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The dysmorphic cervical spine in Klippel-Feil syndrome: interpretations from developmental biology

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The authors conducted a study to identify radiological patterns of Klippel-Feil syndrome (KFS), and they present a new interpretation of the origin of these patterns based on recent advances in understanding of embryonic development of the spine and its molecular genetic control.

The authors studied radiographs and computerized tomography (CT) scans as well as magnetic resonance images or CT myelograms obtained in 30 patients with KFS who were referred for treatment between 1982 and 1996; the patients had complained of various neuroorthopedic complications. Homeotic transformation due to mutations or disturbed expression of Hox genes is a possible mechanism responsible for C-1 assimilation, which was found to have occurred in 19 cases (63%). Notochordal defects and/or signaling problems, which result in reduced or impaired Pax-1 gene expression, may underlie vertebral fusions. This, together with asymmetrical distribution of paraxial mesoderm cells and a possible lack of communication across the embryonic midline, could cause asymmetrical fusion patterns, which were present in 17 cases (57%). The wide and flattened shape of the fused vertebral bodies and their resemblance to the embryonic cartilaginous vertebrae as well as the process of progressive bone fusion with age suggest that the fusions occur before or, at the latest, during chondrification of vertebrae.

The authors suggest that the aforementioned mechanisms are likely to be, at least in part, responsible for the observed patterns in KFS that affect the craniovertebral junction and the cervical spine.

Key Words * Klippel-Feil syndrome * craniovertebral anomaly * segmentation * Hox gene * Pax gene * asymmetry

The authors of recent molecular studies used to investigate transgenic mice and naturally occurring mutant mouse strains to elucidate the genetic specification of the mammalian body plan, including the axial skeleton, have identified a number of developmental control genes and their roles in segmentation. The dramatic demonstration of not only gene conservation but functional conservation between various animal model systems and humans, exemplified by the discovery of the "master gene" role for the Pax-6 gene in eye development,[43] underscores that these studies can provide unique insights into congenital malformation.[56] In our report we argue that new knowledge emerging from animal studies about the genetic control of the formation of the axial skeleton can potentially provide new paradigms to explain some of the segmentation defects that characterize certain dysmorphic syndromes. To illustrate this contention we focus on one particular syndrome, Klippel-Feil syndrome (KFS), which is characterized by a diversity of segmentation defects. Thus, the aim of this paper, after providing a brief review of

the KFS phenotype and the characteristic radiological patterns of the cervical spine and craniovertebral junction, is to interpret, or reinterpret, these features in the light of current developmental biology. To illustrate how this knowledge might be used to understand the dysmorphology of KFS we speculate on how the normal morphogenetic mechanisms (and particularly their genetic control) can be perturbed to generate some of the more common features of KFS in the cervical spine and craniovertebral junction.

In 1912, Maurice Klippel and André Feil described an autopsy finding of extensive cervical and thoracic vertebral fusions in a 46-year-old tailor with low posterior hairline, restriction of neck movements, and short neck.[29] Today, the term Klippel-Feil syndrome identifies a phenotype in which failure of segmentation in the cervical spine has occurred, although the classic clinical triad is only present in approximately half of the cases in which cervical fusion has occurred.[21,22] The incidence of the syndrome has been estimated to be one in 42,000 individuals.[20] Klippel-Feil syndrome usually occurs in conjunction with a number of different anomalies, the frequency of which largely depends on patient selection. The most common abnormalities associated with KFS are skeletal anomalies (such as Sprengel's deformity, basilar invagination, skull asymmetry, and scoliosis), hearing impairment, congenital heart diseases, ocular malformations, cranial and facial asymmetry, cleft palate,[21,37,38] genitourinary malformations,[45] and mirror movements.[22,50,62] Other rare associations reported to occur in conjunction with KFS include partially or completely split cervical cord,[9] anomalous rib,[48] neurenteric cyst,[61] neurenteric fistula that causes recurrent meningitis,[19] and dermoid cyst.[12,47] The exact causes of KFS are unknown, although genetic factors for C2-3 (autosomal dominant) and C5-6 (autosomal recessive) fusions have been suggested,[20] and environmental factors such as alcohol consumption may also have a role.[49]

CLINICAL MATERIAL AND METHODS

We reviewed the common radiological features of the cervical spine that were identified in a sample group of 30 patients with KFS and various neuroorthopedic complaints who were referred to the authors between 1982 and 1996. Radiographs and computerized tomography (CT) scans as well as magnetic resonance (MR) images or CT myelograms were carefully analyzed to identify radiological patterns of the malformation. Special attention was given to fusion patterns including asymmetry, progression of bone fusion with age, and the shape of the fused vertebral bodies. The patient population consisted of 16 males and 14 females with a mean age at the time of the clinical presentation of 19.3 years (range 2 months-66 years). Details of the patient population, including levels of fusion, presence of left-right asymmetrical fusion, presenting symptoms, clinical and radiological features, associated anomalies, and family history are summarized in Table 1.

TABLE 1
CLINICAL SUMMARY OF 30 PATIENTS WITH KFS*

Case No.	Age (yrs), Sex	Fusion Levels	Asymmetry	Presenting Symptoms	Clinical Features	Radiological Features	Associated Anomalies	Family History
1	0.2, F	C2-T5	yes	poor respiration, intubated & ventilated at birth; deformed SN	SN, low hairline, RNM, Sprengel's deformity	VF, prominent lt-rt ossification, ant midsagittal bone defect at C-7	high arched palate, mediastinal & intradural neurenteric cysts, completely split cord at C1-7	NK
2	1, F	C5-7, L3-4	no	short stature & dysmorphic features	SN, RNM, rt Sprengel's deformity	VF	ASD & pulmonary stenosis, long fingers, single kidney, widely spaced nipples, L3-4 & midthoracic fusions & kyphoscoliosis	NK
3	1.5, F	OC-C1 (rt), C2-3 (pos)	yes	episodes of floppiness w/ bradycardia & breath holding	no dysmorphic features, alert, rt arm flaccid paresis	VF, ant & pos C-1 SB, lat defects in C-2 arch, C-2 slipped forward on C-3, cord damage	NK	father; C2-3 pos fusion
4	2, M	OC-C1, C2-3	yes	facial asymmetry, SN, transient neck pain	SN, RNM	VF, dens aplasia, ant C-1 SB, cervical ribs, cervical hemivertebrae, prominent lt-rt ossification	hypospadias, anal atresia, single rt kidney, lumbar scoliosis	NK
5	2.5, M	C2-3, C4-5 (pos)	no	breath holding episodes, incidental finding on chest x-ray	SN, minimal RNM, rt Sprengel's deformity, prominent lt mandible	VF, ossification in cervical discs, prominent lt-rt ossification	rt ribs 2-3 fused, lt T-8 hemivertebra	NK
6	5, M	C2-7	no	aching discomfort in legs & wrists, rt knee gave way, increasing cervicothoracic kyphos	SN, RNM, cervicothoracic kyphos	VF, pos C2-T1 SB	cervicothoracic kyphoscoliosis	NK
7	6, M	OC-C7, T12-L5	no	stiff, kyphotic neck, small sternomandibular distance, impaired forward gaze	marked cervical kyphosis, complete RNM, bowel incontinence	extensive VF (one-bone spine deformity), absent clivaxial angle, laminar fusions	short, stubby fingers & toes, in-curving of 5th fingers, bilat cryptorchism	NK
8	6, M	OC-C1, C2-3, C5-6	no	neck pain, rt arm & leg weakness	RNM, mild tetraparesis, rt hyperreflexia, upgoing lt planter	VF, BI, bilat cervical ribs, SB at C-5 & C-6, AA subluxation	NK	uncle; SN (NI)

* Abbreviations: AA subluxation = atlantoaxial subluxation; ant = anterior; ASD = atrial septal defect; BI = basilar invagination; FM = foramen magnum; HA = headache; NI = not investigated; NK = not known; PDA = persistent ductus arteriosus; pos = posterior; RNM = restriction of neck movements; SB = spina bifida; SN = short neck; VF = vertebral fusions; VSD = ventricular septal defect.

TABLE 1, CONTINUED
CLINICAL SUMMARY OF 30 PATIENTS WITH KFS

Case No.	Age (yrs), Sex	Fusion Levels	Asymmetry	Presenting Symptoms	Clinical Features	Radiological Features	Associated Anomalies	Family History
9	7, F	OC-C1 (pos), C2-T1	yes	neck pain, torticollis, gait difficulties	SN, RNM	VF, os odontoideum, AA subluxation, ant C-1 SB, absent pos elements, wide FM, cervical ribs	partially split cord at medulla-C2, occipital meningocele, hypoplastic lt lung, tracheal stenosis, 1 kidney, VSD/ASD, PDA	NK
10	7.5, M	C2-3, C4-6, T1-5	yes	restriction of lt hand extension & lt shoulder abduction	SN, minimal RNM, lt Sprengel's deformity	VF, C7-T1 hemi-vertebrae	lt ribs 1-2 fused	NK
11	11, F	OC-C1 (ant lt-rt), C2-3, C7-T1	no	one episode of collapse while horse back riding	RNM	VF, BI, AA subluxation, cervical rib	upper thoracic scoliosis	NK
12	11, M	OC-C1 (pos lt-rt), C2-4, C5-T2	yes	neck pain, occasional stumbling	SN, low hairline, RNM, hyperreflexia, minimal rt leg paresis	VF, short clivus, prominent lt-rt ossification	lt T-3 hemi vertebra, anal atresia, cleft palate, renal ectopia	NK
13	11, F	C2-T2	yes	increasing lt torticollis	facial asymmetry, RNM	hemi vertebral fusions, cervical scoliosis, progressive bone fusion	occipital meningocele, scalp epidermal cyst, hydrocephalus, partially split cervical cord	NK
14	11, M	OC-C1 (ant), C2-4, C5-7, T1-3	yes	rt torticollis, high lt shoulder, short lt leg	rt torticollis, lt Sprengel's deformity, cervicothoracic scoliosis (C5-T4)	VF	Chiari I, hypoplastic rt side of T-2 vertebra	NK
15	11, M	C2-5, C6-7, T1-3	yes	tracheomalacia, fistula at age 1 yr, kyphoscoliosis, neurogenic bladder	SN, RNM, high thoracic scoliosis, rib hump & prominent scapula, small stature, rigid thoracic spine	VF, pos C-1 & C-7 SB, rt C-7 & T-2 hemi vertebrae, progressive bone fusion	NK	NK
16	12, M	C2-3, C4-5, C6-7	no	transient tetraplegia after minor head injury, delayed milestones in motor development	SN, RNM, facial asymmetry, mixed hearing loss, wasted intrinsic muscles, mild tetraparesis, hyperreflexia, upgoing plantars	VF, os odontoideum, AA subluxation, cord compression	claw hands, rt flexion deformity of 4th & 5th fingers	NK

* Abbreviations: AA = atlantoaxial subluxation; ant = anterior; ASD = atrial septal defect; BI = basilar invagination; FM = foramen magnum; HA = headache; NI = not investigated; NK = not known; PDA = persistent ductus arteriosus; pos = posterior; RNM = restriction of neck movements; SB = spina bifida; SN = short neck; VF = vertebral fusions; VSD = ventricular septal defect.

TABLE 1, CONTINUED
CLINICAL SUMMARY OF 30 PATIENTS WITH KFS

Case No.	Age (yrs), Sex	Fusion Levels	Asymmetry	Presenting Symptoms	Clinical Features	Radiological Features	Associated Anomalies	Family History
17	16, M	OC-C1, C2-3	no	progressive gait & swallowing difficulties, stiff & numb legs, occipital HA	SN, RNM, facial asymmetry, tetraspasticity, hyperreflexia, upgoing plantars, nystagmus	VF, BI, hypoplastic dens, AA subluxation, prominent lt-rt ossification	Chiari I	brother; C2-3 & C4-5 fusions
18	19, M	OC-C2 (pos)	yes	occipital HA, nausea, easy choking when drinking, heavy legs, unsteady gait	mild dysarthria, nystagmus, gag hyporeflexia	VF, BI	Chiari I	NK
19	20, F	C2-T5	no	marked deformity of neck, submandibular hirsutism, facial hypoplasia	RNM, Sprengel's deformity, SN, rt conductive hearing loss, hyperreflexia, strabismus, mirror movements	VF, hypoplastic vertebrae, upper cervical SB, very wide FM, small pos fossa	partially split cord from FM to C-2, polycystic ovaries, Chiari III, high arched palate, bifid uvula	NK
20	21, M	C4-6	no	transient tetraplegia after hyperflexion injury of neck	minimal RNM, residual lt arm weakness, hyperreflexia, muscle wasting, spinal ataxia	VF, C3-4 degenerative changes	posttraumatic syrinx	NK
21	23, F	OC-C1, C2-3	yes	rt torticollis, occipital HA, neck & bilat shoulder pain	SN, RNM, facial asymmetry, bilat absent sterno-mastoid muscles	VF, short clivus	Chiari I, large rt vertebral artery impressing pons	sister had encephalocele, torticollis, 1 kidney (NI)
22	25, M	OC-C1, C2-3	yes	neck & occipital pain, numbness in fingertips, leg stiffness	SN, RNM, hyperreflexia, bilat Hoffmann's reflex	VF, short clivus, BI	Chiari I, syrinx	NK
23	30, F	OC-C1, C2-3	yes	dizzyspells, nystagmus, dysphagia, nasal speech, lt arm paresthesia, occipital HA	minimal RNM, nystagmus, slightly hoarse voice, rt-sided tongue atrophy, impaired taste on rt, ataxia	VF, BI	Chiari I, syrinx	NK

* Abbreviations: AA subluxation = atlantoaxial subluxation; ant = anterior; ASD = atrial septal defect; BI = basilar invagination; FM = foramen magnum; HA = headache; NI = not investigated; NK = not known; PDA = persistent ductus arteriosus; pos = posterior; RNM = restriction of neck movements; SB = spina bifida; SN = short neck; VF = vertebral fusions; VSD = ventricular septal defect.

TABLE 1, CONTINUED
CLINICAL SUMMARY OF 30 PATIENTS WITH KFS

Case No.	Age (yrs), Sex	Fusion Levels	Asymmetry	Presenting Symptoms	Clinical Features	Radiological Features	Associated Anomalies	Family History
24	32, M	OC-C1, C2-3, C4-5	yes	numbness in arms & legs, weakness in arms, unsteady gait	RNM, 4+5 spastic tetraparesis, hyperreflexia, lt up-going plantar, nystagmus, rt 12th cranial nerve palsy	VF, dysplasia of C-1 lat masses, AA subluxation, short deformed dens, ant medullary compression	Chiari I	NK
25	38, F	OC-C4, C5-T2	yes	neck pain, clumsy rt arm, crunching sensation in neck when turning head	SN, RNM, hairy patch at low back, lt divergent squint, minimal weakness of shoulder & hip muscles	VF, C4-5 degenerative changes, dens fused to clivus, absent divo-axial angle, laminar fusions, prominent lt-rt ossification, C-5 butterfly vertebra, C-4, C-7, T-1 hemivertebrae	bilat ribs 1-3 fused, om o-vertebral bone	great-grand-mother & 2 cousins had KFS
26	40, M	C6-7, T1-2	no	complete tetraplegia after traffic accident	no significant clinical features	VF, C5-6 fracture dislocation & cord compression	rib necks 1-3 enlarged	NK
27	46, F	OC-C1 (ant lt-rt), C2-3	no	neck pain, cough-HA, nausea, giddiness, swallowing problems	SN, RNM, decreased left gag & palatal movements	VF, pos C-1 SB, short divus, BI	Chiari I	aunt had SN (NI)
28	48, F	OC-C1 (pos), C2-7	no	neck pain, weak & numb rt arm, urinary frequency, lt occipital HA, occasional stumbling	SN, RNM, stiff lumbar spine, bilat 6th cranial nerve palsy & mild hearing loss, mild rt hemiparesis, rt C6-T1 hypesthesia	VF, ant C-1 SB, short divus, cervical ribs, C-2 articulates w/clivus, prominent lt-rt ossification	completely split cord at medulla C-3	NK
29	50, F	OC-C1 (ant lt-rt), C2-3, C4-6	yes	lt scapular pain, numbness in lt axilla & upper arm	lt Sprengel's deformity, restriction of lt shoulder movements, hypesthesia in lt axilla	VF, degenerative changes at C3-4	NK	NK
30	66, F	OC-C1, C2-3	yes	neck pain, dizzy spells	SN, RNM, deteriorating lt hearing, rt deafness, positive Romberg's sign	VF, hypoplastic dens, anterior C-1 SB, rheumatoid changes, BI	high arched palate, rheumatoid arthritis	NK

* Abbreviations: AA subluxation = atlantoaxial subluxation; ant = anterior; ASD = atrial septal defect; BI = basilar invagination; FM = foramen magnum; HA = headache; NI = not investigated; NK = not known; PDA = persistent ductus arteriosus; pos = posterior; RNM = restriction of neck movements; SB = spina bifida; SN = short neck; VF = vertebral fusions; VSD = ventricular septal defect.

RESULTS

Clinical and Radiological Findings

Neck pain (10 patients), gait difficulties (six patients), weakness or numbness of limbs (six patients each), occipital headache (five patients), torticollis (four patients), dizziness (four patients), and swallowing problems (three patients) were the most frequent chronic symptoms. In three patients the presence of vertebral fusion was an incidental finding when radiographs were obtained following acute cervical trauma. The most common clinical features were restriction of neck movements (25 cases), short neck (18 cases), Sprengel's deformity (seven cases), and facial asymmetry (five cases), whereas paresis (nine cases), hyperreflexia (eight cases), deafness (four cases), and other cranial nerve palsies (five cases) were the most common neurological signs.

In all patients one or more levels of fusion in the cervical spine had occurred. The most frequently involved

vertebral levels at which fusion had occurred were C-1 assimilation to occiput and between C2-3 (Fig. 1). Other radiological features included anterior or posterior spina bifida in 10 patients, basilar invagination in eight, atlantoaxial subluxation in six, cervical ribs in five, hemivertebra in three, hypoplastic odontoid process in three, os odontoideum in two, and dens aplasia in one patient.

Fig. 1. Bar graph showing the number of cervical fusions by involved level. Total number exceeds 30 because in 29 patients there was more than one fused level between occiput and T-1. O = occiput.

The most common associated anomalies were Chiari I malformation (eight cases), partially or completely split cervical cord (five cases), high arched or cleft palate (four cases), enlarged or fused ribs (four cases), scoliosis (four cases), single or ectopic kidney (four cases), syrinx (three cases), anal atresia (two cases), occipital meningocele (two cases), and cardiac septal defect (two cases).

In three cases there was a positive family history for cervical spine fusions: two cousins and a great-grandmother of one patient, the father of another, and the brother of a third patient had proven cervical vertebral fusions. In three other cases, the family history was suggestive of KFS, but these cases were not confirmed radiographically.

Observed Radiological Patterns of Malformation

In 11 patients (37%) only subaxial fusions were demonstrated, and in three the diagnosis was made incidentally after the patients sustained a severe spinal cord injury.

In 19 patients (63%) either partial (nine patients) or complete (10 patients) assimilation of atlas to occiput was demonstrated. In eight of the 19 patients an associated C2-3 fusion was revealed, and in 10 more extensive subaxial fusions were found that sometimes extended into the thoracic spine (Fig. 2). In one patient vertebral fusions had formed between occiput-C2.

Fig. 2. Left: Midsagittal reformatted CT myelogram obtained in a patient in whom atlas assimilation into occiput, basilar invagination, C2-3 anterior and posterior fusion and atlantoaxial subluxation causing anterior medullary compression were revealed. Right: Line diagram showing the fusion pattern. O = occiput.

In two patients midline fusion through the craniovertebral junction was observed, and in both the clivoaxial angle was absent (Fig. 3). Only one mobile segment from the clivus to T-2 was demonstrated in one of these patients, whereas in the other almost complete fusion of the spine was revealed, with a fusion bar connecting the dorsal part of the vertebral bodies ("one-bone spine").

Fig. 3. Left: Lateral cervical radiograph showing extensive fusions of the anterior and posterior elements between clivus and T-2. Right: Traced-line diagram illustrating an axial fusion through the craniovertebral junction and the single motion segment between C4-5. O = occiput.

In 17 cases (57%) there was marked left-right asymmetry of fusion, which was more prominent when vertebral bodies showed left and right halves of ossification (four cases) or when hemivertebrae were found (five cases). Hemivertebrae, when present, seemed to demonstrate independent fusion patterns on the left and right sides (Fig. 4). In 13 of the patients in whom asymmetrical vertebral fusion was found, C-1 assimilation to occiput was present, but asymmetry was found only in seven cases in the region of C-1 assimilation.

Fig. 4. Left: Anteroposterior cervical radiograph revealing marked left-right asymmetrical fusion pattern of hemivertebrae. Right: Line diagram in which the numbers of individual segments are indicated on the left and right sides.

In seven cases (23%), axial CT or MR imaging revealed that the fused vertebral bodies had a small anteroposterior diameter: they were narrow and wide with distinct left and right halves and a midsagittal sclerotic zone. In some cases a small round area was visible in the middle of the vertebral body (Fig. 5).

Fig. 5. Axial CT scan (obtained through a bone window) revealing a fused vertebral body with small anteroposterior diameter and a midsagittal sclerotic zone separating the left and right halves. Note the round sclerotic area in the midline, which may mark the position of the notochord (arrowhead).

In two patients in whom radiographs were obtained before 1 year of age and also years later, an increase in the number of fused levels was demonstrated; thus, progressive bone fusion seemed to occur during the aging process (Fig. 6).

Fig. 6. Left: Radiograph, lateral view, obtained 2 weeks after birth demonstrating well-segmented posterior cervical elements and fusion between C3-5. Note the shadow of a large occipital meningocele (arrowhead). Right: Lateral cervical radiograph obtained in the same patient at 8 years of age demonstrating that the bone fusion increased and now affects anterior and posterior elements of C3-7.

DISCUSSION

There have been several attempts to identify clinical patterns of KFS to determine those patients at high risk,[37,38,42] whereas other investigators have analyzed radiological findings and fusion pattern.[39,57] Assimilation of the atlas with C2-3 fusion and also more extensive fusions of the cervical vertebrae have already been identified as radiological patterns of the malformation.[38,59] Although there is some data on the causes of the abnormality,[6,20,49] in our report we endeavor to integrate, for the first time, the putative role of recently described genetic factors, known to be associated with vertebral anomalies in transgenic and mutant mice, with the development of the clinical dysmorphology just described (Table 2). To contextualize this exercise we provide a brief review of the normal embryonic development of the spine and summarize our present knowledge of its genetic control (for a full account of vertebral column development, see Dietrich and Kessel[14]).

TABLE 2 OBSERVED RADIOLOGICAL PATTERNS AND SUGGESTED DEVELOPMENTAL MECHANISMS	
Observed Pattern	Suggested Developmental Mechanism
homeotic transformation	<i>Hox</i> genes
vertebral fusions	<i>Pax</i> genes
lt-rt asymmetrical fusion	paraxial mesoderm deficiency, lack of communication across midline
lt-rt ossification & progressive bone fusion	vertebral fusion occurs before or during chondrification

Development of the Spine

The mammalian body axis is established during gastrulation when cells migrate through the primitive streak and the three layers of the embryonic disc are generated. In the midline some of the cells pass through the anterior tip of the streak (called the primitive node) and give rise to a rodlike structure, the notochord. This causes the overlying ectoderm to become the neural plate, which later will form the neural tube. The paraxial mesoderm, lying on either side of the notochord, segments progressively in a craniocaudal direction to form the paired blocks of tissue known as somites, which subsequently transform into epithelial spheres. The first five (occipital) somites appear in stage 9 (at approximately 20 days), followed by the seven cervical somites over the next 2 to 4 days.[40] Later, while the

dorsolateral parts of the somites retain their epithelial arrangement to form dermamyotomes, the ventromedial parts lose their epithelial structure, and in these areas (the so-called sclerotomes) the cells will migrate toward the midline to surround the notochord and form the perichordal cellular zone. A distinction between lateral and axial differentiation needs to be recognized,[37,59] because the lateral parts of sclerotomes separate into low-cell density cranial and high-cell density caudal halves from stage 13 onward (at approximately 28 days). The loose halves contain the spinal nerves, dorsal root ganglia, and the intersegmental vessels, whereas the dense caudal halves give rise to the lateral processes and neural arches of vertebrae. During the process of resegmentation, the loose half of a sclerotome and the dense half of the sclerotome cranial to it will form a vertebra. Axially, the perichordal region also subsequently shows zones of high- and low-cell density (from stage 14 onward; at approximately 32 days). The high-cell density zone contributes to the formation of intervertebral discs, whereas the low-density areas develop into the centra of vertebrae.[18,27,40,58]

It has been shown experimentally that the somites, and even the unsegmented paraxial mesoderm, are already skeletogenically predetermined with respect to the morphological features characteristic of their axial level. For example, thoracic somites that are heterotopically grafted to the cervical region give rise to ribs in the host embryos.[28] Consequently, the developmental fate of sclerotome cells must be specified long before the identity of the individual vertebral segment is morphologically apparent. This morphogenetic specification of vertebral phenotype, along the embryonic axis, is an early event controlled by the Hox genes.[26]

Homeotic Transformation (C-1 Assimilation) and Hox Genes

The Hox genes are a family of regulatory genes (with a phylogenetically highly conserved domain called the "homeobox"), which appears to play a fundamental role in the establishment of the body plan, including specification of the axial skeleton. All vertebrates, including human beings, contain 38 Hox genes that are distributed on four linkage groups (or clusters) designated Hox A, B, C, and D on chromosomes 6, 11, 15, and 2, respectively (Fig. 7).

Fig. 7. Diagram illustrating the chromosomal organization of Hox genes in the mouse and human and their derivation from an ancestral complex equivalent to that found in *Drosophila*, the fruit fly. The salient points are 1) the presence of four clusters (A, B, C, and D) on different chromosomes, resulting

from of cluster duplication during evolution; 2) the existence of so-called paralogous groups defined vertically across the clusters and consisting of up to four genes, each on a different chromosome, linked by common origin from an ancestral gene and identified by a common arabic numeral (thus, HoxA-4, B4, C4, and D4 are paralogues); 3) some paralogues have been lost during the course of evolution; 4) the expression of the genes along the anteroposterior axis of the embryo maps in a 1:1 fashion with their sequence within the cluster and along the 3' to 5' (axis of the chromosome. Thus, HoxA-3, for example, has a more anterior limit to its expression domain than does HoxA-10.

Although their downstream target genes are as yet unknown, it is known that Hox genes are needed to establish correct positional specification within the craniocaudal sequence of somites (for a review, see references[14,23,31]). In situ hybridization analysis indicates that axial expression of Hox genes follows a general principle: the more 3' the position of a gene in the chromosomal cluster, the more anterior is its boundary of expression in the neural tube and the prevertebrae.[15] Mutations in Hox genes, and teratogen-induced disturbance of Hox gene expression, can both cause alterations of the number and identity of those cervical vertebrae that form at or near the anterior limit of their expression domain.[5,8,25,44,55] For instance, inactivation of homeobox-containing gene Hox-D3 results in mutant mice in which the atlas assimilates to the basiocciput.[7] Thus, by losing the function of a Hox gene, the first cervical vertebra is transformed into a more rostral identity, which is termed an "anterior homeotic transformation." Conversely, extension of an expression domain rostrally can transform structures into a more caudal identity, a phenomenon known as "posterior homeotic transformation." This is exemplified by the "gain-of-function" transgenic mutation of Hox-D4, whereby the occipital region of the skull is changed into cervical vertebral phenotypes, leaving the cervical spine itself unchanged[34] (Fig. 7). Given this sensitivity of the occipitocervical junction to perturbation by changes in Hox gene expression, such genetic changes might prove to be the underlying causes of malformations in this part of the human body. Thus, assimilation of the atlas into the occiput, detected in 19 of our 30 cases, can be interpreted as an anterior homeotic transformation. However, there was no evidence of multiple segmental fusions caudal to the craniovertebral junction in any of the experimental mutant mice. Therefore, although mutations in Hox genes or, perhaps, environmental disturbance of Hox gene expression (by teratogens) might be causes of occipital assimilation of C-1 in patients with KFS, it is unlikely that such mechanisms can be used to explain the extensive vertebral fusions observed.

Vertebral Fusions and Pax Genes

Another group of regulatory genes, the Pax genes are considered to be much stronger candidates for causing congenital vertebral fusions. They also possess a phylogenetically well-conserved DNA sequence called the "paired-box" and many of them contain the "homeobox" sequence as well. Like the homeobox, the paired-box also encodes DNA-binding domains, a typical feature of a regulatory protein.[4] This family, unlike the classic clustering of the Hox genes, consists of nine genes divided into four classes that are dispersed around the genome and are not clustered.[53,54] As Barinaga[2] and Read[46] have indicated, mutations in several Pax genes are now known to be causally involved in some major human birth defects, such as aniridia (PAX-6) and Waardenburg syndrome Types I and III (PAX-3). Human and murine Pax genes are expressed in diverse cell types, but all contribute to development of the early nervous system, except the members of the first class, Pax-1 and -9.[4,53,54]

These two genes (Pax-1 and -9) control segmentation of the somites and sclerotomes to establish intervertebral boundaries.[33] In particular, the Pax-1 gene has been found to be pivotal in the reorganization of the sclerotome.[11] Normally, signaling from the intact notochord and/or the floor plate of the neural tube (by signal proteins such as Sonic hedgehog; see Left-Right Asymmetrical Fusion) is necessary for the occurrence of sufficient Pax-1 gene expression in somites and in sclerotomes during primary segmentation, which, in turn, is required for the formation of the ventral parts of the vertebrae[30,60] (Fig. 8). During chondrification of the vertebrae, the Pax-1 gene is strongly expressed in the developing discs. This might be a late function of Pax-1 compared with the patterning of early sclerotome cells, but again it represents maintenance of the boundaries between axial skeletal elements. In this respect the Pax-1 gene acts like a "resegmentation gene." [60]

Fig. 8. Diagram depicting the range and sequence of tissue interactions that underlie the cell-signaling events necessary to build a vertebral body. Initially, expression of the regulatory gene, Pax-1, is involved in primary segmentation of the paraxial mesoderm into somites (not shown here; see text). Subsequently, a peptide signal encoded by the Shh gene, emanating from the notochord and the ventral floor plate of the neural tube, acts on the somite to induce sclerotome differentiation. The sclerotome itself then differentially expresses Pax-1, with expression ventrally reflecting the dorsoventral specification of each vertebra. Within this ventral expression domain of the sclerotomes, much more intense expression is demonstrated at those axial levels at which the intervertebral discs will form, and this appears to function in the resegmentation of the vertebrae (see text for further details).

Analysis of the undulated mutant mouse reveals a mutation within the Pax-1 paired-box domain that encodes the DNA-binding region of the protein; the phenotype displays a dysmorphic vertebral column in which vertebral bodies and intervertebral discs are fused, misshapen, or absent, and proximal regions of the ribs are either missing or malformed.[4,60] Mutation at another locus (Danforth's short-tail) causes early degeneration of the notochord, which results in downregulation of Pax-1 in the sclerotome, and produces a similar disruption to the ventral aspects of the vertebral primordia.[31] Perhaps not surprisingly, PAX-1, the human homologue,[1] is expressed in the human vertebral column at least as early as 7 weeks of development, in the intervertebral disc primordia.[53] Furthermore, the experimental use of antisense strategies to inactivate Pax-1 messenger RNA during somitogenesis produces fusions,[52] further supporting the idea that Pax-1 is critical in the development of a properly segmented vertebral column. As with the Hox homeoproteins, the identity of the downstream target genes, that is, those in which expression is regulated by the Pax proteins, is largely unknown.

Thus, we can conclude that impaired or reduced PAX-1 expression, for whatever reason, will result in local or widespread atypical fusion between the sclerotomal primordia. The phenotypic consequence will be vertebral fusions, even through the craniovertebral junction, which is sometimes observed clinically. Although the likelihood that mutation in the PAX-1 gene is responsible for the KFS phenotype has been considered,[53] it has not been rigorously investigated to date. Whatever level in the signaling cascade is affected, it is by no means a foregone conclusion that the original cause is necessarily always genetic. Given that only in a small minority of patients with KFS is there strong evidence of a genetic basis[6,21] (in only three patients in this series was there evidence of a

positive family history for vertebral fusions), many of these clinical cases may simply reflect a nongenetic disruption (such as by teratogens) during that window of development in which crucial morphogenetic events are taking place along the axis of the embryo. The localization and the extent of the congenital anomaly to, and along, a particular region of the axis would thus reflect the timing and duration, respectively, of the teratogenic insult.

We believe that these phenomena may be, at least in part, responsible for the formation of subaxial fusions and for the two cases in which axial fusions involved the clivus.

Left-Right Asymmetrical Fusion

In previous reports on fusion patterns the investigators have mainly concentrated on the difference between ventral and dorsal fusion patterns, that is, fusion of vertebral bodies or laminae. Not much has been written about the left-right asymmetrical fusion, and yet the incidence was nearly 60% in our series. Von Torklus and Gehle,[59] in describing types of unilaterally disturbed segmentation in the atlantoaxial region, assumed that they resulted from an early embryonic disturbance of the notochord. Other investigators have mentioned asymmetrical fusion between the two sides of occipitalized C-1, which was demonstrated in seven of our 19 patients in whom C-1 assimilation was found, but they did not provide any further explanation.[13,24,41]

Research on the regulation of normally occurring left-right asymmetric organs (such as the development of the heart from the heart tube) in vertebrates has revealed that the responsible genes are expressed during and immediately after gastrulation[32,64] and led to speculation that the left-right axial information is contained in the extracellular matrix early in development.[63] During gastrulation the notochordal process originates from the primitive node, and cells migrate through the primitive streak to form the mesoderm. It has been proposed that an intact notochord is necessary to induce sclerotome development, and a signal protein, encoded by the Sonic hedgehog (Shh) gene and secreted by both the notochord and ventral floor plate of the neural tube, serves to induce Pax-1 expression and sclerotome differentiation in the paraxial mesoderm[16,17] (Fig. 8). The same Shh gene is strongly expressed in the primitive node, suggesting that this gene also plays a key role during gastrulation. Additionally, the Shh gene is expressed in a left-right asymmetric pattern during gastrulation, which makes it a candidate agent that normally establishes left-right differences.[32]

Injury to the primitive node/primitive streak complex, reducing the number of paraxial mesodermal cells, could impair the formation of the skeletal-neural axis of the embryo.[35] This impairment, together with an insufficiency of notochord-derived signal that is necessary to maintain Pax-1 expression in the sclerotome and primitive node-derived signal for symmetrical-asymmetrical patterning (both can be mediated by Shh gene product as discussed previously), may lead to both faulty segmentation and disturbed symmetry, which eventually cause asymmetrical fusion patterns. Faulty signaling across the embryonic midline might also play a role because asymmetrical fusions were often associated with split vertebral bodies or hemivertebrae.

Left-Right Ossification and Progressive Bone Fusion

Although recognized clinically, it is rarely stated explicitly that the fused vertebral bodies are in fact flattened and wide. Additionally, in a young child the extent of a segmentation failure cannot be truly appreciated because the ossification of the vertebral bodies is incomplete early on, and therefore the final pattern of fusion is not obvious until early adolescence.[3,22,57] In seven of our cases it was obvious that the ultimate shape of the fused vertebral bodies and the chondrified vertebral centra of the human embryo were similar. The small anteroposterior diameter, the wide vertebral bodies, and midsagittal division or groove are all normal features at the chondrification stage of vertebral development (6-10 weeks postfertilization)[10] (Fig. 9). This, together with the observation that bone fusion progresses with age, suggests that the fusions occur before or during the chondrification stage. Thus, whereas the fusion pattern is established early, it will only become manifest with ossification in the preexisting cartilaginous fusions.

Fig. 9. Photomicrograph showing a transverse histological section of cartilaginous cervical vertebra of an 8-week-old human embryo with small anteroposterior diameter, wide and narrow shape, midsagittal groove, and the area of the notochord (arrowhead). Note similarities to the axial view of a fused vertebral body (see Fig. 5). Alcian-blue stain, magnification bar represents 100 μ m.

CONCLUSIONS

The observed radiological patterns in the present series of patients with KFS have led us to postulate the following hypotheses. 1) Homeotic transformation caused by mutations or disturbed expression of Hox genes is a possible factor for C-1 assimilation. 2) Notochordal defects and/or signaling problems, which result in reduced or impaired Pax-1 gene expression, are likely to be among the several causes of vertebral fusions. 3) This, together with asymmetrically distributed paraxial mesodermal cells and a possible lack of cellular communication across the embryonic midline, could generate the frequent left-right asymmetrical fusions. 4) The wide and flattened shape of the fused vertebral bodies, their resemblance to the embryonic cartilaginous vertebrae, and progressive bone fusion with age suggest that the fusions simply occur before or, at the latest, during chondrification of vertebrae, and bone fusion simply occurs as a result of ossification through the preexisting cartilaginous fusion bars (Table 2).

Although speculative, these conclusions clearly indicate the potential value of integrating modern molecular knowledge, emerging from contemporary developmental biology, with problems of clinical dysmorphology and its interpretation. Although the role of Hox and Pax genes in human vertebral dysmorphogenesis remains to be fully elucidated, we nevertheless contend that molecular and genetic perspectives such as these must be integrated with the traditional clinical and, indeed, anthropological interpretations of causality.

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