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APPLICATION OF PERSONAL COMPUTER TO AN ANALYSIS OF SMALL *DE NOVO* CHROMOSOMAL INSERTION: A CASE OF *DE NOVO* 3q2 TRISOMY WITH ins(8;3)

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Summary To identify the origin of a small inserted segment in a *de novo* 8p+ chromosome, an originally programmed computerized database for chromosomal aberration syndromes was utilized. The system selected 3q2 trisomy and 10q2 trisomy as candidates. As a result of a careful comparison of several high-resolution banding patterns among chromosomes 3, 10 and the inserted segment, her karyotype was disignated as: 46,XX,−8,+der(8), inv ins(8;3)(p21.1;q26.32q24) *de novo*. A small segment from 3q24 to 3q26.32 was trisomic, and invertedly inserted into the short arm of chromosome 8. This computerized database was considered to be useful for analyses of the small *de novo* inserted chromosomal segment.

Key Words 3q2 trisomy, personal computer, diagnosis, chromosomal aberration syndrome

INTRODUCTION

It is often difficult to identify the origin of a small *de novo* extra chromosomal segment inserted into a chromosome, even if several banding and high-resolution banding techniques were used to analyse. We tried to analyse the origin of a small inserted segment in a *de novo* 8p+ chromosome using computerized database for chromosomal aberration syndromes, originally programmed by one of us (K.N.).

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MATERIALS AND METHODS

Personal computer database for chromosomal aberration syndromes (PC-DCAS). The system was written by Basic language, and programmed to drive by "MENU" screen. One can select "Data entry" or "Syndrome reference" on the MENU. To obtain rapid access time, the database was programmed to be composed of 500 wells, to which sequential coded numbers were given (001–500). Coded number of each well was compared to each of clinical findings. If a finding was positive in a syndrome, a flag "1" was given to the corresponding well with the same coded number of a syndrome. Namely, clinical findings were input by a present or absent manner. Thus, the frequency was not reflected in the database. Practically, total 245 clinical findings were selected and coded numbers were given to each (Table 1). These findings were summarized in each 93 chromosomal aberration syndromes (de Grouchy and Turleau, 1984) (Table 2). The data were directly input into hard disk (40-MB) of IBM Japan-5560 personal computer (operated by MS-DOS) to obtain rapid access time.

The reference system was programmed to be able to refer one finding or a combination of maximum ten findings, and maximum ten candidate syndromes, which matched all of referred findings, to be shown on CRT within a few seconds ("AND" system). Experiences suggested that selecting a combination of three or four findings was reasonable for analysing a small *de novo* extra chromosomal rearrangement. The system can also be driven by a floppy disk, though it needs a bit more time to access.

Patient. The propositus, a 1-year-old girl, is the second child born to healthy, unrelated parents, when the mother was 23 and the father was 30 years of age. The mother gained 15 kg in weight during the pregnancy. Baby girl was delivered spontaneously at 41 weeks. Her weight was 3,180 g, length 49.0 cm, and head circumference 35.5 cm. Apgar score was 9. A cleft palate was noted soon after birth as well as cleft lip of left side, which went to surgery at 4 months of age.

At 13 months of age, when she was referred to us, failure to thrive and developmental retardation were obvious. Her length was 73.5 cm (−0.6 S.D.), weight 6,650 g (−5.7 S.D.), head circumference 46.5 cm (+0.9 S.D.). Her craniofacial dysmorphism included brachycephaly, wide protruding forehead, epicanthal folds, synophrys, protruding glabella, strabismus, long eyelashes, flat and wide nasal bridge, cleft palate, cleft lip, large mouth with downturned corners, micrognathia, low-set ears and prominent anthelices. Short neck, diastasis recti abdomini, small pelvis, hypoplastic labia minora were noted in the trunk. The extremities showed proximal implantation of the thumbs, clinodactyly and hypoplastic nails of 5th fingers, dorsiflexed great toes and severe hypotonia. The dermal ridges were hypoplastic and supernumerary flexion creases were seen in the palms (Fig. 1). The brain CT scan showed cavum septi pellucidi. Combined hearing defect was de-

Table 1-I. Code numbers of clinical findings input in personal computer database for chromosomal aberration syndromes (PC-DCAS).

001	mean birth weight:>2500g	063	long eyelashes
002	mean birth weight:2500-3000g	064	large glabella
003	mean birth weight: normal	065	protruding glabella
004	small birth length (46cm)	066	Brushfield's spots
005	hypotonia	067	small eyes
006	hypertonia	068	large eyes
007	severe hypotrophy	069	squinty eyes
008	corpulent infants	070	Doe's eyes
009	short stature	071	minor ocular anomalies
010	high stature	072	severe micro- or anophthalmia
011	dolichomorphism	073	retinoblastoma
012	peculiar cry	074	aniridia
013	laryngeal hypotonia	075	protruding nose bridge
014	recurrent infections	076	flat nose bridge
015	survival in adulthood	077	wide nose bridge
016	subnormal growth	078	aplastic nose bones (boxer nose)
017	short life expectancy	079	Greek profile
018	overgrowth	080	short nose
019	seizure	081	long nose
020	pleasant personality	082	bulbous nose
021	aggressivity	083	beaked nose
022	obesity	084	broad nose
023	microcephaly	085	pointed nose
024	macrocephaly	086	upward nares (anteverted nostrils)
025	dolichocephaly	087	downward nares
026	brachycephaly	088	long upper lip
027	trigonocephaly	089	short upper lip
028	turricephaly	090	thin upper lip
029	craniosynostosis	091	thin lips
030	wide sutures/fontanels	092	everted lower lip
031	prominent metopic suture	093	chewing lower lip
032	high forehead, frontal bossing	094	thick lips
033	receded forehead	095	deep philtrum
034	low forehead	096	flat philtrum
035	narrow forehead	097	unilateral grin
036	temporal indentation/ frontal & parietal bossing	098	cleft lip
		099	cleft palate
037	abnormal hairline on forehead	100	high arched palate
038	protuberant occiput	101	long philtrum
039	round and flat face	102	short philtrum
040	oval face	103	small mouth
041	long face	104	wide mouth
042	triangular face	105	down-turned mouth
043	depressed midface	106	oval-shape mouth
044	elfin face	107	turtle beak-shape mouth
045	small face	108	carplike mouth
046	high cheekbones	109	pursed mouth
047	round cheeks (heavy cheeks)	110	macroglossia
048	upward slant of palpebral fis.	111	glossoptosis
049	downward slant of palpebral fis.	112	rabbit teeth
050	narrow palpebral fissures	113	dental anomalies
051	large palpebral fissures	114	micrognathia
052	almondlike fissures	115	protruding chin
053	blephalophimosis	116	large mandible
054	hypertelorism	117	effaced angles of the mandible
055	hypotelorism	118	pointed chin
056	epicanthus	119	prominent maxilla
057	exophthalmos	120	oral anomalies
058	deep set eyes	121	low-set ears
059	ptosis	122	posteriorly rotated ears
060	arched eyebrows	123	small ears
061	synophris	124	large ears
062	abnormal eyebrows	125	detached ears

Table 1-II. Code numbers of clinical findings input in personal computer database for chromosomal aberration syndromes (PC-DCAS).

126	faun-like ears	187	brachydactyly
127	flat helix	188	brachymesophalangia
128	folded helix	189	brachymetacarpia
129	protruding anthelix	190	camptodactyly
130	aplastic anthelix	191	long fingers
131	aplastic or adherent lobe	192	arachnodactylia
132	protruding tragus	193	elongated second phalange
133	protruding antitragus	194	tapered fingers
134	preauricular dimples, fistula, tag	195	overlapping fingers
135	deafness	196	thumb anomalies
136	short neck with redundant skin	197	proximally implanted thumbs
137	long, thin neck	198	anomalies of the radial axis
138	flat nape	199	pointed fingertips
139	pterygium colli	200	flexion contracture (fingers)
140	low hairline	201	malposition of fingers & toes
141	short sternum	202	abnormal fingers
142	large thorax	203	hypoplastic nails
143	long thorax	204	dysplastic nails
144	wide thorax	205	club feet
145	pectus excavatum	206	rocker-bottom feet
146	funnel chest	207	dorsiflexion of big toe
147	gynecomastia	208	abnormal toes
148	wide-spaced nipples	209	palmature
149	supernumerary nipples	210	deep furrows
150	low-set nipples, abnormal nipples	211	lymphoedema
151	supernumerary ribs/rib anomaly	212	hemangioma
152	scoliosis	213	marbelized skin
153	narrow pelvis	214	nevi
154	decreased acetabular angles	215	dimples
155	hernias	216	ulceration of the scalp
156	diastasis recti	217	dry skin and scarce, thin hair
157	retentio testis, micropenis	218	thick subcutaneous tissue
158	testicular atrophy	219	hirsutism
159	macroorchidism	220	abnormal palmar creases (simian crease etc.)
160	hypospadias		
161	hyperplasia of labia minora	221	immature ridges
162	hypoplasia of labia minora	222	hypermature ridges
163	streak gonads	223	distal axial triradius
164	abnormal uterus	224	excess of arches
165	anal atresia and perianal malformation	225	excess of whorls
166	primary amenorrhea	226	excess of ulnar loops
167	absence of puberty	227	supernumerary flexion creases
168	ambiguous genitalia	228	absence of triradii b and c
169	hypogonadism	229	deep plantar crease
170	slender limbs	230	t'
171	stocky limbs	231	t''
172	hyperflexed limbs	232	cardiac malformation
173	pleading posture	233	renal and urinary tract malformation
174	froglike position		
175	cubitus valgus	234	digestive malformation
176	radioulnar synostosis	235	cerebral malformation
177	absent knee cap	236	corpus callosum agenesis
178	genu valgum	237	severe ocular anomalies
179	ligamental hyperlaxity	238	osteoarticular, minor malformation
180	collar bone agenesis	239	osteoarticular, severe malformation
181	long hands	240	similar to Aarskog syndrome
182	short stubby hands	241	similar to de Lange syndrome
183	long palms	242	similar to Pierre Robin syndrome
184	syndactyly	243	thymus aplasia
185	hexadactyly or polydactyly	244	vertebral anomalies
186	clinodactyly	245	similar to Treacher-Collins syndrome

Table 2. List of syndromes input in personal computer database for chromosomal aberration syndromes (PC-DCAS).

No.	Syndrome	No.	Syndrome	No.	Syndrome
01	1q32→qter trisomy	33	9p trisomy	64	16p trisomy
02	1q23 or 5→qter trisomy	34	9p tetrasomy	65	16q trisomy
03	1q25→q32 trisomy	35	9p2 monosomy	66	16q monosomy
04	1q4 monosomy	36	r(9)		
05	r(1)	37	9q3 trisomy	67	17q2 trisomy
06	2p2 trisomy	38	9 trisomy	68	18 trisomy
07	2q3 trisomy	39	10q2 trisomy	69	18q2 trisomy
08	3q2 trisomy	40	10p trisomy	70	18 p&q trisomy
09	3p2 monosomy	41	10p monosomy	71	18p monosomy
10	3p2 trisomy	42	10q2 monosomy	72	18q2 monosomy
11	3p monosomy	43	r(10)	73	r(18)
12	4p monosomy	44	11q2 trisomy	74	19q trisomy
13	4p trisomy	45	trisomy by t(11;22)	75	20p trisomy
14	4q2 & 3 trisomy	46	11q2 monosomy	76	21 trisomy
15	4q3 monosomy	47	11p13 monosomy	77	r(21)
16	5p monosomy	48	11p trisomy	78	21q1 monosomy
17	5p trisomy	49	12p trisomy	79	The cat-eye syndrome
18	5q3 trisomy	50	12p monosomy	80	r(22)
19	6p2 trisomy	51	12q2 trisomy	81	Turner syndrome
20	6q2 trisomy	52	13 trisomy	82	Noonan syndrome
21	r(6)	53	13q2&3 trisomy	83	47,XXX
22	7q3 trisomy	54	13q1 trisomy	84	48,XXXX
23	7q2 trisomy	55	13q3 monosomy or r(13)	85	49,XXXXX
24	7q3 monosomy	56	13q monosomy & retinoblastoma	86	Klinefelter syndrome
25	7q2 monosomy	57	14q1 trisomy	87	46,XX male
26	7q1 monosomy	58	14 trisomy	88	47,XYY
27	7p2 trisomy	59	r(14)	89	48,XXYY
28	7p2 monosomy	60	15q1 trisomy	90	49,XXXXY
29	8 trisomy	61	15q2 trisomy	91	fra(X)(q27 or 28)
30	8q2 trisomy	62	15q1 monosomy & Prader-Willi syndrome	92	Triploidy
31	8p trisomy	63	r(15)	93	Tetraploidy
32	8p2 monosomy				

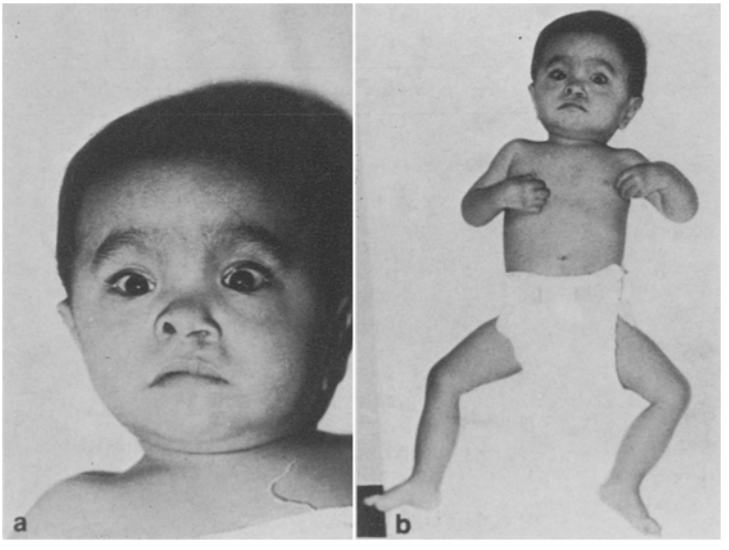

Fig. 1. The propositus at 13 months of age.

tected as well as chronic otitis media. Her developmental quotient was 42 at 13 months.

Cytogenetics. A conventional G-banded analysis of the propositus revealed 46,XX,8p+ karyotype, in which a small extra segment was inserted. The karyotypes of the parents were normal. Prometaphase cells of peripheral lymphocytes from the propositus were obtained by ethidium bromide and BrdU treatment, and used for GTG-, QFQ- and RBG-banding analyses.

RESULTS

In her clinical findings, cleft lip, short nose, low nasal bridge and epicanthal folds were selected to refer after several trials. PC-DCAS selected 1q4 monosomy, 3q2 trisomy, 4q3 monosomy, 7p2 monosomy and 10q2 trisomy as candidates. Because monosomies were considered to be excluded in the 8p+ segment, several banding patterns of chromosomes 3 and 10 were compared carefully to the inserted extra segment. As a result, a small segment from 3q24 to 3q26.32 seemed to be trisomic and invertedly inserted into 8p (Fig. 2). Her karyotype was designated as: 46, XX, −8, +der(8),inv ins(8;3)(p21.2;q26.32q24) *de novo*. Plasma somatostatin value, 23 pg/ml (RIA), was considered to be within normal limits of infants (Koshimizu *et al.*, 1985).

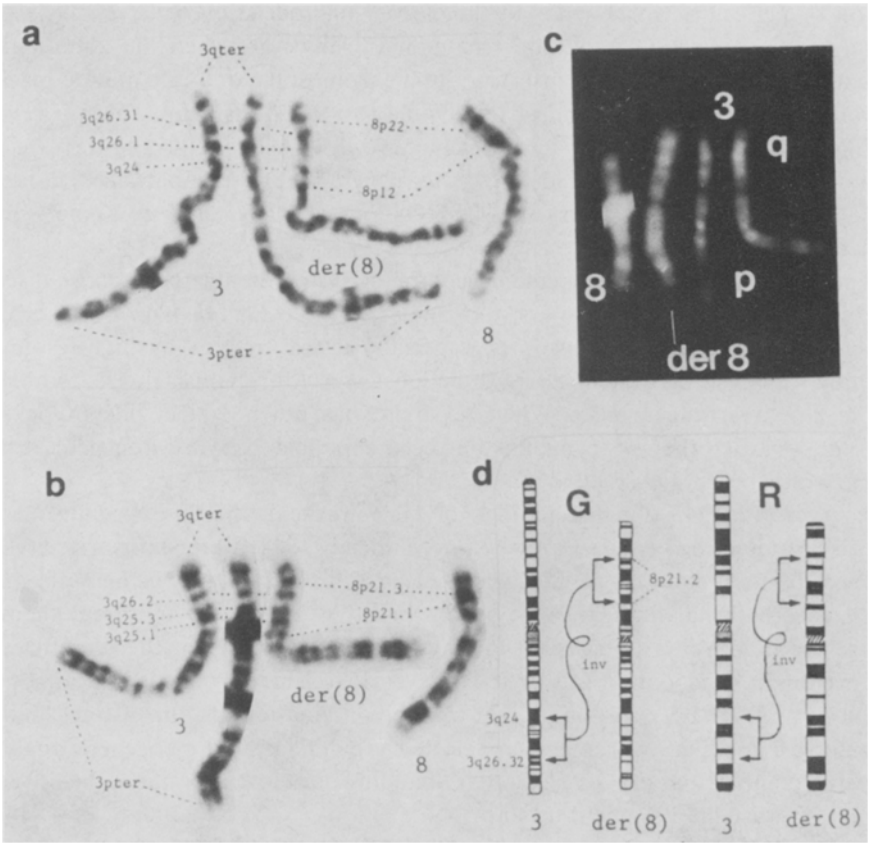

Fig. 2. Partial karyotypes of chromosomes 3 and 8. a: GTG-(850-band stage), b: RBG-(550-band stage), c: QFQ-bandings. d: Idiograms of chromosomes 3 and 8 indicating inverted insertion of a segment from 3q24 to 3q26.32 into 8p21.2.

DISCUSSION

The computer databases for malformation syndromes are now available, *e.g.*, POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations; Danks and Bankier, 1985), London Dysmorphology Database (Winter *et al.*, 1984; Winter and Baraitser, 1987). BDIS (Computerized Birth Defects Information System; Center for Birth Defects Information Services, Inc., 1986) and so on. Among them, London Dysmorphology Database has known to be supplemented chromosomal syndromes (Brandl and Grimm, 1987). However, this database is expensive and, most importantly, it cannot be driven in most of personal computers popular in Japan because of a difference in operating system.

As a practical problem, it is easy to identify the origin of abnormal chromosomes or segments, when the abnormality is derived from parental balanced trans-

location or pericentric inversion. In the case of microdeletion, it is relatively easy to analyse by using high-resolution techniques. However, when the abnormal *de novo* extra segment is small and inserted into a chromosome or a free minute marker, it is considerably difficult or almost impossible to identify its origin, even if several banding techniques were used in prometaphase cells. Those procedures are not economic. Thus, we considered to try to programme a computerized database originally, which can be driven in MS-DOS operated personal computers most popular in Japan.

The main purpose of our personal computer system is not to diagnose directly from the clinical findings, but to assist an analysis of the small *de novo* extra segment by focusing into a few chromosomes, especially in an analysis by high-resolution techniques. Thus, this system seems to be most useful for cytogeneticists to analyse such *de novo* rearrangements. When a patient has not a typical phenotype of a syndrome, or when the syndrome has not been experienced by a cytogeneticist, this system also seems to be useful.

As the data, 245 clinical findings of chromosomal aberration syndromes in the textbook described by de Grouchy and Turleau (1984) were summarized. The frequency of these findings could not be reflected in the system. Namely, frequent as well as occasional findings were evenly input by a present or absent manner. Because the description of physical findings of the syndromes in the literature has been impressive and authoritative, it is clever to select only distinct findings for reference to PC-DCAS. In the present case, a combination of four distinct findings were referred, and five syndromes were selected as candidates for cytogenetic analyses. A careful comparison of G-, R- and Q-banding patterns identified the inverted insertion of a small 3q segment into 8p.

Trisomy for 3q2 region has been well documented in about 40 reports. The main features include abnormal configurations of the head, brain malformations and/or seizures, hypertrichosis, hypertelorism, ocular anomalies, nose with abnormal bridge and anteverted nostrils, long philtrum, maxillary prognathism, down-turned corners of the mouth, high-arched palate or cleft palate, micrognathia, malformed auricles, short and/or webbed neck, chest deformities, clinodactyly and congenital heart malformations (Steinbach *et al.*, 1981). Most of these findings were observed in the present case.

Somatostatin gene locus has known to be assigned to 3q28 by *in situ* hybridization (Zabel *et al.*, 1983). It is reasonable that somatostatin value of the present case was within normal limits of infants, because 3q28 was not involved in the trisomic segment.

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