 21 (Kjær *et al.*, 1998a; Russell and

Kjær, 1999); spina bifida/myelomeningocele (Kjær *et al.*, 1996a, 1998b, 1999a); and fragile X syndrome (Hjalgrim *et al.*, 2000; Kjær *et al.*, 2001b).



**Figure 8** Schematic drawing of the human palate indicating the frontonasal (yellow), maxillary (red), and palatine (orange) fields.



**Figure 9** Field contours on a photograph of a child, aged 2 months, with a cleft lip. Yellow: frontonasal. Red: maxillary. Orange: palatine. Light and dark blue: mandibular. The arrows indicate the direction of cell migration. The cleft lip is located at the border region between the frontonasal and maxillary fields.

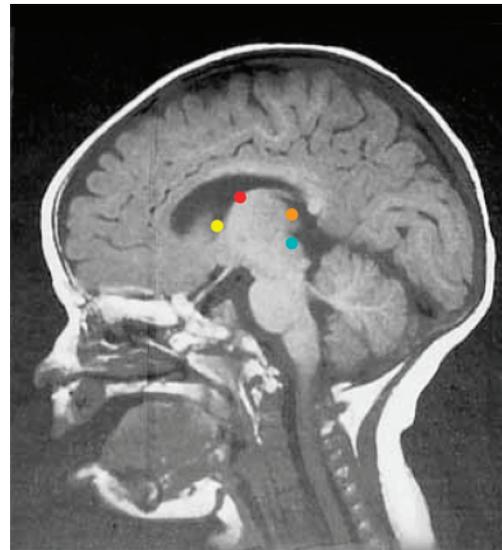
*The cranium and its connection to the vertebral column*

In orthodontic diagnostics, cranial findings on profile radiographs can only be related to the cervical column, as this is the only other body part that can be seen. The notochord controls the development and association between the cervical spine and cranium, as mentioned previously in the cerebellar and cervical spine field (Kjær, 1998a). Recent publications on adults confirm this prenatally observed association between skeletal jaw deviations, malocclusions, cranial base, and cervical spine malformations (Sonnesen and Kjær, 2007a,b, 2008a,b).

As the entire body develops from molecular genetic signalling, the future may reveal new and interesting relationships between the cranium and body parts controlled by the same genes. As an example, specific cranial base malformations in Meckel syndrome are associated with extra digits on the hands and feet (Kjær *et al.*, 1999a,b). A schematic illustration of the body axis (Kjær, 1998a), including the notochord, is shown in Figure 10. In the future, focus should also be given to the relationship between the cranium and brain, both developed from the neuroectoderm. As an example, the frontal lobes of the hemispheres are not



**Figure 10** Schematic drawing of the human body axis, including the complete spine with the notochord (red) and craniofacial bones (green). The arrows mark the direction of the neural crest cell migration.



**Figure 11** Magnetic resonance scan of a child, aged 14 years. The coloured dot marks the probable location of crest areas from which the cranium has developed. Yellow: frontonasal. Red: maxillary. Orange: palatine. Blue: mandibular.

separated in holoprosencephaly, which indicates an association between midaxial malformations in the brain and in the frontonasal cranial field (Kjær *et al.*, 1991; Keeling, 1994). The face, jaws, and teeth develop from areas on the neural crest, formerly located in the brain (Figure 11). This association between the brain and cranium will be an interesting field of focus for orthodontics and neurology in the future.

## Conclusion

Prenatal autopsies of severely malformed crania have revealed that a single area or field in the cranium can be affected by malformations or that several fields can be malformed. Prenatal tissue is useful for complete mapping of malformations because histological examinations are possible. This allows for a pathogenetic insight and improved understanding of postnatal development.

The exact borderlines between fields and the exact genetic background for field malformations are not known. Both aspects are currently discussed in the literature. For visualization of prenatal pathology, the fields affected by malformation are superimposed on the radiographs used in orthodontic practice for diagnostics. It has been shown in the present article, by several examples, how prenatal findings are similar to postnatal observations. Accordingly, postnatal diagnostics and knowledge on pathogenesis are supported and strengthened by findings in prenatal pathology.

How the prenatal fields and cranial patterning can contribute further to orthodontic diagnostics and treatment planning may be a matter of future debate and future research.

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## References

- Bang E, Kjær I, Christensen L R 1995 Etiologic aspects and orthodontic treatment of unilateral localised arrested tooth development combined with hearing loss. *American Journal of Orthodontics and Dentofacial Orthopedics* 108: 154–161
- Becktor J P, Einersen S, Kjær I 2000 A sella turcica bridge in subjects with severe craniofacial deviations. *European Journal of Orthodontics* 22: 69–74
- Becktor K B, Sverrild L, Pallisgaard C, Burhøj J, Kjær I 2001 Eruption of the central incisor, the intermaxillary suture, and maxillary growth in patients with a single median maxillary central incisor, SMMCI. *Acta Odontologica Scandinavica* 59: 361–366
- Becktor K B, Reibel J, Vedel B, Kjær I 2002 Segmental odontomaxillary dysplasia: clinical, radiological and histological aspects of four cases. *Oral Diseases* 8: 106–110
- Buyse M L (ed.) 1990 Birth defects encyclopedia. Center for Birth Defects Information Services, Inc., Dover
- Chavéz-Lomeli M E, Mansilla Lory J, Pompa J A, Kjær I 1996 The human mandibular canal arises from three separate canals innervating different tooth groups. *Journal of Dental Research* 75: 1540–1544
- Gilbert-Barness E (ed.) 1997 Potter's pathology of the fetus and infant. Mosby, St Louis
- Gilbert-Barness E, Debich-Spicer D 2004 Embryo and fetal pathology. Cambridge University Press, Cambridge
- Hansen L, Kjær I 2004 A premaxilla with a supernumerary tooth indicating a developmental region with a variety of dental abnormalities: a report of nine cases. *Acta Odontologica Scandinavica* 62: 30–36
- Hansen L, Skovgaard L T, Nolting D, Hansen B F, Kjær I 2005 Human prenatal nasal bone lengths: normal standards and length values in fetuses with cleft lip and cleft palate. *Cleft Palate–Craniofacial Journal* 42: 165–170
- Hjalgrim H, Hansen B F, Brøndum-Nielsen K, Nolting D, Kjær I 2000 Aspects of skeletal development in fragile X syndrome fetuses. *American Journal of Medical Genetics* 95: 123–129
- Keeling J W (ed.) 1993 Fetal and neonatal pathology. 2nd edn. Springer-Verlag, London.
- Keeling J W 1994 Fetal pathology. Churchill Livingstone, Hong Kong
- Keeling J W, Kjær I 1994 Diagnostic distinction between anencephaly and amnion rupture sequence based on skeletal analysis. *Journal of Medical Genetics* 31: 823–829
- Keeling J W, Hansen B F, Kjær I 1997 Pattern of malformations in the axial skeleton in human trisomy 21 fetuses. *American Journal of Medical Genetics* 68: 466–471
- Kjær I 1997 Can the location of tooth agenesis and the location of initial bone loss seen in juvenile periodontitis be explained by neural developmental fields in the jaws? *Acta Odontologica Scandinavica* 55: 70–72
- Kjær I 1998a Neuro-osteology. *Critical Reviews in Oral Biology and Medicine* 9: 224–244
- Kjær I 1998b Prenatal traces of aberrant neurofacial growth. *Acta Odontologica Scandinavica* 56: 326–330
- Kjær I, Græm N 1990 Simple autopsy method for analysis of complex fetal cranial malformations. *Pediatric Pathology* 10: 717–727
- Kjær I, Hansen B F 1995 Human fetal pituitary gland in holoprosencephaly and anencephaly. *Journal of Craniofacial and Genetic Developmental Biology* 15: 222–229
- Kjær I, Hansen B F 2000 The prenatal pituitary gland—hidden and forgotten. *Pediatric Neurology* 22: 155–156
- Kjær I, Nolting D 2008 Immunohistochemical PGP 9.5 positivity in human osteoblasts may indicate that compensatory and dysplastic craniofacial growth are under control by peripheral nerves. *Orthodontics and Craniofacial Research* 11: 196–200

- Kjær I, Keeling J W, Græm N 1991 The midline craniofacial skeleton in holoprosencephalic fetuses. *Journal of Medical Genetics* 28: 846–855
- Kjær I, Keeling J W, Græm N 1994a Cranial base and vertebral column in human anencephalic fetuses. *Journal of Craniofacial Genetics and Developmental Biology* 14: 235–244
- Kjær I, Kocsis G, Nodal M, Christensen L R 1994b Aetiological aspects of mandibular tooth agenesis—focusing on the role of nerve, oral mucosa, and supporting tissues. *European Journal of Orthodontics* 16: 371–375
- Kjær I, Hansen B F, Keeling J W 1996a Axial skeleton and pituitary gland in human fetuses with spina bifida and cranial encephalocele. *Pediatric Pathology* 16: 909–926
- Kjær I, Keeling J W, Hansen B F 1996b Pattern of malformations in the axial skeleton in human trisomy 18 fetuses. *American Journal of Medical Genetics* 65: 332–336
- Kjær I, Keeling J W, Hansen B F 1997a Pattern of malformations in the axial skeleton in human trisomy 13 fetuses. *American Journal of Medical Genetics* 70: 421–426
- Kjær I, Keeling J, Russell B, Daugaard-Jensen J, Hansen B F 1997b Palate structure in human holoprosencephaly correlates with the facial malformation and demonstrates a new palatal developmental field. *American Journal of Medical Genetics* 73: 387–392
- Kjær I *et al.* 1997c A new craniofacial disorder involving hypertelorism and malformations of external nose, palate and pituitary gland. *Journal of Craniofacial and Genetic Developmental Biology* 17: 23–34
- Kjær I, Keeling J W, Reintoft I, Nolting D, Hansen B F 1998a Pituitary gland and sella turcica in human trisomy 21 fetuses related to axial skeletal development. *American Journal of Medical Genetics* 80: 494–500
- Kjær I, Wagner A, Madsen P, Blichfeldt S, Rasmussen K, Russell B 1998b The sella turcica in children with lumbosacral myelomeningocele. *European Journal of Orthodontics* 20: 443–448
- Kjær I, Hansen B F, Reintoft I, Keeling J W 1999a Pituitary gland and axial skeleton malformations in human fetuses with spina bifida. *European Pediatric Surgery* 9: 354–358
- Kjær I, Keeling J W, Hansen B F 1999b The prenatal human cranium. Normal and pathologic development. Munksgaard, Copenhagen
- Kjær I, Becktor K B, Lisson J, Gormsen C, Russell B G 2001a Face, palate and craniofacial morphology in patients with a solitary median maxillary central incisor. *European Journal of Orthodontics* 23: 63–73
- Kjær I, Hjalgrim H, Russell B G 2001b Cranial and hand skeleton in fragile X. *American Journal of Medical Genetics* 100: 156–161
- Kjær K W, Hansen B F, Keeling J W, Kjær I 1999a Skeletal malformations in fetuses with Meckel syndrome. *American Journal of Medical Genetics* 84: 469–475
- Kjær K W, Hansen B F, Keeling J W, Nolting D, Kjær I 1999b Malformation of cranial base structures and pituitary gland in prenatal Meckel syndrome. *Acta Pathologica, Microbiologica, et Immunologica Scandinavica* 107: 937–944
- Lauridsen H, Hansen B F, Reintoft I, Keeling J W, Kjær I 2001 Histological investigation of the palatine bone in prenatal Trisomy 21. *Cleft Palate–Craniofacial Journal* 38: 492–497
- Lauridsen H, Hansen B F, Reintoft I, Keeling J W, Skovgaard L T, Kjær I 2005 Short hard palate in prenatal trisomy 21. *Orthodontics and Craniofacial Research* 8: 91–95
- Le Douarin N M, Teillet M-A 1974 Experimental analysis of the migration and differentiation of neuroblasts of the autonomic nervous system and of neuroectodermal mesenchymal derivatives, using a biological cell marking technique. *Developmental Biology* 41: 162–184
- Lisson J A, Kjær I 1997 Location of alveolar clefts relative to the incisive fissure. *Cleft Palate–Craniofacial Journal* 34: 292–296
- Lomholt J F, Keeling J W, Hansen B F, Ono T, Stoltze K, Kjær I 2003 The prenatal development of the human cerebellar field in Down's syndrome. *Orthodontics and Craniofacial Research* 6: 220–226
- Lomholt J F, Hansen B F, Keeling J W, Reintoft I, Kjær I 2004 Subclassification of anencephalic human fetuses according to morphology of the posterior cranial fossa. *Pediatric and Developmental Pathology* 7: 601–606
- Mølsted K, Kjær I, Dahl E 1993 Spheno-occipital synchondrosis in three-month-old children with clefts of the lip and palate: a radiographic study. *Cleft Palate–Craniofacial Journal* 30: 569–573
- Mølsted K, Kjær I, Dahl E 1995 Cranial base in newborns with complete cleft lip and palate: radiographic study. *Cleft Palate–Craniofacial Journal* 32: 199–205
- Nielsen B W, Mølsted K, Kjær I 2005a Maxillary and sella turcica morphology in newborns with cleft lip and palate. *Cleft Palate–Craniofacial Journal* 42: 610–617
- Nielsen B W, Mølsted K, Skovgaard L T, Kjær I 2005b Cross-sectional study of the length of the nasal bone in cleft lip and cleft palate. *Cleft Palate–Craniofacial Journal* 42: 417–422
- Nielsen S H, Becktor K B, Kjær I 2006 Primary retention of first permanent mandibular molars in 29 subjects. *European Journal of Orthodontics* 28: 529–534
- Nolting D, Hansen B F, Keeling J W, Kjær I 2002 Histological examinations of bone and cartilage in the axial skeleton of human triploidy fetuses. *Acta Pathologica, Microbiologica, et Immunologica Scandinavica* 110: 186–192
- Parner E T, Heidmann J M, Kjær I, Væth M, Poulsen S 2002 Biological interpretation of the correlation of emergence times of permanent teeth. *Journal of Dental Research* 81: 451–454
- Russell B G, Kjær I 1999 Postnatal structure of the sella turcica in Down syndrome. *American Journal of Medical Genetics* 87: 183–188
- Schumacher R, Seaver L H, Spranger J 2004 Fetal radiology. A diagnostic atlas. Springer-Verlag, Berlin
- Silau A M, Hansen B F, Kjær I 1995 Normal prenatal development of the human parietal bone and interparietal suture. *Journal of Craniofacial Genetics and Developmental Biology* 15: 81–86
- Sonnesen L, Kjær I 2007a Cervical vertebral body fusions in patients with skeletal deep bite. *European Journal of Orthodontics* 29: 464–470
- Sonnesen L, Kjær I 2007b Cervical column morphology in patients with skeletal Class III malocclusion and mandibular overjet. *American Journal of Orthodontics and Dentofacial Orthopedics* 132: 427.e7–427.e12
- Sonnesen L, Kjær I 2008a Cervical column morphology in patients with skeletal open bite. *Orthodontics and Craniofacial Research* 11: 17–23
- Sonnesen L, Kjær I 2008b Anomalies of the cervical vertebrae in patients with skeletal Class II malocclusion and horizontal maxillary overjet. *American Journal of Orthodontics and Dentofacial Orthopedics* 133: 188.e.15–e.20
- Sonnesen L, Pedersen C E, Kjær I 2007 Cervical column morphology related to head posture, cranial base angle and condylar malformation. *European Journal of Orthodontics* 29: 398–403
- Spranger J *et al.* 1982 Errors of morphogenesis: concepts and terms. Recommendations of an International Working Group. *Journal of Pediatrics* 100: 160–165
- Tabatabaie F, Sonnesen L, Kjær I 2008 The neurocranial and craniofacial morphology in children with solitary median maxillary central incisor (SMMCI). *Orthodontics and Craniofacial Research* 11: 96–104
- Taylor E 1988 (ed). *Dorland's illustrated medical dictionary*, 27th edn. W.B. Saunders Company, Philadelphia

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