

Further Delineation of Kabuki Syndrome in 48 Well-Defined New Individuals

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Kabuki syndrome is a multiple congenital anomaly/mental retardation syndrome. This study of Kabuki syndrome had two objectives. The first was to further describe the syndrome features. In order to do so, clinical geneticists were asked to submit cases—providing clinical photographs and completing a phenotype questionnaire for individuals in whom they felt the diagnosis of Kabuki syndrome was secure. All submitted cases were reviewed by four diagnosticians familiar

with Kabuki syndrome. The diagnosis was agreed upon in 48 previously unpublished individuals. Our data on these 48 individuals show that Kabuki syndrome variably affects the development and function of many organ systems. The second objective of the study was to explore possible etiological clues found in our data and from review of the literature. We discuss advanced paternal age, cytogenetic abnormalities, and familial cases, and explore syndromes with potentially informative overlapping features. We find support for a genetic etiology, with a probable autosomal dominant mode of inheritance, and speculate that there is involvement of the interferon regulatory factor 6 (*IRF6*) gene pathway. Very recently, a microduplication of 8p has been described in multiple affected individuals, the proportion of individuals with the duplication is yet to be determined. © 2004 Wiley-Liss, Inc.

KEY WORDS: developmental delay; hypoglycemia; wide palpebral fissures; finger pads; left ventricular outflow tract obstruction; van der Woude syndrome; popliteal pterygium syndrome

INTRODUCTION

Kabuki syndrome was described simultaneously by two Japanese groups [Kuroki et al., 1981; Niikawa et al., 1981], as

This article contains supplementary material, which may be viewed at the American Journal of Medical Genetics website at <http://www.interscience.wiley.com/jpages/1552-4825/suppmat/index.html>.

Grant sponsor: SHARE's Child Disability Center; Grant sponsor: Steven Spielberg Pediatric Research Center; Grant sponsor: UCLA Intercampus NIH/NIGMS Medical Genetics Training Program; Grant number: GM08243; Grant sponsor: NIH/NICHD; Grant number: HD22657.

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Received 6 May 2004; Accepted 10 May 2004

DOI 10.1002/ajmg.a.30340

a sporadic multiple congenital anomaly/mental retardation syndrome of unknown cause. The facial features of affected individuals are reminiscent of those of the Kabuki theater actors. The current literature refers to more than 300 individuals with this as the suggested diagnosis, and provides an estimated incidence of 1/32,000 [Niikawa et al., 1988]. Case series have been reported by a number of groups, which confirm occurrence in diverse races, consistently equal sex ratios, and high variation in morbidity. The syndrome is generally assumed to be genetic. Recently an approximately 3.5 Mb duplication of chromosome 8p22-8p23.1 was reported in six unrelated individuals with Kabuki syndrome; the proportion of people with the syndrome who have the duplication is yet to be determined [Milunsky and Huang, 2003].

The diagnosis of Kabuki syndrome is a clinical one for which no validated diagnostic criteria have been published. Affected individuals possess a recognizable facial gestalt. In our opinion, this is absent in a percentage of individuals described in the literature. Both phenotypic and genetic heterogeneity influences estimates of feature frequencies and complicates efforts to identify an etiology. In this study, we place a high priority on diagnostic homogeneity and have used four diagnosticians familiar with the Kabuki syndrome face and phenotype to review each diagnosis.

This study is designed first to further describe the features of the syndrome, providing data valuable for families, diagnosticians, and health professionals planning prospective medical care for an individual with Kabuki syndrome. Its second purpose is to explore possible etiological clues by evaluating paternal age, reviewing reported cytogenetic abnormalities and familial cases, and discussing syndromes with overlapping features.

Establishing an association between a syndrome and advanced paternal age supports a genetic or epigenetic etiology. An advanced paternal age association is evident in certain types of mutations, most notably base pair substitution [Crow, 2000].

MATERIALS AND METHODS

The Kabuki syndrome literature was reviewed to prepare a checklist of all syndrome features that had previously been described (see the online Appendix 1 at <http://www.interscience.wiley.com/jpages/1552-4825/suppmat/index.html>). Clinical geneticists (see author list) completed the checklist for each of the individuals they had confidently diagnosed with Kabuki syndrome. A case was included only if the majority of four reviewers (Judith Allanson, Dian Donnai, Connie Schrandler-Stumpel, and Linlea Armstrong) were confident that the submitted facial photograph depicted an individual with the recognizable facial gestalt of Kabuki syndrome. Clinical findings of these individuals, as described by the geneticist completing the checklist, and interpreted by the first author from photographs, are used to compile the feature frequencies presented.

Parental age data from this survey, and previously published series are summarized. To avoid resampling and bias, only series with a minimum of five individuals whose paternal age is provided are included. Insufficient data are provided in most publications to allow independent assessment of diagnostic reliability. Because the individuals' years of birth and cultural origins are diverse, and most populations do not collect paternal age data, no formal comparison between the paternal ages observed among our patients and the paternal ages observed in general is possible. Vital statistical data from the United States (1970, 1999) [Center for Disease Control, National Center for Health Statistics, division of Data Services, 1970, 1999] and United Kingdom (1998) [Office for National Statistics, 1998] are summarized for comparison. Averages calculated are approximate.

The literature concerning individuals with cytogenetic differences or positive family histories was identified by a PubMed search, and is reviewed. Other syndromes sharing some of Kabuki syndrome's more specific features (long palpebral fissures, blue sclera, finger pads, lip pits, and diaphragmatic hernia) were identified by London Dysmorphology Database [London Dysmorphology Database, Oxford Medical Databases, 2000] and Possum [Pictures of Standardized Syndromes and Undiagnosed Malformations POSSUM (TM), 2000] searches, and the syndrome features compared.

RESULTS AND DISCUSSION

Unless otherwise referenced or specified, frequencies refer to cumulative incidences, and are derived from our data.

Study Population

Sixty-eight surveys, complete with photograph, were collected. Forty-eight individuals were selected by the referees for inclusion in the study. The remainder were excluded because they were previously published (three), because alternative diagnoses were suspected (Smith-Magenis syndrome and deletion 9p), or because there was diagnostic uncertainty. Current ages of the individuals range between 2 and 30 years. Thirty-seven percent are female and 63% are male. Represented are Caucasians, Hispanics, and Blacks living in North America (27), South America (7), Europe (13), and Israel (1). Individuals had been referred to Genetics services for a variety of reasons, including malformation(s), mental retardation, failure to thrive, microcephaly, and hypotonia. Most referrals occurred within the first 2 years of life and some within days of birth. For recent referrals there was generally no significant time delay before identification of the diagnosis. All cases were considered to be sporadic. Consanguinity was a feature in a minority of families (4%).

Intrauterine and Neonatal Periods

Most pregnancies were unremarkable; however cystic hygroma (one pregnancy at 12 weeks) and a two-vessel cord (two pregnancies) were reported. The frequency of premature births was 19%. Gestational age adjusted birth head circumferences, lengths, and weights equal to or less than the 5th centile were found in 35% (n = 20), 19% (n = 27), and 20% (n = 40), respectively. Neonatal/early infantile hypoglycemia was recognized in 8%. In one study individual, insulin was measured and was increased.

Cranium and Face

Figure 1a depicts representative faces of study individuals. Sixty-five percent of individuals beyond the neonatal period have microcephaly. True craniosynostosis is a feature in 6%. The forehead generally appears tall (92%). In a proportion, the cheekbone (29%) and chin (27%) is relatively underdeveloped.

The periorbital features are among the most specific. It is typical for the eyebrows to be placed relatively high on the forehead (83%). The impression often is that the eyebrow is being pulled up at its middle; "arched" is a commonly used descriptor (80%). The lateral third of the eyebrow is usually sparse or appears notched (73%). In some photographs, surprise or attentiveness seems to be expressed; this is in contrast to the "expressionless" Kabuki syndrome face sometimes described (see neurological section). The lashes are long and prominent (80%). Palpebral fissures are long (78%), so much so that often they extend beyond the conjunctiva. The upper lids frequently appear heavy or thick (65%), and may be described as ptotic or droopy. Epicanthic folds are common (31%), and the lateral lower lids tend to be everted (81%). People with Kabuki syndrome often sleep with their eyes open (lagophthalmos),

a



b



Fig. 1. **a:** The columns of photos illustrates the faces of individuals in this study at different ages. Note the tall foreheads and the high eyebrows. Sometimes attentiveness or surprise is expressed, while at other times the face may be described as expressionless. The distinctive ocular and nasolabial patterns are represented (contributors of photographs: David J Aughton, Stephen R Braddock, John Graham, Alasdair Hunter, Nancy

Mizue Kokitsu-Nakata, Sarah M. Nikkel Dagmar Wiczorek). **b:** A baby's ear with preauricular pit, hypoplastic nails, fingers with pads, and lower back with increased hair (contributor of photographs: David J Aughton). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

and complications can result [Toriello and Droste, 2002]. Twenty-five percent have blue sclera. Abnormalities of the visual apparatus include coloboma (4%), congenital glaucoma (2%), and optic nerve hypoplasia (2%). The incidence of strabismus is 19%, of astigmatism is 8%, and of nystagmus is 6%.

Examining the nasobuccal region is helpful when contemplating the diagnosis of Kabuki syndrome. Typically the nose has a tethered tip (63%), its tip can be broad (46%). Often the philtrum is prominent, broad or trapezoid (60%); the upper lip

tented (60%) or cleft (2%); the lower lip prominent or droopy (31%), with an extenuated depression in the midline (13%) and pits (10%). The tongue can be fissured (2%). The palate is variably described as cleft (46%), high arched (31%), narrow (17%), or incompetent (6%). Two individuals in our study had natal teeth. The studies of Mhanni et al. [1999] and Matsune et al. [2001] specifically evaluated dentition in people with Kabuki syndrome: Malocclusion, hypodontia and/or abnormal tooth shape are described in almost all of their carefully evaluated individuals.

The external ears are normally placed, but are typically prominent (81%), and may be simple in form (27%). The auricle in general (42%), or more specifically the lobe (35%), may be large. Thirteen percent have a periauricular dimple, pit, or fistula. The middle ear is subject to recurrent infection in 54%. Twenty-seven percent have decreased hearing; the degree, mechanism, and laterality are variable. Hearing loss may contribute to global delay, speech difficulties, and behavior problems.

Growth and Feeding

Problems with suck, swallow, reflux, aspiration pneumonia, and/or failure to thrive are described in 56% of babies. Seventeen percent of individuals require gastrostomy tube placement early in life, for up to 7 years. A host of factors including hypotonia and congenital heart defect probably contribute to the feeding problems; in addition, a specific oromotor dysfunction has been proposed [Upton et al., 2003]. Postnatal stature is short in 35%. Three study individuals were investigated and found to have a delayed bone age; two were investigated and found to have growth hormone deficiency. Obesity commonly develops around the time of puberty (29%, $n = 7$). Data from this small number of young adults suggests that the problem may be most significant during the early teenage years, and less evident in the late teen years.

Cardiovascular Malformations

A cardiovascular malformation is documented in 23 (48%) of the 48 individuals, and has been suspected in an additional two (4%). Previous literature reviews have shown cardiovascular malformations in 30% [Niikawa et al., 1988; Schrandt-Strumpel et al., 1994; Kawame et al., 1999] to 55% [Hughes and Davies, 1994; Digilio et al., 2001] of individuals with Kabuki syndrome.

Table I summarizes the lesions in individuals in this study and those previously described [Lin and Botto, 2003]. Data from this study show that although atrial and ventricular septal defects are the most common cardiovascular malformations, left-sided obstructive malformations (31%) are significantly more common than in the general population (14%) [Ferencz et al., 1997]. The spectrum of left-sided lesions includes not only coarctation, bicuspid aortic valve, and

hypoplastic left heart, but mitral and aortic stenosis, and multiple levels of obstruction in the form of Shone's complex (supramitral ring, parachute mitral valve, subaortic stenosis, and coarctation of the aorta). In contrast to the predominance of left-sided defects is the relative paucity of complex cardiovascular malformations.

A predominance of left-sided obstructive defects occurs also in Turner syndrome (coarctation, bicuspid aortic valve, aortic/mitral stenosis, and hypoplastic left heart syndrome), where altered embryonic blood flow has been proposed as a likely mechanism. The spectrum of cardiovascular malformations in Kabuki syndrome shows greater diversity than in Turner syndrome.

Gastrointestinal System

Structural and functional abnormalities of the abdominal organs can be serious. These include diaphragm (8%), anal (6%), and biliary system (2%) malformations, and secretory diarrhea (4%). The literature describes individuals in whom the Kasai procedure or a liver transplant has been lifesaving [Ewart-Toland et al., 1998; Van Haelst et al., 2000].

Genitourinary and Endocrine Systems

A proportion of individuals will experience recurrent urinary tract infections, often attributable to structural abnormalities and possible immune dysfunction. Common findings include renal dysplasia/agenesis (21%), horseshoe/ectopic kidney (19%), and hydronephrosis/vesico-ureteric reflux (13%). One of the individuals in this study died at 5 years with renal failure and pulmonary hypertension.

Among males, hypospadias (7%), cryptorchidism (15%), and micropenis (4%) occur. Hypoplasia of the labia may be noted in females (6%).

Nineteen percent of girls develop areolar fullness in infancy. The fullness is not associated with other signs of estrogenization. Three females in the study have begun to menstruate. Onset for one was in young childhood, concurrent with elevated gonadotropins; onset for a second was delayed, and she has been found to have decreased gonadotropins. These were not isolated endocrine differences in these girls. The first had hyperinsulinism with hypoglycemia until 6 months of age; the second has concomitant growth hormone deficiency.

TABLE I. The Distribution and Type of Cardiovascular Malformation in 154 Individuals With Kabuki Syndrome

Type of CVM	Number of individuals with a CVM (%)			
	New ^a	Lin and Botto, 2003	Total	BWIS ^b
Total	23	131	154	
Heterotaxy, single ventricle		1 (<1%)	1 (<1%)	(<1%)
Conotruncal	1 (4%)	13 (10%)	14 (9%)	(12%)
Atrioventricular canal	0	3 (2%)	3 (2%)	(7%)
Right-sided obstruction	1 (4%)	8 (6%)	9 (6%)	(8%)
Left-sided obstruction	7 (30%)	40 (31%)	47 (31%)	(14%) $P \leq 0.001$
ASD, VSD	14 (61%)	50 (38%)	64 (42%)	(28%)
PDA	0	4 (3%)	4 (3%)	(2%)
Anomalous veins, total, partial	0	5 (4%)	5 (3%)	(2%)
Ebstein	0	2 (2%)	2 (1%)	(1%)
Not stated	0	5 (4%)	5 (3%)	

ASD, atrial septal defect; BWIS, Baltimore-Washington Infant Study; CVM, cardiovascular malformation; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

All percentages rounded.

^aAmong the new individuals, an additional two (4%) had a possible cardiac abnormality. One individual had a murmur attributed to a patent ductus arteriosus and one individual had aortic regurgitation without a known aortic valve anomaly.

^bFerencz et al., 1997.

Musculoskeletal and Skin

Persistence of fetal finger pads is characteristic but not universal (88%), and similar pads can be seen on the toes. Their presence is not correlated to age, and they do not seem to decrease with aging. Sixty-seven percent have brachydactyly, brachymesophalangy, or clinodactyly of the fifth finger. Thirteen percent have a single palmar crease, and eight percent have disproportionately small feet. Deformed vertebrae (6%), clavicle lypo-/aplasia (8%), rib abnormalities (2%), sacral sinus or dimple (21%), and caudal appendage (2%) are each described in Kabuki syndrome. The occurrence of blue sclera (25%), chest deformities (6%), and lax joints (50%), as well as hernias (10%) and hyperelastic skin (6%) point to connective tissue involvement. Thirteen percent have small, hypoplastic, or deep-set nails. Some have increased body hair (4%). A number of these features are depicted in Figure 1b.

Immune System

Kabuki syndrome is associated with increased rates of infection and autoimmune phenomena. One of the individuals in our survey has a history of recurrent immune thrombocytopenia purpura (ITP), a condition that has been previously described in Kabuki syndrome [Watanabe et al., 1994; McGaughran et al., 2001]. Abnormalities of the immune system have been demonstrated in the laboratory [Hostoffer et al., 1996; Chrzanowska et al., 1998; Ming et al., 2002]. Hypogammaglobulinemia was found in two of the individuals in this study (for further discussion see accompanying article by Ming et al.). Neuroblastoma occurred in one individual; however, no increased risk of cancer has been recognized in Kabuki syndrome.

Development and Behavior

A mild to moderate global delay of development appears to be typical (see related papers in this issue). Most individuals attend special education programs. Hypotonia (60%), seizures (17%), an "expressionless face" (15%), and dysarthria (10%) are described. People with Kabuki syndrome are generally happy; some are described as hyperactive, emotionally disturbed, or anxious. Personality and behavior details are available on too few of the current study individuals to provide a profile. Parent contributed data from the Kabuki Syndrome Network—Survey [2001] offers insights into this important area [www.kabukisynndrome.com/survey.html].

Paternal Age

Data from the study and the literature suggest an association with advanced paternal age. The average paternal and maternal ages in this study are 34 years ($n = 39$) and 28.9 years ($n = 42$), respectively. The average paternal age did not vary with birth year (data not shown). Figure 2a shows the observed birth frequencies of the study population plotted by paternal age. The comparison lines are the frequencies of affected births that would have been expected in the respective comparison populations (described in the Materials and Methods section), assuming no paternal age effect. The observed data points are consistently to the right of comparison points, that is, our data are skewed in comparison to the distribution of expected births. Maternal age data are similarly represented; maternal age data are not skewed in comparison to the distribution of expected births. Figure 2b illustrates the same data and effect in a complementary way. These plots show that observed Kabuki syndrome births are underrepresented in young fathers (where the ratios are below one) and overrepresented in older fathers (where the ratios are above one). In the

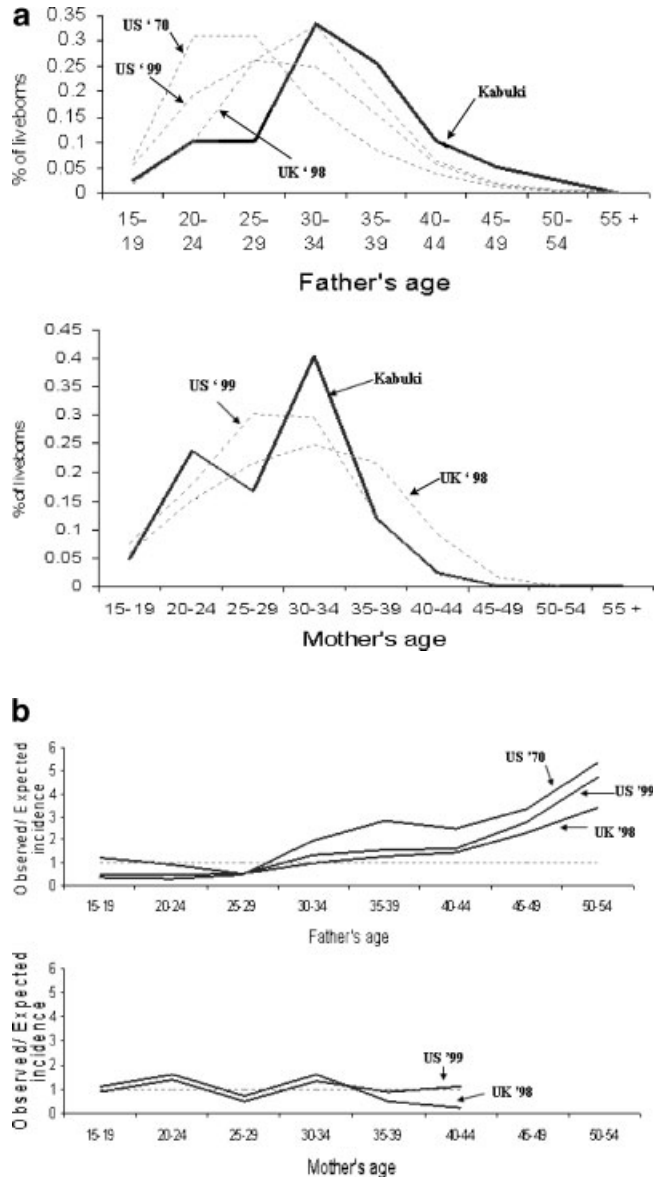


Fig. 2. The same parental age data are represented in two complementary ways: **a:** The distribution of livebirths affected with Kabuki syndrome by paternal age observed in the study (solid line), and that which would have been expected in the comparison populations (as described in Materials and Methods section) assuming no paternal age effect, that is, the distributions of livebirths in the listed countries and years (dashed). **b:** The ratio of the observed data to each of the expected data sets. (The dashed line marks one).

absence of a parental age effect, the ratio would be approximately one across all ages, which is the pattern seen for the maternal age data.

The paternal age data reported in the literature are summarized in Figure 3. The average paternal ages of all series are greater than the US means derived from vital statistics, and the mean paternal age of 27 years quoted by The American College of Medical Genetics in their Statement of Guidance for Genetic Counseling in Advanced Paternal Age [American College of Medical Genetics Statement on Guidance for Genetic Counseling in Advanced Paternal Age, 1996]. The overall weighted series average surpasses the UK control

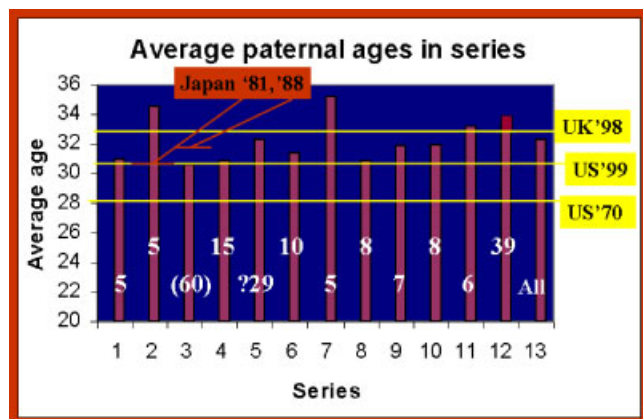


Fig. 3. This is a summary of the paternal age data in the literature. Bars 1–11 each represent a published series [Kuroki et al., 1981; Niikawa et al., 1981, 1988; Philip et al., 1992; Schrandt-Stumpel et al., 1994; Burke and Jones, 1995; Galan-Gomez et al., 1995; Ilyina et al., 1995; Wilson, 1998; Mhanni et al., 1999; Shotelersuk et al., 2002], bar 12 refers to the present study, bar 13 provides a weighted average of the data in bars 1–12. Each bar is marked with the number of individuals in the series. A bracket is marked on bar 3 to highlight possible diagnostic heterogeneity in this series. The question mark on bar 5 indicates that it is unclear whether data from all individuals in the series were included in the calculation of the published average paternal age. Only in two Japanese studies were control data given, (the control values are plotted with the respective studies). The comparison average paternal age estimates are calculated from the vital statistics of selected comparison populations (see Materials and Methods section). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

value. One study [Niikawa et al., 1988] has an average paternal age below its control paternal age; however, interpretation may require caution. Firstly, there is evidence that this series is causally heterogeneous, including, for example, children with chromosome abnormalities (2 of 62 have unbalanced karyotype). Secondly, the authors indicate that some of the individuals resembled a parent. If these represent non-sporadic diagnoses, their inclusion would dilute any paternal age effect.

Conditions including achondroplasia, Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, and the type 2 multiple endocrine neoplasias show strong paternal mutation bias and paternal age effects. Each is due to a point mutation. Other disorders such as neurofibromatosis type 1 show a milder paternal mutation bias and paternal age effect, and the disease causing mutations are heterogeneous with point mutations comprising a subset [Crow, 2000]. Our data suggest that Kabuki syndrome may be related to mutations associated with paternal aging.

Cytogenetics

Classical cytogenetic studies have not identified a putative genomic region. No individual in our survey has a karyotype abnormality identifiable by classical studies. Occasional isolated reports of co-occurrence of convincing diagnoses of Kabuki syndrome with common cytogenetic differences, such as 45,X [Wellesley and Slaney, 1994], and mosaicism for a marker [McGaughan et al., 2001] are to be expected by chance. All balanced rearrangements reported to date are familial and shared with a phenotypically normal parent [Niikawa et al., 1988; Fryns et al., 1994; Galan-Gomez et al., 1995; Lynch et al., 1995].

The report by Niikawa et al. [1988] of Kabuki syndrome in two individuals (cases 29 and 60) with a ring sex chromosome, led to speculation of a syndrome gene at a breakpoint within the sex chromosome. Subsequent reports of six individuals

(see below) with ring X chromosome and “Kabuki-like” features, but features distinct from Kabuki syndrome, call into question the diagnosis of Kabuki syndrome in the two girls. Unfortunately their pictures are not published. Reports of cytogenetic differences in people with a “Kabuki-like” phenotype or manifestations reminiscent of Kabuki syndrome [Dennis et al., 1993; Jardine et al., 1993; El Abd et al., 1997; McGinniss et al., 1997; Lo et al., 1998; Stankiewicz et al., 2001] have likewise been unrevealing with respect to clues for gene mapping of Kabuki syndrome. In none of these individuals with published facial photos has the gestalt been similar enough to Kabuki syndrome to suggest that these cases would inform the search for the etiology of Kabuki syndrome.

Milunsky and Huang [2003] found an 8p22-8p23.1 duplication in six unrelated individuals described to have Kabuki syndrome. The proportion of people with the syndrome who have the duplication is yet to be determined. Recently Miyake et al. [2004] did not confirm this duplication in the 28 patients they studied.

Familial Cases

In the study all diagnoses are sporadic. Of the growing number of proposed familial cases in the literature, we have chosen to highlight the three that we judge as most probable based on review of facial and other supportive features. Lynch et al. [1995] describe the only family in which both affected individuals have mental retardation, and they are monozygotic twins. In our opinion each baby’s facial photograph is consistent with Kabuki syndrome, but the second twin has more pronounced facial features. Other findings consistent with the diagnosis of Kabuki syndrome found in both twins are small birth weight, failure to thrive, finger pads, short fifth fingers, hypotonia, and microcephaly. In addition the first twin has coarctation of the aorta, and the second twin has cleft palate, an abnormality of the biliary system, and recurrent infections. The twins demonstrate some feature discordance despite sharing the same presumed mutation, on a background of highly similar genetics and prenatal environment. Tsukahara et al. [1997] describe a mother and daughter (family 1). Based on the facial photographs we consider the diagnosis of Kabuki syndrome in this pair highly probable. Supportive features in the child are her low weight, cleft palate, short fifth fingers, finger pads, congenital heart defect, diaphragmatic hernia, hypoplastic vertebrae, breast development at age 1.25 years, sacral dimple, and developmental delay. The mother has a cleft palate and short fifth fingers; her intelligence was not formally assessed. Halal et al. [1989] published a family in which transmission from father to son and daughter was proposed. Based on facial photographs, we categorize the father’s diagnosis as possible, and that of the offspring as probable. Other features in the father are short stature, chronic ear drainage with hearing loss, missing teeth, stubby fingers, small feet, and recurrent knee pain. Both children had failure to thrive and congenital hip dislocation as babies, and have short stature, microcephaly, some teeth missing, finger pads, hyperextensible joints, and delayed bone age. The boy also has blue sclera, diaphragmatic eventration, small feet, and micro-penis. The girl has a pre-auricular pit. All three family members have normal intelligence.

Familial cases provide support for a (epi)genetic etiology, and autosomal dominant inheritance. They also imply the influence of stochastic influences and possibly genetic or environmental modifiers. Where a milder phenotype is seen in the parent compared to the child, parental somatic mosaicism is a theoretical possibility. However, a subtler pattern of features might be expected in a multiple malformation/mental retardation syndrome, with autosomal dominant inheritance and variable expressivity, if fitness is affected.

TABLE II. A Comparison of the Features in Three Syndromes

	Kabuki	Van der woude	Popliteal pterygium
Inheritance	(AD)	AD	AD
Variability	+	+	+
Lip pits	+	+	+
Isolated cleft lip or palate	+	+	+
Hypodontia	+	+	+
Natal teeth	+	+	
Hypoplastic nails	+		+
Syndactyly	+	+	+
Malformations of the external genitalia			
Micropenis	+		+
Labial hypoplasia	+		+
Signs of connective tissue abnormality	+		+
Arched eye brows	+	–	–
Long palpebral fissures	+	–	–
Everted lower eye lids	+	–	–
Blue sclerae	+	–	–
Ankyloblepharon	–	?	+
Tethered nasal tip	+	–	–
Syngnathia	–	–	+
Skin over hallux having a pyramidal form	–	–	+
Popliteal webs	–	?	+
Malformations of internal organs	+	?	–
Endocrine abnormalities	+	–	–
Immune abnormalities	+	–	–
Development and behavior differences	+	–	–

+, has been reported as a feature; ?, has been reported in questionable case(s); –, has not been reported.

Syndromes of Interest With Overlapping Features

In trying to predict the gene(s) involved in Kabuki syndrome, we considered syndromes with overlapping features. Early recognition of lip pits as a feature of Kabuki syndrome was made by Franceschini et al. [1993] and Kokitsu-Nakata et al. [1999]. Such lip pits are rare, but are found also in the allelic van der Woude and popliteal pterygium syndromes. A microdeletion at the van der Woude critical region has been excluded in two individuals with lip pits and Kabuki syndrome by Makita et al. [1999], who hypothesized a contiguous gene syndrome.

Table II compares and contrasts the van der Woude, popliteal pterygium, and Kabuki syndromes. Van der Woude syndrome is associated with haploinsufficiency of the interferon regulatory factor 6 (*IRF6*) gene, while popliteal pterygium syndrome is associated with missense mutations in that gene and a presumed dominant negative mechanism [Kondo et al., 2002]. The *IRF6* gene product is a transcription factor of unknown function with expression along the medial edge of the fusing palate, tooth buds, hair follicles, genitalia, and skin throughout the body [Kondo et al., 2002]. We speculate that at least some of the features found in Kabuki syndrome are caused by a disturbance within the *IRF6* gene pathway, based on the overlaps between these three syndromes. Alternatively the features apparently common between Kabuki syndrome and the other syndromes could have distinct biochemical bases.

ACKNOWLEDGMENTS

We thank the described individuals and their families. We thank Dian Donnai and Connie Schrandt-Stumpel for reviewing the individual photographs. We appreciate Annick Toutain's interest in contributing to the project. JMG receives support from SHARE's Child Disability Center and the Steven Spielberg Pediatric Research Center. In addition, some of this work was supported by the UCLA Intercampus NIH/NIGMS

Medical Genetics Training Program Grant GM08243, an NIH/NICHD Grant HD22657 from the U.S. Department of Health and Human Services, Public Health Service.

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