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Cytogenetics of cranial base tumors

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Summary

Many different tumor types can arise in or invade the skull base. The more common tumors include, but are not limited to, angiofibromas, chondrosarcomas, chordomas, hemangiopericytomas, meningiomas, carcinomas, olfactory neuroblastomas, paragangliomas, pituitary adenomas, and rhabdomyosarcomas. Several of these tumors, including meningiomas, hemangiopericytomas, and rhabdomyosarcomas are characterized by nonrandom cytogenetic abnormalities. In this paper, we review the recognized chromosomal aberrations in cranial base tumors and illustrate the insights that can be gained into the genetic basis of tumor formation using karyotypes from skull base tumors that we have examined. As in tumors in other locations, chromosomal findings may be of diagnostic and prognostic value in cranial base tumors.

Introduction

Cancer is a genetic disease of somatic cells. Activation of oncogenes, loss of tumor suppressor genes, and genomic instability are common in solid tumors [1–6]. Cytogenetic abnormalities in hematologic malignancies are useful markers for diagnosis and prognosis and point to locations of specific genes where molecular disruptions have occurred [7]. Cytogenetic analysis of tumors has led to the localization and isolation of several tumor suppressor genes, including RB1, TP53 [8], DCC, and FAP/MCC (reviewed in [9]). In addition, cytogenetic studies have played a significant role in our understanding of the pathogenesis of colon cancer [10].

Numerous tumor types can arise in the skull base or invade this region. Although we present and discuss our results on chromosome abnormalities in cranial base lesions, we limit our literature review to the tumors we examined and some of the more common tumors in this area: angiofibromas, chondrosarcomas, chordomas, hemangiopericytomas, meningiomas, nasopharyngeal carcinomas, olfactory neuroblastomas, paragangliomas, pituitary adenomas, and rhabdomyosarcomas. The clinical features and histopathology of these tumors are well described (reviewed in [11]). Most primary skull base tumors are benign and/or slow growing, exhibiting few mitoses in histopathologic sections and responding poorly to tissue culture. Therefore, few classical cytogenetic analyses of primary cranial base tumors have identified chromosome abnormalities.

Molecular cytogenetic techniques, specifically, the use of fluorescence *in situ* hybridization (FISH), increase the success of identifying chromosome abnormalities in human tumors (e.g., [12, 13]). However, this method is most useful for identifying in interphase nuclei nonrandom chromosome abnormalities known to be associated with or diagnostic for a given tumor type. It is not useful, except as a shotgun method, for interphase cells from tumors in which a nonrandom numerical or structural chromosome abnormality has not yet been identified.

Table 1. Clinical, pathologic, and cytogenetic data on our cranial base lesions

Case	Age[a]	Gender	Histopathologic diagnosis	Location	Karyotype
1	13	M	Cemento-ossifying fibroma	Left maxillary sinus, nasal cavity, left orbit, pterygoids, middle cranial fossa posteriorly	46,XY,t(1;18)(q21;q21.3),t(3;10)(p13;q22),t(6;11)(p22;p15)[20]
2	32	F	Leiomyosarcoma	Sphenoid sinus, clivus	69,XX,+2,+3,+3,+4,+5,+i(6p),+i(6p),+7,+7,+9,+9,–10,+der(10)t(1;10)(q25;q26),+der(10)t(1;10)(q25;q26),+11,+der(11)t(?;11)(?;p15),–12,+der(12)t(1;12)(q21;q24),+der(12)t(1;12)(q21;q24),+15,+17,+18,+20,+20,+20,+mar1,+mar[consensus]
3	16	F	Neuroendocrine carcinoma	Central skull base	46,XX,t(6;11)(p22.2;q13),add(22)(q13)[12]/46,XX[7]
4	45	M	Recurrent amelanotic spindle cell malignant melanoma	Left maxilla, pterygopalatine fossa, cavernous sinus	46,XY[15]/92.<4n>,XXYY[5]/52–82.<3n>,XY,–X,t(1;3;4)(q11;p11;q31),der(6)t(X;6)(q11;q11),der(9)t(9;21)(p13;q11)del(9)(p13),i(15q),–17,der(19)t(17;19)(q21;q13),–21,+10mar,±various chromosomes[cp9]
5	3	M	Embryonal rhabdomyosarcoma	Infratemporal fossa with extension into cranial cavity	46,XY[8]/46,XY,t(1;4)(q21;q34),add(1)(p34),inv(3)(p13q26.2),t(4;19)(q21;q13),add(5)(q33),del(11)(q24),+13,del(14)(q24),–15[4]/46,XY,–2,der(3)t(2;3)(q13;p14),del(5)(p13p15),inv(7)(q22q36),del(11)(q23),–13,+2mar[3]
6	53	F	Undifferentiated carcinoma	Central face/right orbit, sphenoid sinus, frontal sinus, frontal dura	46,XX[3]/46,XX,?dic(17;20)(p12;q11),+der(17)t(17;?)(p12;?),der(19)t(19;?)(p13.2;?),–20[cp15]
7	38	M	Recurrent hemangiopericytoma	Middle fossa dura	44–51,XY,del(1)(p32p21),del(1)(p21),der(2)t(2;15)(2pter→2q36::15q11.1→15q22),del(4)(q21),inv(5)(q21q34),del(5)(q13),+der(5)t(5;8)(5pter→5q11::hsr::8q11→8qter),del(6)(p12.2),–8,del(9)(p21.2),–10,der(11)t(1;11)(p13;p15),del(11)(q14q23),del(12)(q22),del(12)(q13),inv(13)(q21q34),–15,der(17)t(2;15;17)(15q25→15q15::17p11.2→17q22::2q22→2qter),der(17)t(5;17)(q14;q23),+der(18)t(6;12;18)(12q11→12q24::18p11.2→18q23::6p21.1→6pter)[cp10]/68–93,<4n>,XXYY,idemx2[cp11]
8	39	M	Chondrosarcoma	Posterior nasal vestibule, involving the ethmoid bone	46,XY
9	6	M	Fibromatosis	Right infratemporal fossa, right mandible, right middle fossa, pterygoids	46,XY
10	50	M	Pituitary adenoma	Sella turcica	46,XY
11	6	M	Soft tissue sarcoma, high grade with both undifferentiated and rhabdomyoblastic components	Skull base, left middle fossa, left infratemporal fossa and parapharyngeal space	47,XY,r(6),+12[12]/48,XY,r(6),+12,+mar[2]/47,XY,+7[2]
12	12	M	Olfactory neuroblastoma	Cribriform plate, left nasal sinus, nasal septum, rostrum of sphenoid, nasopharynx, frontal sinus	46,XY

Table 1. Continued.

Case	Age[a]	Gender	Histopathologic diagnosis	Location	Karyotype
13	62	F	Meningioma	Orbits, ethmoids, cribriform plate, nasal bone, anterior cranial base	44,XX,add(3)(q26.3),der(17)t(17;21)(p11.2;q11),add(18)(p11.2), –19,–21,–22,+mar[6]/46,XX[12]
14	59	F	Paraganglioma	Right vagal nerve suture at jugular foramen	46,XX
15	3	F	Embryonal rhabdomyosarcoma	Left posterior nasopharyngeal mass	46,XX
16	29	F	Fibrosarcoma	Left infratemporal fossa, mandible, floor of middle cranial fossa	46,XX
17	9	F	Meningioma	Right orbit and ethmoidal bones	45,XX,–22/46,XX,–22,+mar
18	47	F	Pleomorphic adenoma, myxoid variant; recurrent × 6	Left infratemporal fossa, left external auditory canal, facial nerve	46,XX,inv(9)(p11q13)[1]/43–47,XX,inv(9)(p11q13),ins(14;8)(q32.3;q13q22), +r[3][cp15]/91–92,XXXX,inv(9)(p11q13),ins(14;8)(q32.3;q13q22)[cp2]

[a] Age at current surgery

Molecular karyotyping of interphase nuclei, even in the absence of metaphase chromosomes has proven useful in cytogenetic analysis of bladder carcinomas, breast tumors, testicular tumors, gastric tumors, and brain tumors (e.g., [13]). However, molecular cytogenetic investigation of primary skull base tumors has been limited to the assessment of loss of chromosome 22 in meningiomas [13] and the characterization of marker chromosomes and other chromosomal abnormalities in various individual neoplasms. In this paper, we review the recognized chromosomal aberrations in cranial base tumors and provide examples of karyotypes from tumors that we have examined.

Materials and methods

Fresh tumor specimens for cytogenetic analysis were isolated under sterile conditions in the operating room or under semisterile conditions in the surgical pathology laboratory, minced, and dissociated by our standard trypsin/collagenase digestion (20 min incubation in trypsin in Hanks' balanced salt solution (284 units/ml; Worthington Biochemical Company), followed by overnight disaggregation in collagenase (42.6 units/ml; Worthington Biochemical Company)), and cultured in "Initial Culture Medium" (Alpha-MEM (Earle's salts) with nucleosides (Irvine Scientific, Santa Ana, CA), supplemented with 13% fetal bovine serum, 5 μg/ml amphotericin B, 5 μg/ml chloramphenicol, 10 μg/ml clindamycin, 100 μg/ml penicillin G, 100 μg/ml streptomycin, and 2 mM L-glutamine). After one week in culture, the cells that were not harvested were plated in Alpha-MEM supplemented with 10% fetal bovine serum, 50 μg/ml gentamicin and 2 mM L-glutamine. Cultures were periodically passaged upon approaching confluence, by detachment of the cells with trypsin/EDTA (0.25 g/0.1 g/l, Irvine Scientific), and cells were frozen at each passage. A cytogenetic harvest was carried out as soon as actively dividing cells were observed in the cultures using standard techniques. Briefly, cells were arrested in metaphase by treatment for 5 h in 0.1 μg/ml Colcemid. Ethidium bromide (10 μg/ml) was added to the culture 3 h prior to termination of Colcemid action, to retard chromosome condensation. After brief trypsinization to release the cells from the flask, they were swollen in hypotonic 0.075 M KCl for 20 min at 37° C, and fixed in 3:1 methanol: acetic acid. Slides were prepared by the usual cytogenetic technique, baked overnight, and banded by a modified Klinger–Giemsa method [14]. Cytogenetic analysis of twenty metaphase cells was carried out in most cases, and karyotypes expressed in accordance with the International System for Chromosome Nomenclature [15].

Results

We have initiated cell cultures on approximately forty skull base tumors over the past four years. About one half of these failed to proliferate in culture, primarily because they were slow growing and/or benign and standard cell culture conditions are inadequate for these tumors. We successfully cultured and karyotyped eighteen cranial base tumors (Table 1). Of these, seven (39%) had normal karyotypes, which could suggest that the tumor cells have not undergone gross genetic alterations and therefore, exhibit slow growth and relatively benign behavior. Alternatively, normal karyotypes could be the result of normal stromal cell proliferation in culture rather than tumor cell growth, and simply reflect the constitutional karyotype of the patient. The remaining eleven tumors had either abnormal karyotypes or were mosaic, with both normal and abnormal clones. We will review briefly the karyotypic findings in each of the chromosomally abnormal tumors that we analyzed and then discuss cytogenetic findings in other cranial base lesions.

Case 1: This cemento-ossifying fibroma from a patient with nonfamilial bilateral multicentric retinoblastoma showed three balanced translocations, although the constitutional karyotype of the patient was normal [16]. Although the karyotype resembles that of a radiation-induced sarcoma, and bilateral retinoblastoma patients often develop an excess of these tumors, the tumor was outside the radiation field in this patient, according to medical records. Furthermore, the histopathology does not indicate

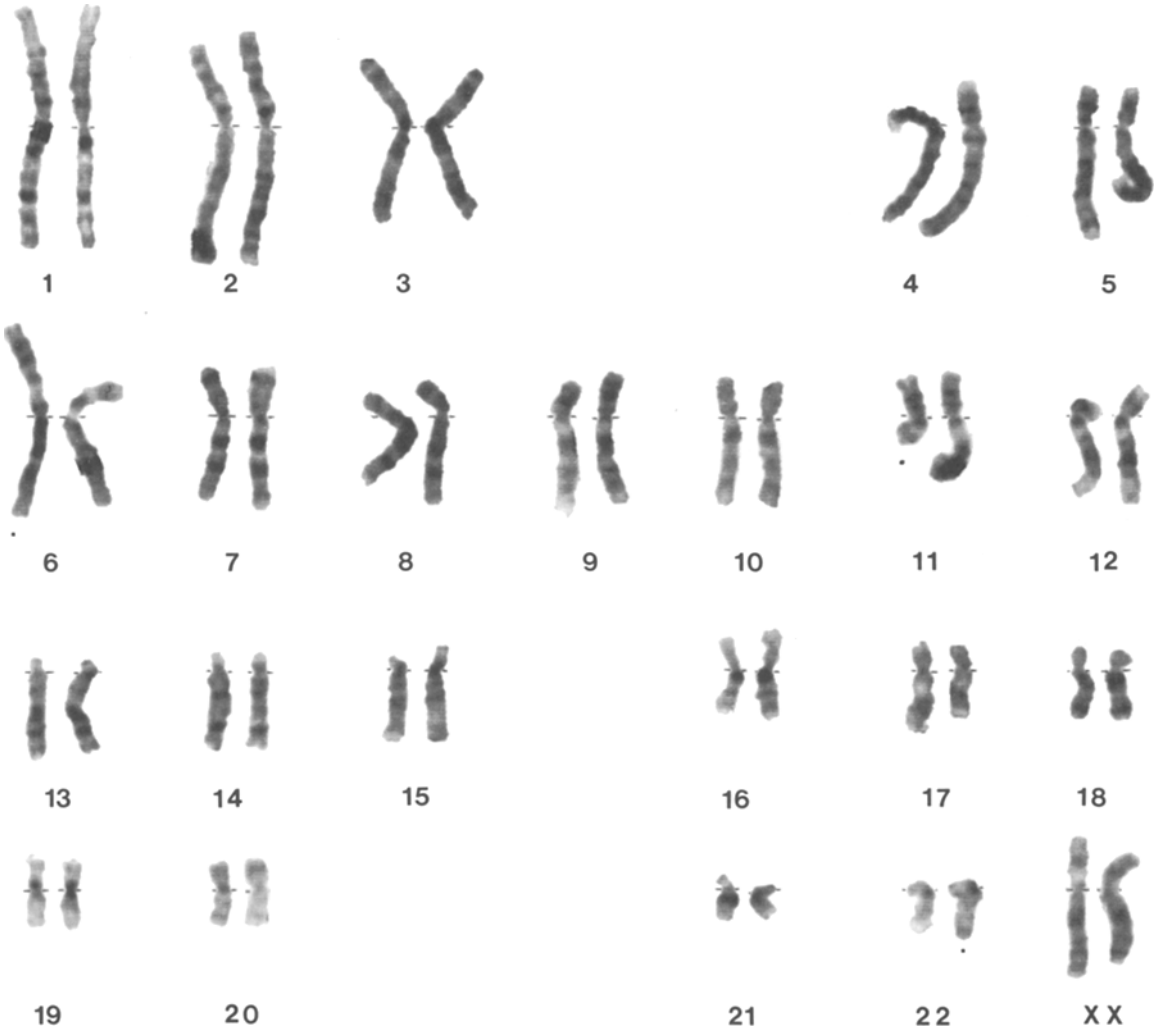

Fig. 1. Representative trypsin-Giemsa banded karyotype from case 3. 46,XX,t(6;11)(p22.2;q13),add(22)(q13). Dots below chromosomes, structural abnormalities.

the presence of sarcoma, but is clearly consistent with a benign cemento-ossifying fibroma. This case represented the first reported cytogenetic analysis of this tumor type.

Case 2: The karyotype from this sinonasal leiomyosarcoma is described in detail elsewhere [17]. Briefly, analysis showed near-triploid and near-tetraploid chromosome numbers with extensive structural and numerical aberrations. Three consistent structural abnormalities, including i(6p), der(10)ins (10;1)(q26;q23q44), and der(12)t(1;12)(q11;q24) were observed in the majority of cells. Other clonal structural arrangements were also present, including a der(11)t(11;?)(p15;?) and del(21)(q22). A large number of numerical chromosome alterations, including trisomies 7 and 20, were observed. Consistent karyotypic aberrations, especially del(1)(p13), rearrangements at 11p15 and 21q22, and trisomies 7 and 20, appear to be emerging as key findings in leiomyosarcoma, although understanding their significance requires cytogenetic analyses and clinicopathologic correlation of the findings in additional tumors.

Case 3: Primary cultures of this high grade, neu-

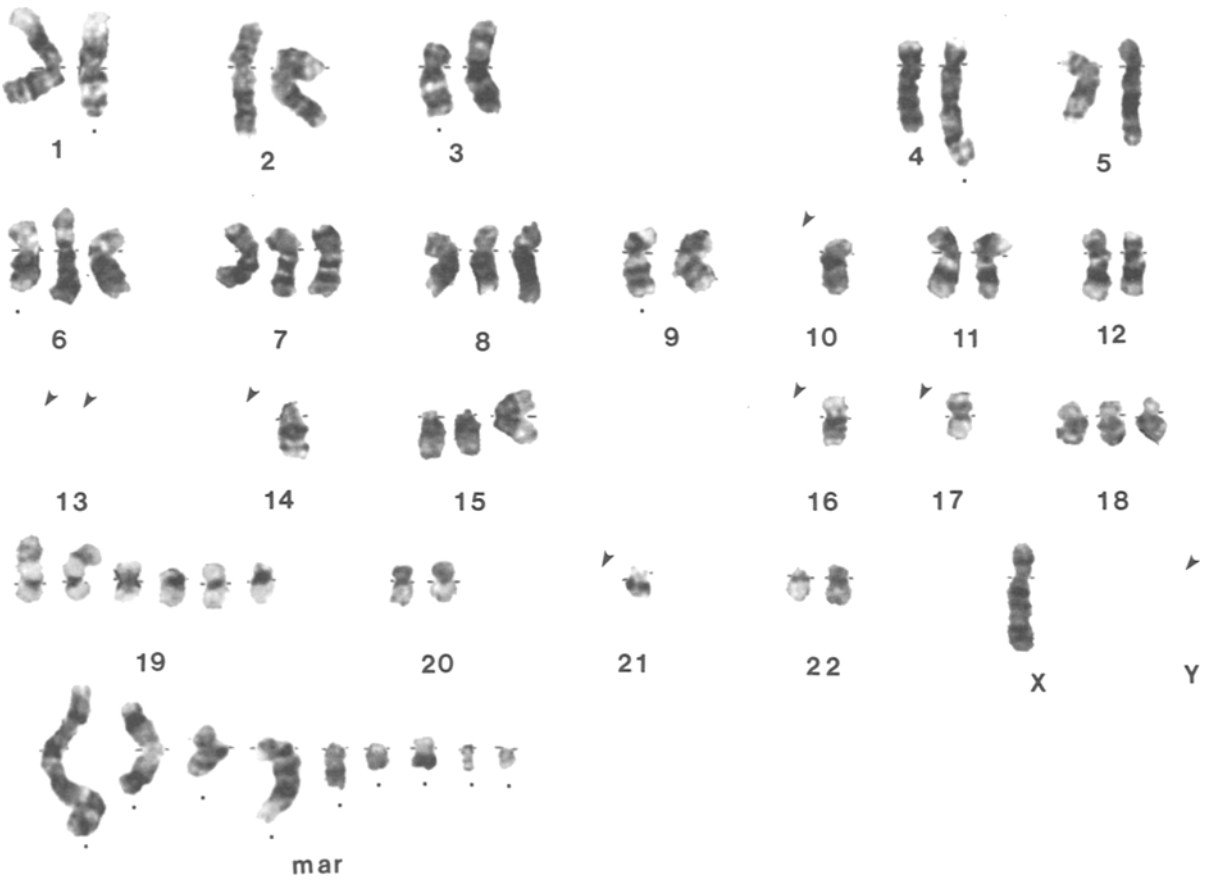

Fig. 2. Karyotype from case 4. 56, t(X;6)(q11;q11), –Y,t(1;3;4)(q11;p11;q31), +6, +7, +8, der(9)t(9;21)(p13;q11), –10,–13, –13, –14, +i(15q), –16, –17, t(17;19)(q21;q13), +18, +der(19)t(17;19)(q21;q13), +19, +19, +19, –21, +9mar. Dots below chromosomes, structural abnormalities; arrowheads, numerical abnormalities; mar, marker chromosomes.

roendocrine carcinoma with focal glandular differentiation expressed a mosaic karyotype with an apparently normal clone and one with a translocation between chromosomes 6 and 11 and an abnormal chromosome 22 with unidentifiable chromatin attached to the distal long arm (Fig. 1). These exact chromosome abnormalities have not been reported previously in head and neck tumors. However, other rearrangements of 6p and 11q13 have been seen in head and neck squamous cell carcinomas and in carcinomas of the lung [18, 19].

Case 4: Immunocytochemical analysis of this metastatic amelanotic spindle cell malignant melanoma showed positive staining for S-100 protein and absence of HMB-45 protein. Karyotypic analysis of primary and passage 2 cultures showed a normal clone, one with a near-tetraploid chromosome pattern without clonal structural abnormalities, and one that appears to be near-triploid with multiple structural chromosome abnormalities, consistent with the diagnosis of melanoma (Fig. 2). Structural abnormalities of chromosomes 1, 6, and 9, resulting in monosomy 6q and 9p and duplication of 1q, are nonrandom chromosome findings in malignant melanoma development and progression [20].

Case 5: This embryonal rhabdomyosarcoma expressed desmin and myoglobin on immunocytochemical staining and exhibited radiation changes on histopathologic analysis. The mosaic karyotype is rather unusual, with a normal clone, and two

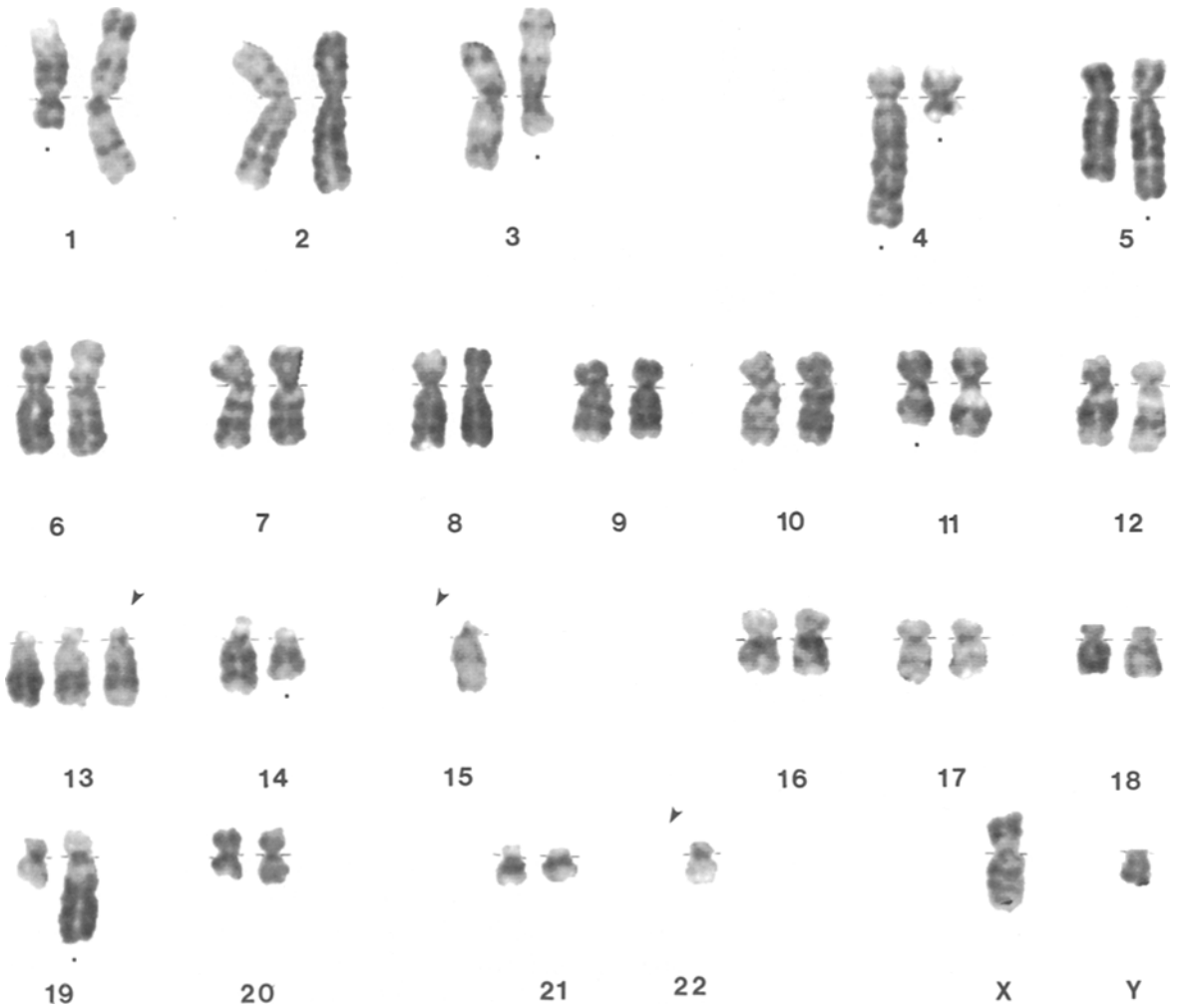

Fig. 3. Karyotype from one clone in case 5. 45, XY, t(1;4)(q21;q34), add(1)(p34), inv(3)(p13q26.2), t(4;19)(q21;q13), add(5)(q33), del(11)(q24), +13, del(14)(q24), –15, –22. Dots below chromosomes, structural abnormalities; arrowheads, numerical abnormalities.

chromosomally distinct abnormal clones observed in cultures at passages 1 and 2 (Figs 3 and 4). The large number of karyotypic changes may be in part the result of radiation therapy, chemotherapy, or both. In contrast to alveolar rhabdomyosarcomas, in which a t(2;13)(q35;q14) results in alteration of the PAX3 paired box gene [21–23], embryonal rhabdomyosarcomas often express full or partial trisomy 2 and/or 20 [24]. The findings in the present tumor, including rearrangements involving 1q21 and 19q13 and loss of 11q23–24, are consistent with rhabdomyosarcomas reported previously [25, 26]. Although the breakpoints appear to differ in the two abnormal clones, both have deletions of 11q23–24, which may be associated with loss of a tumor suppressor gene [26]. Further understanding of the genetic basis of embryonal rhabdomyosarcoma requires chromosomal and molecular genetic analysis of additional tumors.

Case 6: Although this tumor was originally thought to be a hemangiopericytoma, it appears to be an undifferentiated carcinoma, since immunocytochemistry shows positive staining for prekeratin and AE1/AE3, negative reticulin staining, and negative antibody reactions for factor VIII, vimentin, des-

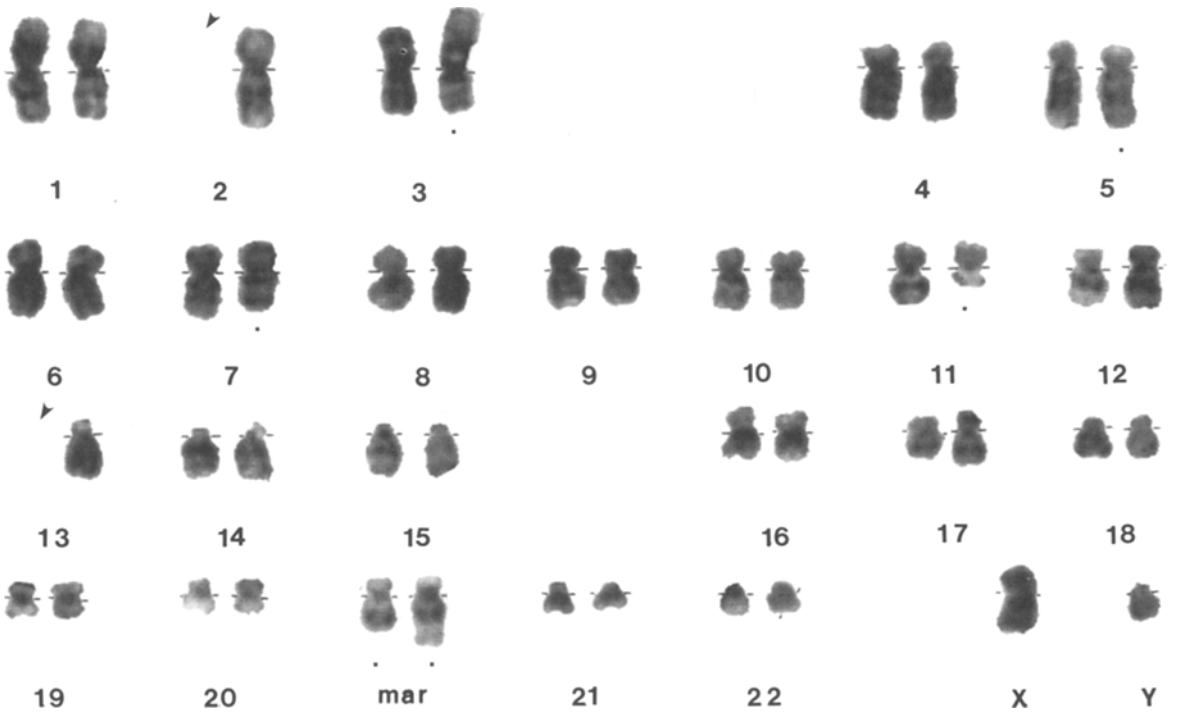

Fig. 4. Karyotype from the second clone in case 5. 46,XY,–2,der(3)t(2;3)(q13;p14),del(5)(p13p15),inv(7)(q22q36),del(11)(q23), –13,+2mar. Dots below chromosomes, structural abnormalities; arrowheads, numerical abnormalities; mar, marker chromosomes.

min, actin, and S-100. Karyotypic analysis of this rapidly growing tumor at passages 2 (9 days), 3 (23 days), and 4 (30 days) showed a mosaic chromosome pattern with an apparently normal clone and one that appears to have partial trisomy 17. The significance of this finding is not clear at this time.

Case 7: The patient had a 16 year history of hemangiopericytoma, first observed in the right parotid gland with extension to the skull base, treated four times with surgery, twice with radiation therapy, and finally, again with skull base surgery after the tumor recurred in the middle fossa dura (from which cell cultures were initiated). Cytogenetic analysis of cells from primary cultures harvested 22 days after initiation and passage 1 (28 days) and passage 2 (35 days) cultures expressed very complex chromosome abnormalities in a near-diploid cell line and a near-tetraploid one representing a duplication of the former [27]. Radiation therapy may have caused some of the structural rearrangements. As in our case, eight of the 14 hemangiopericytomas reported in the literature to have undergone karyotypic analysis showed chromosome abnormalities involving numerous chromosomes [28–32]. Our tumor had deletions of the long arm of chromosome 12. Deletions of 12q are nonrandom findings in hemangiopericytomas, suggesting the possibility that a tumor suppressor gene may be located in this chromosomal region.

Case 11: Four and seven day harvests of primary cultures of this tumor, characterized histopathologically as a high grade soft tissue sarcoma with undifferentiated and rhabdomyoblastic components, showed a mosaic chromosome pattern. Trisomy 12 and a ring chromosome 6 were expressed in two of three clones (Fig. 5) and trisomy 7 was the sole finding in the third clone. Trisomy 12 has been reported in several cases of rhabdomyosarcoma [33]. In solid tumors, trisomy 7 is found to be associated with stromal cells in head and neck squamous cell carcinomas, renal cell carcinomas, and gliomas [34–36].

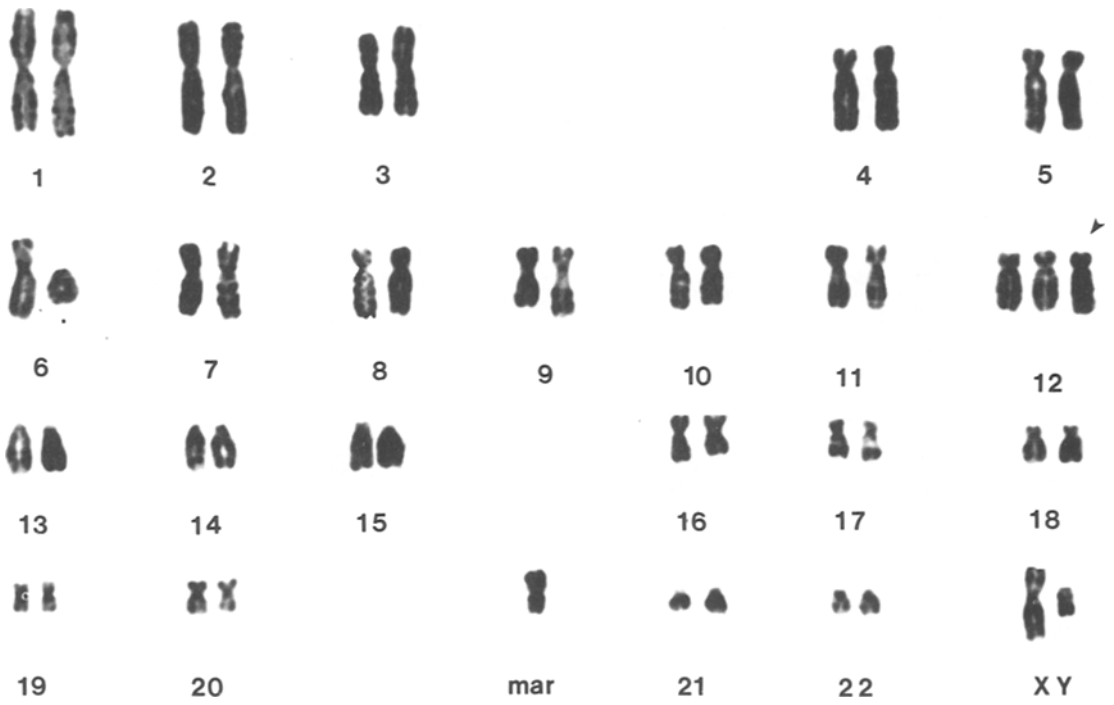

Fig. 5. Karyotype from case 11. 48,XY,r(6),+12,+mar. Dots below chromosomes, structural abnormalities; arrowheads, numerical abnormalities; mar, marker chromosome.

Case 13: This meningothelial cell neoplasm arranged in whorls was harvested after 11 days (primary culture), 13 days (passage 1), and 71 days (passage 2) in culture and expressed a mosaic chromosome pattern with a normal cell line and one with several numerical and structural chromosome abnormalities, including monosomy 22 (Fig. 6). Monosomy 22 is a consistent chromosomal finding in at least one half of meningiomas [37–39]. Meningiomas associated with neurofibromatosis type 2 express molecular alterations, including loss of the merlin gene, the protein product of which appears to play a role in linking the cell membrane to the cytoskeleton [40]. The significance of the other chromosome changes in our patient are not known, but may have evolved over the 11 year history of the tumor.

Case 17: This meningioma showed a mosaic chromosome pattern with monosomy 22 in the stemline and a supernumerary marker chromosome in a sideline (Fig. 7). As discussed above, monosomy 22 is characteristic of meningiomas.

Case 18: The patient from whom this tumor was removed had a history of six prior surgeries to control pleomorphic adenoma of the left parotid region. During her last surgery, a deep infratemporal fossa tumor was removed. The current tumor was described as pleomorphic adenoma, myxoid variant. Harvests of primary and passage 1 tissue cultures (6, 8, 15, 29 days) showed a mosaic chromosome pattern with inv(9)(p11q13) as a constitutional chromosome polymorphism and rearrangements of chromosomes 8, 9, and 14 (Fig. 8). Pleomorphic adenomas of the salivary glands have been well characterized cytogenetically, and found to be composed of three subgroups, one expressing aberrations of 8q12, one with rearrangements of 12q13–15, and one with normal karyotypes [41]. Our breakpoint at 8q13 is in the G-negative band adjacent to 8q12; therefore, the chromosome could actually be rearranged at the same location common to pleomor-

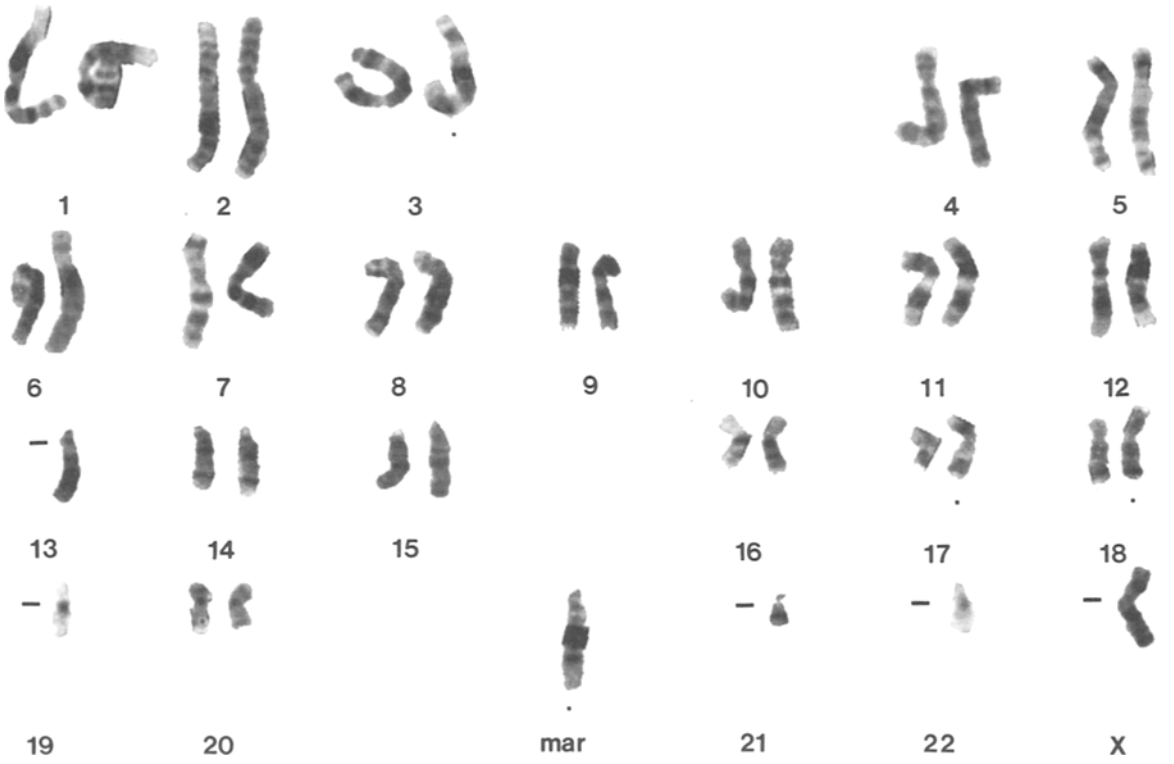

Fig. 6. Karyotype from case 13. 42,X,–X,add(3)(q26.3),–13,der(17)t(17;21)(p11.2;q11),add(18)(p11.2),–19,–21,–22,+mar. Dots below chromosomes, structural abnormalities; dashes, numerical abnormalities (losses); mar, marker chromosome.

phic adenomas of the salivary glands. The near-tetraploid clone with the same abnormalities seen in the near-diploid cell line most likely represents karyotypic evolution.

Discussion

The following is a brief review of cytogenetic findings in common cranial base lesions not mentioned above, including angiofibromas, chondrosarcomas, chordomas, nasopharyngeal carcinomas, olfactory neuroblastomas, paragangliomas, and pituitary adenomas. No reports of chromosome abnormalities in angiofibromas and paragangliomas could be identified. However, paragangliomas have been reported to express an autosomal dominant mode of inheritance. Linkage analysis showed strong evidence of linkage to 11q23–qter [42]. Further, genomic imprinting appears to play a role in paragangliomas, since expression of the phenotype requires inheritance of the disease gene from a male carrier.

Cytogenetic analysis of chondrosarcomas shows consistent rearrangements involving bands 12q13–15 [43, 44]. This breakpoint region has been reported in other tumors [43], including a soft tissue chondroma, hemangiopericytomas, myxoid liposarcomas, lipomas, uterine leiomyosarcomas, myomas, and pleomorphic adenomas of the salivary gland. Rearrangements of chromosome 1 have also been reported in chondromatous tumors [43]. A t(9;22)(q22–31;q11–12) is considered a nonrandom chromosomal aberration in extraskeletal myxoid chondrosarcomas [45].

Chromosome analyses of only four chordomas have been reported. Persons *et al.* [46] analyzed two sacral chordomas and found a normal karyotype in one case and a mosaic karyotype with two distinct abnormal clones in the other, 44,XY,t(1;3)(q42;q11), –2,der(7)t(2;7)(q23;q32),–21/46,X,t(Y;8)(q12;q22),

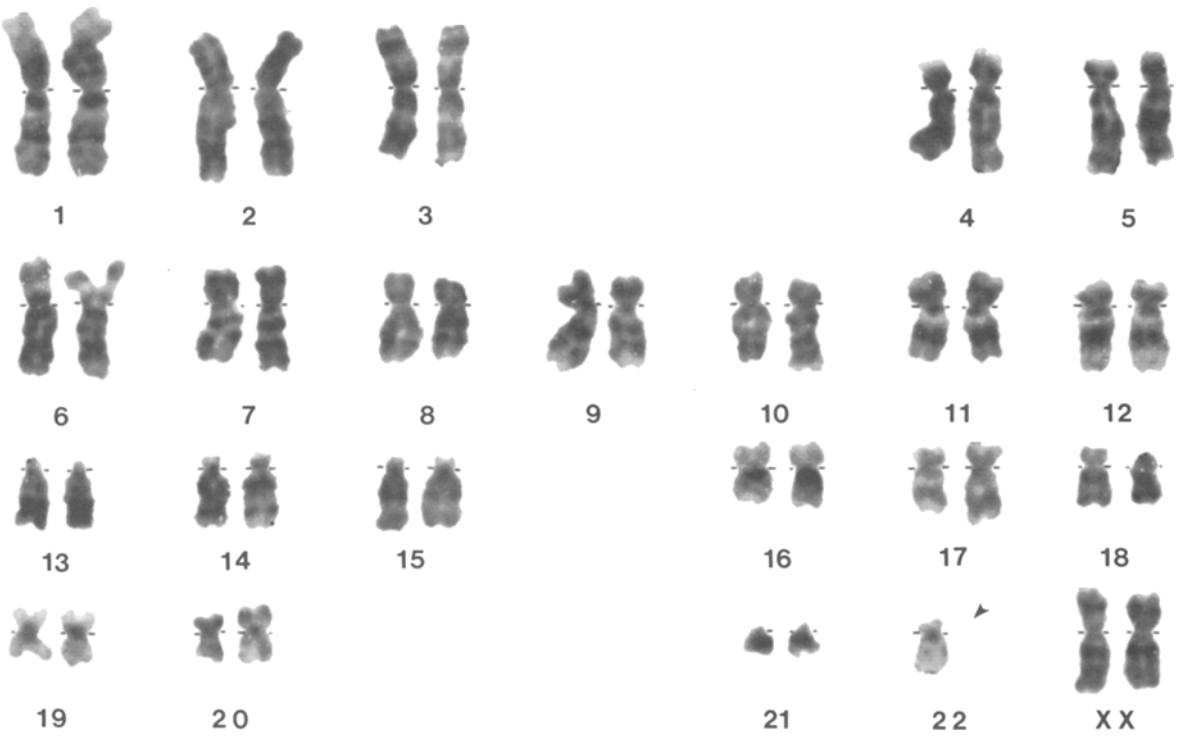

Fig. 7. Karyotype from case 17. 45,XX,–22. Arrowheads, numerical abnormalities.

t(1;14)(p34;q32),t(5;10)(q13;p11). Gibas *et al.* [47] analyzed two sacral chordomas that both expressed numerical and structural aberrations. One tumor was hypodiploid with a structural abnormality, der (21)t(1;21)(q21;q22). The other tumor was near-triploid and expressed numerous structural rearrangements, including a der(21)t(2;21)(q11;q22). Thus, although not seen in the first two tumors, the latter two tumors exhibited structural abnormalities of band 21q22, suggesting possible involvement of this band in tumor formation.

Numerous chromosome abnormalities have been seen in nasopharyngeal carcinomas, including loss of chromosome 3. Molecular analysis showed loss of heterozygosity for either one or both DNA probes, RAF1 and D3S3 at 3p25 and 3p14, respectively, in 35 of 36 informative nasopharyngeal carcinomas examined [48]. These results are similar to our recent and as yet unpublished findings in oral squamous cell carcinoma, suggesting the involvement of key tumor suppressor genes on chromosome 3p in the development of head and neck tumors.

Few cytogenetic analyses of olfactory neuroblastomas or esthesioneuroblastomas have been published. VanDevanter *et al.* [49] observed a 47,XY,+8 karyotype in one tumor after short term culture. Previous reports of cytogenetic analysis of olfactory neuroblastoma cell lines showed partial trisomy 8, t(11;22)(q24;q12) (that is characteristic of small blue round cell tumors), and other aberrations [50, 51].

Pituitary adenomas appear to be characterized cytogenetically by numerical and structural chromosome abnormalities, including del(18)(p11) in one case [52, 53]. However, no consistent chromosome changes have been reported in the literature.

Although chromosome analyses of hematologic malignancies began in earnest in the 1970s, solid tumor cytogenetics is still in a youthful stage. Chromosome analysis of cranial base lesions is in its infancy. More common malignancies, such as meningiomas, are revealing their genetic etiologies after examination of large numbers of tumors, identification of consistent chromosome abnormalities, and through careful dissection of the molecular genetic alterations present in the tumors. The significance

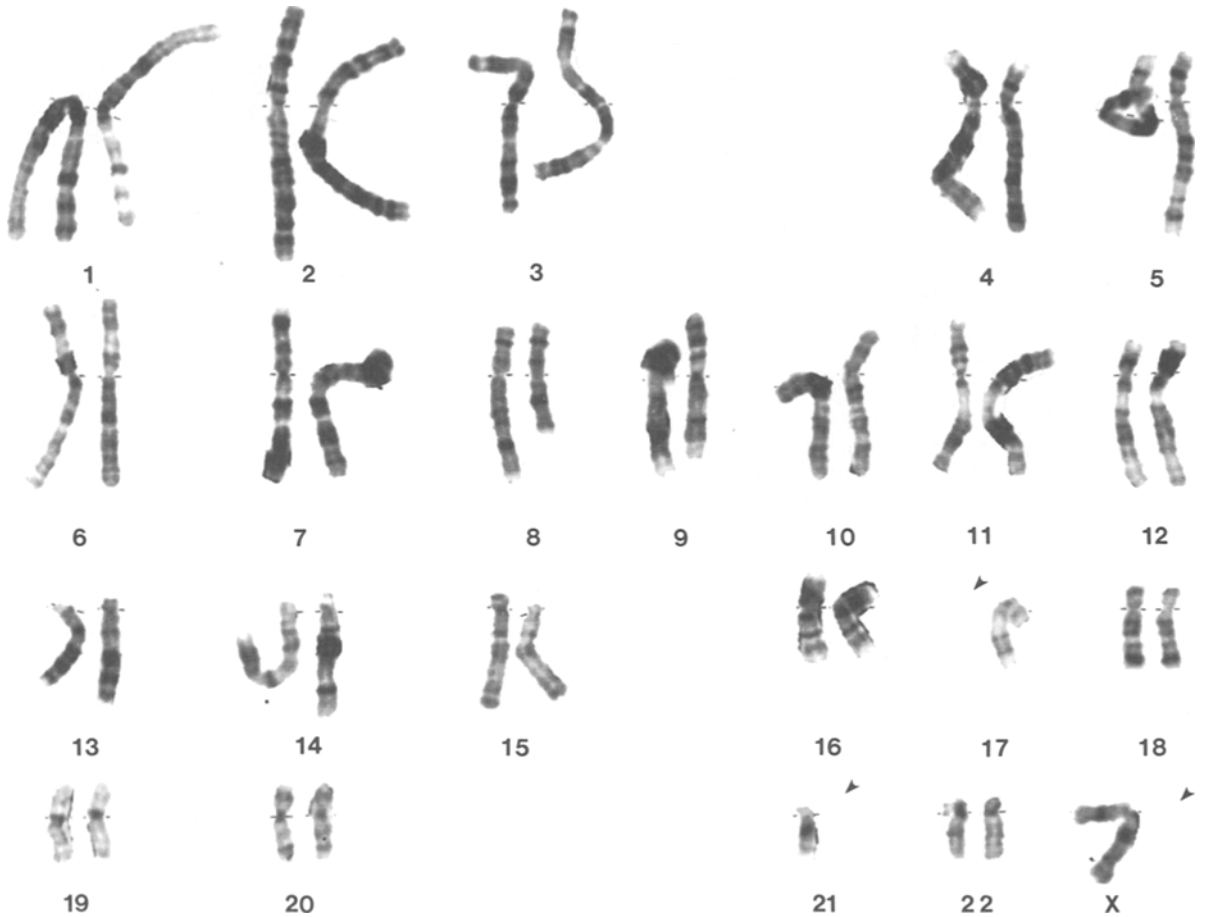

Fig. 8. Karyotype from case 18. 43,X,-X,ins(14;8)(q32.3;q13q22),inv(9)(p11q13),-17,-21. Dots below chromosomes, structural abnormalities; arrowheads, numerical abnormalities.

of many of the chromosome abnormalities reported here is unknown, due to the small numbers of tumors of each type that have undergone cytogenetic analysis. Further systematic study of cranial base tumors by teams consisting of surgeons, pathologists, cytogeneticists, and molecular geneticists will shed light on the genetic changes that result in tumorigenesis and provide diagnostic and prognostic, and perhaps, therapeutic tools.

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