Hum Genet (1986) 74:143–154

Human Genetics

Wiedemann-Beckwith syndrome: presentation of clinical and cytogenetic data on 22 new cases and review of the literature

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Summary. The main features of Wiedemann-Beckwith syndrome (WBS) include macroglossia, abdominal wall defects, visceromegaly, gigantism, hypoglycemia, ear creases, nevus flammeus, and mid-face hypoplasia. Twenty-two cases of WBS were examined clinically and cytogenetically, and compared to 226 previously reported cases. Aspects of the clinical evaluations are discussed. All individuals examined were chromosomally normal with no evidence of 11p abnormality as has been reported recently. The relevance of a possible relationship between clinical findings, chromosome abnormalities, and genes present on 11p is discussed. Transmission of this condition is most consistent with autosomal dominant inheritance with incomplete penetrance.

Introduction

Individuals with the Wiedemann-Beckwith syndrome (WBS) have macroglossia, abdominal wall defects, somatic gigantism, visceromegaly, neonatal hypoglycemia, and cytomegaly of the adrenal cortex. Its acronym, "EMG syndrome", is derived from *e*xomphalos, *m*acroglossia, and *g*igantism, the syndrome's major triad of clinical findings. While this syndrome is a clearly delineated clinical entity, there is a wide variability of clinical and pathologic features (Sotelo-Avila et al. 1980). The variability of expression raises important questions concerning diagnostic recognition and inheritance.

Here we report the clinical and high resolution cytogenetic findings on 22 previously unreported children with WBS and review the literature. Clinical findings, mortality rate, growth data, prenatal diagnosis, and inheritance of the syndrome are also discussed.

Materials and methods

A careful review was made of the medical records of all children diagnosed with WBS between November 1962 and April 1985 in the Department of Medical Genetics at Indiana University School of Medicine. WBS was identified in 25 children. Complete records, family histories, and physical examinations were obtained in 22 of the 25 cases.

Chromosome analysis was performed on 19 of the patients. Peripheral blood leukocytes were cultured using standard laboratory techniques. High resolution chromosomes were obtained following a modified ethidium bromide procedure (Ikeuchi 1984). For each individual, 20 cells were examined with three cells photographed and karyotyped.

Growth data were compared to standard growth charts (Hamill et al. 1979). Likelihood ratios for various models of inheritance were calculated using the PAP genetic analysis program (Hasstedt and Cartwright 1979). Likelihoods for the patient's pedigrees were not corrected for ascertainment, while likelihoods for the pedigrees collected from the literature were corrected by dividing them by the likelihood of the original nuclear family. Statistical analyses were performed using the SPSSx statistical package (SPSS Inc 1983).

Observations

Manifestations

The component anomalies of WBS, many of which are present at birth, are listed in Table 1. The clinical findings of each

Table 1. Major clinical findings in Wiedemann-Beckwith syndrome

Macroglossia	Abdominal wall defects
Facial nevus flammeus	– omphalocele
Ear anomalies	– umbilical hernia
– (pits and/or creases)	– diastasis recti
Prominent occiput	Cryptorchidism
Maxillary underdevelopment	Clitoromegaly
Hemihypertrophy	Cardiac defects
Muscular hypertrophy	Visceromegaly
Pre- and postnatal gigantism	– liver
Advanced bone age	– kidney
Neonatal hypoglycemia	– spleen
Neonatal polycythemia	Tumors (Wilms)

Pathological findings

Adrenal cortical cytomegaly and cysts
Hypertrophy and hyperplasia of islets of Langerhans
Nephromegaly with prominent lobulation
Persistent nephrogenesis
Medullary dysplasia and medullary sponge kidneys

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Table 2. History and physical findings in 22 patients with Wiedemann-Beckwith syndrome. +, present; −, absent; blank for unknown; N, normal

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	*N*	Percent 27% M/ 73% F
Pedigree	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	R	R	S	S		
Sex	M	F	F	F	F	M	F	F	F	F	M	F	M	M	M	F	F	F	F	F	F	F		
Family history:																								
– sibs	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	+	+	+		10.5%
– feature	−	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	−	−		42.1%
Polyhydramnios		−	−		−	+	−	−		+	−	+	−	−		−		−	−	−	+	+	5/17	29.4%
Hypoglycemia	−	−	+		−	−	+	−	−	+	+	+	−	+	+	+	−	+	−	+	−		10/20	50%
Macroglossia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22/22	100%
Nevus flammeus	+	+	−		+	−	−	+	+	+	+	+	+	+	+	−		+	−	+	−		13/19	68.4%
Mid-face hypoplasia		+	−			+	+	+	+	+	+		+	+	−	+		+	+	+	+	+	15/17	88.2%
Prominent occiput		+	−		+	+	−	−	−	−	−		+	−	−	+		+	+	+	−		8/17	47.1%
Ear crease/pits	+	+	−		+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	−		15/20	75%
Abdomen:																								
– distended	+				+				+	−			+	+	+	−				+	+	+	9/11	81.8%
– omphalocele	−	+	+	−	−	−	+	−	−	−	+	−	−	−	+	+	−	−	+	+	−	−	8/22	36.4%
– umbilical hernia	+	−	−	+	−	−	−	+	−	+	+	+	−	−	+	−	+	+	+	+	−	−	11/22	50%
– diastasis recti	+	+	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	4/22	18.2%
Cryptorchidism	−					−					−		−	−	−								0/6	0%
Clitoromegaly		−	−	−	−		−	−	+	−		−				−	−	−	−	−	−	−	1/16	6.3%
Enlarged labia		−	−	−	−		+	+		−						−	−	−	−	−	−	−	2/14	14.3%
Hemihypertrophy	−	−	−	+		−	−	−		−	+	−	−	+	−	−	+	−	−	−			4/18	22.2%
Cardiac defect	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	+	−	+	+	4/22	18.2%
Mental retardation	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	?	−		0/22	0%
Hepatomegaly		+	+	+	+	+	+		+	+	−	+	+	+	+	+	+	+			+	+	17/18	94.4%
Splenomegaly									+	+	−	+								+	+	+	6/7	85.7%
Nephromegaly		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							15/15	100%
Tumors	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−		−	−	−	−		1/20	5%
Chromosomes		N	N		N	N	N	N	N	N	N	N	N	N	N	N		N	N	N	N	N	19/19	100%

of our 22 patients evaluated are presented in Table 2. Macroglossia was present as a uniform enlargement of the tongue in all but one case (case 11). Other craniofacial characteristics which contributed to a noticeable similarity between patients consisted of mid-face hypoplasia, prominent occiput, and nevus flammeus. Apparent underdevelopment of the maxilla caused a "hollowness" of the mid-third of the face in 88.2% of the cases. Almost half of the patients had a prominent occiput at birth. The facial nevus flammeus was present in 68.4% of the cases. The characteristic ear creases and/or pits were noted in 75% of the individuals. Expression of the latter traits varied from a single crease in the lower portion of the ear to a series of pits on the helix with creases along the entire ear.

Cardiac defects were present in 26.7% of the cases but no specific cardiac abnormality predominated. A tumor was present in only one case (case 3). This infant had an intra-abdominal nephroblastoma.

Various forms of abdominal wall defects were present in 77.3% of our cases. These included omphaloceles, umbilical hernias, and diastasis recti. In 5 of the 22 cases no abdominal wall defects were encountered although these patients presented with a distended abdomen as a result of visceromegaly. Clitoromegaly occurred in only one case, while no genital abnormalities were found in males.

Hemihypertrophy occurred in four of our patients but was not associated with tumor formation. Other minor anomalies were also observed. These included 4/5 syndactyly of the toes (case 4), cleft palate (case 18), and two instances of a supernumerary nipple (cases 10 and 18). Polyhydramnios was present in 29.4% of our cases. Premature births occurred in 33% of the pregnancies.

A review of 226 cases in the literature and a comparison to our cases is presented in Table 3. There was no difference in the male/female ratio in WBS. Primary findings (i.e., at least 70% of the cases) included macroglossia, mid-face hypoplasia, prominent occiput, ear creases and/or pits, omphaloceles, cryptorchidism, visceromegaly, and cytomegaly of the adrenal cortex. Secondary findings present in 30% to 50% of cases included polyhydramnios, hypoglycemia, nevus flammeus, hemihyperthrophy, diastasis recti, umbilical hernias, and cardiac defects.

Growth

The length and weight at birth and at the time of examination in each of the 22 cases are listed in Table 4. Seventy-seven percent of the children were at or above the 90th percentile for length and weight for their gestational age. Growth parameters at the time of our examination included: 65% at or above the 90th percentile for weight, and 68.4% at or above the 90th percentile for height. Significant discrepancies between height and weight were noted in only a few cases. In two cases (cases 3 and 16) the children were at or below the

Table 3. Comparison of major clinical findings in Wiedemann-Beckwith syndrome. Sample size varies due to incompleteness of reports. A complete list of references is available upon request

	This study		Reported cases		Total	
	N	(%)	*N*	(%)	*N*	(%)
Sex:						
– male	6	(27)	100	(54.3)	106/206	(51.5)
– female	16	(73)	84	(45.7)	100/206	(48.5)
Polyhydramnios	5/17	(29.4)	18/28	(64.3)	23/45	(51.1)
Hypoglycemia	10/20	(50)	68/108	(63.0)	78/128	(60.9)
Polycythemia	[1]		8/12	(66.7)		
Hypocalcemia	[1]		[5]			
Macroglossia	22/22	(100)	173/178	(97.2)	195/200	(97.5)
Nevus flammeus	13/19	(68.4)	47/77	(61.0)	60/96	(62.5)
Mid-face hypoplasia	15/17	(88.2)	37/47	(78.7)	52/64	(81.3)
Prominent occiput	8/17	(47.1)	31/37	(83.8)	39/54	(72.2)
Ear creases/pits	15/20	(75)	71/110	(64.5)	86/130	(66.2)
Abdomen:						
– distended	9/11	(81.8)				
– omphalocele	8/22	(36.4)	139/172	(80.8)	147/194	(75.8)
– umbilical hernia	11/22	(50)	26/53	(49.1)	37/75	(49.3)
– diastasis recti	4/22	(18.2)	10/20	(50.0)	14/42	(33.3)
– gut malrotation			20/24	(83.3)		
Cryptorchidism	0/6	(0)	26/26	(100)	26/32	(81.3)
Hypospadias	[0]		[6]			
Cliteromegaly	1/16	(6.3)	2/3	(66.7)	3/19	(15.8)
Bicornuated uterus			[2]			
Enlarged labia	2/14	(14.3)				
Hemihypertrophy	4/18	(22.2)	20/55	(36.4)	24/73	(32.9)
Cardiac defect	4/22	(18.2)	28/72	(38.9)	32/94	(34.0)
Mental retardation			[14]			
Visceromegaly			31/54	(57.4)		
Hepatomegaly	17/18	(94.4)	34/52	(65.4)	51/70	(72.9)
Splenomegaly	6/7	(85.7)	12/15	(80.0)	18/22	(81.8)
Nephromegaly	15/15	(100)	43/45	(95.6)	58/60	(96.7)
Tumors	1/20	(5)				
Cytomegaly of adrenal cortex			21/22	(95.5)		

50th percentile for height and weight at birth but were at the 95th percentile for both at the time of observation.

The mean birth weight and height of the individuals presented in this study and cases reported in the literature are presented in Table 5. The means for both sexes were above the 90th percentile for these parameters. Males born prematurely (before 38 weeks) were at the 90th percentile for height and weight while premature females were at the 10th percentile or below for length and between the 25th and 75th percentiles for weight. At term infants of either sex were above the 90th percentile for length and weight.

Length and weight from a gestational age of 22 weeks to 29 years were obtained from 134 cases including data from this study and the literature (Fig. 1). Average length for males at birth was above the 95th percentile and growth throughout adolescence paralleled the normal growth curve at or above the 95th percentile. The average birth length for females was at the 75th percentile and length increased to the 95th percentile by 18 months. Height of these females remained at or above the 95th percentile throughout adolescence again paralleling the normal growth percentile curves.

The mean weight for males began at the 95th percentile (birth) and followed normal growth curves at the 95th percentile through age 3 years. Data were incomplete for the adolescent years and no conclusion about weight at this age could be made. Mean weight of females followed a curve similar to that for height until approximately age 9 years. The mean weight curve steadily reapproached the norm but appeared to remain between the 75th and 90th percentiles.

Mortality rate

The infant death rate in WBS based on data from this study and the literature is 21% (Table 6). There was no statistical difference in mortality rates between the sexes, or between the sporadic and familial cases, although females appeared to succumb at a higher frequency in the familial cases than in the sporadic ones.

Chromosome analysis

High resolution chromosome analysis was completed on 19 patients (Table 2). All individuals, including the parents of

Table 4. Weight and length: at birth and at time of examination

Case	Sex	Gestation (weeks)	Birth		Examination		
			Weight (kg) [%]	Length (cm) [%]	Age	Weight (kg) [%]	Length (cm) [%]
1	M	40	4.9 [> 95]	57 [> 95]	1 month	5.7 [> 97]	60.5 [> 97]
2	F	40	3.35 [75]	68.6 [> 95]	18 months	13.5 [97]	89.5 [> 97]
3	F	36	2.72 [50]	45.7 [25]	8 months	9.5 [90]	73 [90]
4	F	–	–	–	–	–	–
5	F	41	4.4 [> 95]	53.3 [> 90]	6 years	31.1 [> 97]	120 [90]
6	M	33	4.17 [> 95]	53.3 [> 95]	1.5 months	4.5 [75]	55 [50]
7	F	40	3.16 [50]	53.3 [> 90]	6 years	18.9 [25]	129 [> 97]
8	F	39	4.7 [> 95]	–	9 months	13.2 [> 97]	72 [50]
9	F	40	3.6 [> 75]	–	4 months	6.3 [75]	–
10	F	38	4.54 [> 95]	53.4 [> 95]	18 months	12.4 [> 75]	84 [75]
11	M	42	4.05 [> 95]	55.9 [> 95]	3.5 years	12.8 [10]	95.5 [25]
12	F	34	3.37 [> 95]	–	8 years	27.45 [75]	154.9 [> 97]
13	M	38	3.6 [90]	52.5 [> 90]	2.9 years	17.2 [90]	94.5 [50]
14	M	40	4.16 [> 95]	–	16 months	13.4 [> 90]	87 [> 97]
15	M	40	4.9 [> 95]	58 [> 95]	3 years	19.5 [> 97]	106 [> 97]
16	F	38	2.98 [50]	–	7 years	32.3 [> 97]	130 [97]
17	F	40	3.78 [90]	–	19 months	13.6 [97]	86 [90]
18	F	36	3.4 [> 90]	–	12 years	–	162 [97]
19	F	28	2.64 [> 95]	–	11 years	–	150 [90]
20	F	28.5	2.93 [> 95]	–	10 years	–	132 [75]
21	F	38	3.9 [> 95]	53 [> 95]	3 months	6.55 [97]	59.5 [90]
22	F	28	0.975 [10]	33 [25]	deceased		

Table 5. Mean birth length and weight in Wiedemann-Beckwith syndrome

Sex	Gestation (weeks)	Our cases				Total cases			
		N	Length (cm)	*N*	Weight (kg)	*N*	Length (cm)	*N*	Weight (kg)
Male	< 37	1	53.3	1	4.17	4	48.9 ± 4.2	23	3.08 ± 0.8
	38–42	4	55.9 ± 8.7	5	4.32 ± 0.6	7	57.9 ± 6.7	35	4.03 ± 0.9
Female	< 37	2	39.4 ± 9.0	6	2.66 ± 0.9	7	43.8 ± 8.5	23	2.96 ± 0.8
	38–42	5	56.9 ± 6.7	9	3.87 ± 0.5	12	55.1 ± 4.5	48	3.97 ± 0.7

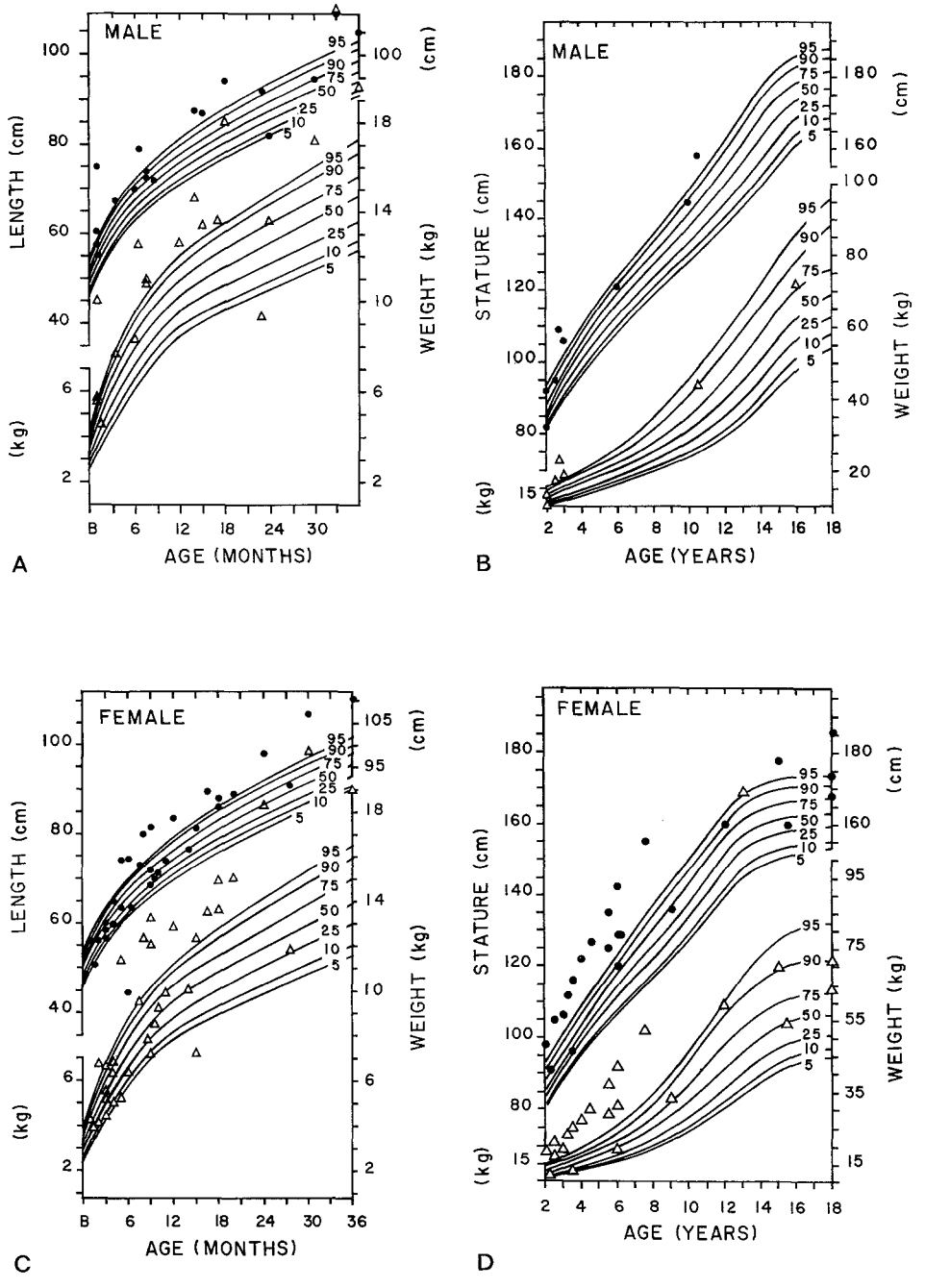

Fig. 1A–D. Growth charts on 134 Wiedemann-Beckwith syndrome patients. **A** Males from birth to 36 months; **B** males ages 2 to 18 years; **C** females from birth to 36 months; **D** females from age 2 to 18 years. ●, length; △, weight

Table 6. Mortality rate in Wiedemann-Beckwith syndrome

	Male		Female	
	N	%	*N*	%
Total	89	(49.2)	92	(50.8)
living	66	(74.2)	77	(83.7)
deceased	23	(25.8)	15	(16.3)
Sporadic	52	(58.4)	60	(65.2)
living	39	(75.0)	54	(90.0)
deceased	13	(25.0)	6	(10.0)
Familial	37	(41.6)	32	(34.8)
living	27	(73.0)	23	(71.9)
deceased	10	(27.0)	9	(28.1)

cases 18–20, were cytogenetically normal. The band level ranged from 550 to 1000 with an average of 725.

Family history

Pedigrees of our families are presented in Fig. 2. In families A–J only the propositi were identified as having WBS. No features of WBS were identified in any relatives of these 10 families and there was no evidence of advanced maternal or paternal age in any of these families. Consanguinity was found in two families (I and R). At least one relative in the remaining eight families (K–R) had one of four common clinical findings (omphalocele, macroglossia, gigantism, and ear creases). Ear creases and/or pits were present in five of the families. In family P the mother had nearly identical ear creases and pits

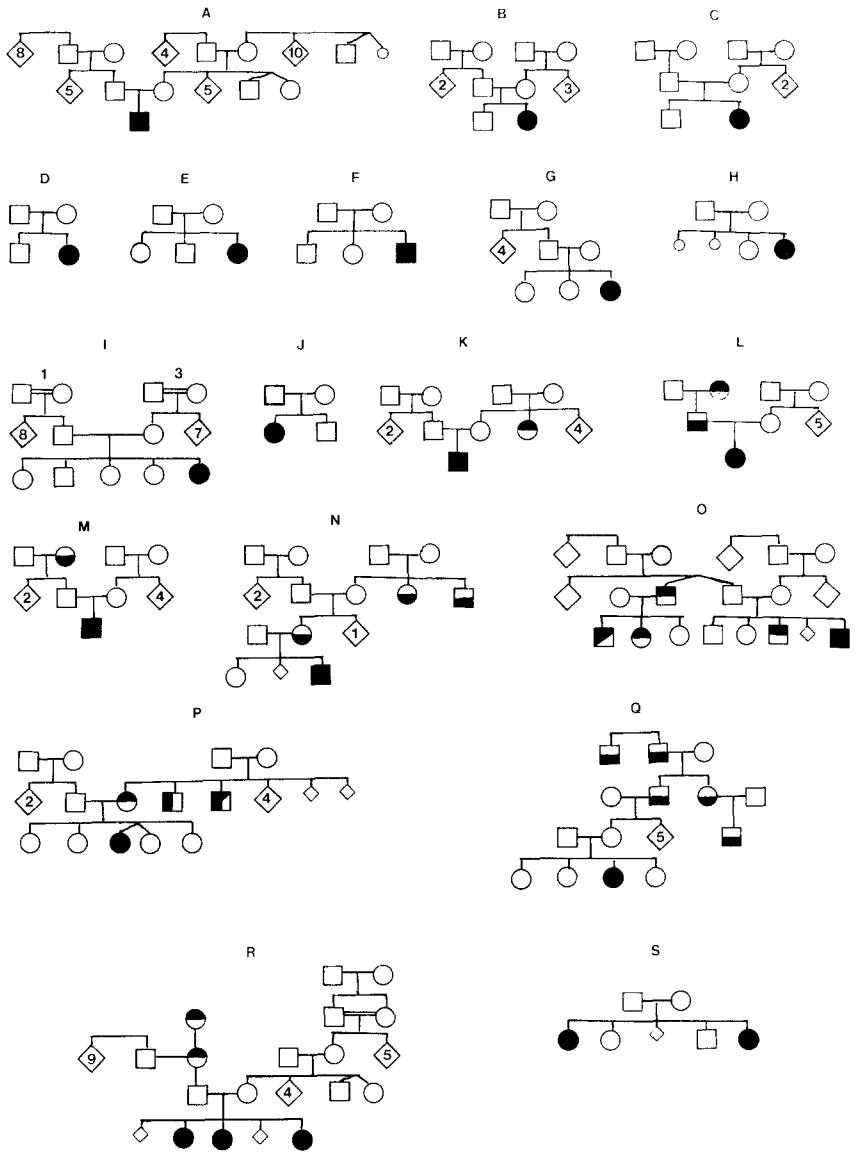

Fig. 2. Pedigrees of the 22 families examined in this study. ▬, Macroglossia; ▭, ear crease pit; ◧, omphalocele; ◩, gigantism; ■, Wiedemann-Beckwith

as her daughter. In addition, one uncle was born with an omphalocele while a second uncle has had exceptional height and weight relative to other family members. This was the only family in which abdominal wall defects were present. The proband had a normal dizygotic twin sister. An elder sib in this family apparently has cerebral palsy and shortening of the optic nerve, while a younger sib had arthrogryposis. In family O ear creases were present in a brother and the father's twin brother. Additionally, one paternal cousin had ear creases while another cousin was at the 95th percentile for growth. Macroglossia, or a "large tongue" which resulted in speech problems, was reported in three of the families. Family Q was reported to have five relatives with a large tongue during childhood. Families R and S had three and two siblings diagnosed with WBS, respectively. The youngest sib in family R also had scoliosis.

Segregation analysis of the 19 families collected in this study indicated that if only diagnosed WBS cases were used (restrictive case), an autosomal recessive mode of inheritance was favored (Table 7). On the other hand, if we consider reports of associated findings in relatives as manifestations of a single WBS gene (broad case), then autosomal dominant inheritance appears to be more likely. Not surprisingly, segregation analysis of the published pedigrees of familial cases (plus the two familial cases of this study) also suggests autosomal dominant inheritance (for both the restrictive and broad cases). However, based on an autosomal dominant hypothesis, penetrance is low, between 30–40% for males and 50–60% for females.

Discussion

Clinical data

Anomalies seen in the Wiedemann-Beckwith syndrome are facultative rather than obligatory. The major WBS abnormalities (macroglossia, abdominal wall defects, hypoglycemia, visceromegaly, and cytomegaly of the adrenal cortex) are not present in every case. The variability of expression of clinical findings in this syndrome indicates a need to establish specific diagnostic criteria to better delineate the syndrome. We suggest the criteria for the diagnosis of WBS as the craniofacial features of ear creases and/or pits, nevus flammeus, and mid-facial hypoplasias (present in over 80% of

Table 7. Parameters for various models of inheritance

Parameters		Our data						Literature					
		Restricted			Broad			Restricted			Broad		
		Model[a]											
		S	AR	AD	S	AR	AD	S	AR	AD	S	AR	AD
Gene frequency	p	–	0.007	0.00003	–	0.007	0.00003	–	0.007	0.00003	–	0.007	0.00003
	q	–	0.993	0.99997	–	0.993	0.99997	–	0.993	0.99997	–	0.993	0.99997
Penetrance	m	–	1.0	0.20	–	1.0	0.40	–	1.00	0.21	–	0.87	0.31
	f	–	1.0	0.50	–	1.0	0.65	–	1.00	0.36	–	0.95	0.46
Log (likelihood)		−273.71	−87.36	−97.99	−310.25	−123.01	−111.78	−161.34	−57.35	−53.43	−281.31	−109.14	−81.64
Likelihood difference		206.35	–	10.63	198.47	11.23	–	107.91	3.82	–	196.73	27.5	–

[a] S, Sporadic; AR, autosomal recessive; AD, autosomal dominant

cases) in conjunction with abdominal wall defects, visceromegaly, gigantisms, and/or macroglossia. Lack of firm diagnostic criteria and the spectrum of abnormalities of WBS may have resulted in the classification of some WBS patients as a new syndrome (Perlman et al. 1973; Greenberg et al. 1986).

Hypoglycemia was present in at least half the cases. Failure to diagnose WBS can be deleterious as tests for hypoglycemia may not be instigated and failure to detect hypoglycemia may lead to permanent brain damage, mental deficiency, or death (Irving 1970).

Little has been reported on the clinical findings of WBS patients in later life. In the older children, gradual "regression" of macroglossia appears to occur probably from accomodation of the tongue to the oral cavity rather than reduction in size. This accomodation can result in prognathism. Mid-face hypoplasia becomes less noticeable with age and the nevus flammeus fades after the first few years. Creases and pits tend to persist but are less prominent with age. Niikawa et al. (1986) reported a lessening of clinical features in WBS with increasing age, although they suggested this could be due to a less than aggressive search for such features. We also noted no difference in the sex ratio of patients with WBS in contrast to previous reports (Smith 1982).

Tumors

Patients with WBS are predisposed to certain malignancies. Sotelo-Avila et al. (1980) reviewed about 200 cases with WBS and found 20 patients who developed 17 malignancies and 5 benign neoplasms. A further review of 13 reports of children that manifested incomplete forms of WBS disclosed 14 with malignancies and three with benign tumors (Sotelo-Avila et al. 1980). Thus there also appears to be an association between tumor formation and with the incomplete forms of WBS. Of the malignancies described in children with WBS, 15 of 17 occurred intra-abdominally and included adrenal carcinomas, nephroblastomas, and one neural crest tumor (Emery et al. 1983). Wiedemann's (1983) review of 388 children with WBS reported 29 children with 32 neoplasms, for a malignant tumor rate of 7.5%. Of these tumors, 26 were intra-abdominal (14 Wilms tumor, 5 adrenal carcinomas, and 7 other types).

There also appears to be an increased risk of malignancies associated with hemihypertrophy and WBS (Ichida and Gardner 1975). Wiedemann (1983) pointed out that hemihypertrophy, either partial or complete, is present in 12.5% of children with WBS. However, hemihypertrophy was present in over 40% of children with neoplasms.

Cardiovascular abnormalities

Cardiovascular abnormalities, although not normally associated with WBS, are among the more common problems in this condition. In one study (Greenwood et al. 1977) cardiovascular conditions were present in 92% of patients with WBS. Congenital structural cardiac defects constitute 58% of these problems while the remainder were isolated cardiomegaly. No specific congenital defects appear to be characteristic; cardiomegaly may be one manifestation of visceromegaly. In the literature review presented in this paper cardiac defects were present in 36.8% of the cases. A fourth of our patients had a cardiac abnormality.

Physical growth

Smith (1982) described the growth in WBS patients as excessive during infancy but often slowing subsequently. Results of this study indicate that excessive growth is present at least through adolescence and probably into adulthood. Growth is characterized by increased birth length and weight, more so for males than females. However, it also may be subnormal for the first few months of life. Height then parallels the normal growth percentiles but at or above the 95th percentile. Finally, premature infants with this condition, especially females, may not show an increase in length for their gestational age.

A possible reason for the rapid growth in most cases may be linked to increased levels of growth hormones, insulin, and/or insulin-like growth factors (e.g., somatomedins). Both insulin and somatomedins have been considered to be responsible for various form of gigantism (Spencer et al. 1980). Somatomedin is thought to be produced from the liver in response to growth hormone release and to stimulate cartilage growth (Mittra 1984). However, growth hormone levels have been reported to be normal in a few infants with WBS (Eaton and Maurer 1971; Schiff et al. 1973; Spencer et al. 1980). In one infant it was suggested that gigantism, macroglossia, and visceromegaly may have resulted from a defect in somatomedin production (Spencer et al. 1980). Further studies are necessary before any relationship between growth hormones and WBS can be confirmed.

A number of investigators, including ourselves, have noted the occurrence of diabetes mellitus in WBS families. Schiff et al. (1973) cited a metabolic similarity between infants with WBS and infants born to diabetic mothers. They suggested that macrosomia may be secondary to fetal hyperinsulinism, thus suggesting a common pathologic-metabolic disturbance may be responsible for macrosomia. Hypoglycemia was noted to occur during one pregnancy in which a mother with WBS gave birth to a son with WBS (Ben-Galim et al. 1977). However, glucose tolerance levels in three mothers of WBS infants have been reported to be normal (Filippi and McKusick 1970; Ben-Galim et al. 1977). One can speculate on an interaction of the maternal genotype (e.g., adult onset diabetes during pregnancy) with the child's genotype resulting in WBS but to date the affect of hypoglycemia in utero has not been documented as a cause of WBS.

Mortality rate

Prognosis for long-term survival of WBS patients is favorable beyond the first month and depends in part on the recognition and treatment of neonatal hypoglycemia. The primary cause of infant death appears to be either congestive heart failure or severe malformations associated with the syndrome.

Prenatal diagnosis

At present only three cases of WBS have been diagnosed in utero. Weinstein and Anderson (1980) reported ultrasound findings of increased amniotic fluid, bilateral cystic kidneys, and a larger than expected fetus at 20 weeks gestation. Subsequent utrasound examinations confirmed growth out of proportion to gestational age and an apparent omphalocele. At 37 weeks, a male infant was delivered with macroglossia, ear creases, nevus flammeus, omphalocele, and bilateral enlarged kidneys. Shapiro et al. (1982) and Winter et al. (1986) separately reported normal ultrasound findings for gestational age with detection of an omphalocele in fetuses who postnatally were diagnosed with WBS and found to have family history of the syndrome. Interestingly, placental weight, size, and thickness were reported to be markedly increased in one case (Shapiro et al. 1982). Considering the probable autosomal dominant inheritance of WBS, ultrasound represents a potential diagnostic tool for prenatal diagnosis of the condition.

Table 8. Chromosome abnormalities reported in Wiedemann-Beckwith syndrome

C and D group reciprocal translocation
46,X,t(X;1)(q26;q26) [skin fibroblasts]
46,XY,−12,+der(12),t(8;12),(q23;p12.5)pat
46,XX,t(11p;22q)mat
46,XY,−11,+rec(11),dup(p13→p15),del(q23→q25) father − 46,XY,inv(11)(p13;q23.3)
46,XX,−11,+der(11),dup(p15?) [de novo]
46,XX,−11,+der(11),dup(p15?) [de novo]
46,XY,−11,+der(11),t(4;11)(q33;p14)pat

Chromosome analysis

Twenty five patients with WBS have been reported to have normal unbanded chromosomes (Wiedemann 1964; Irving et al. 1967; Moncrieff et al. 1970; Sotelo-Avila and Singer 1970; Thorburn et al. 1970; Eaton and Maurer 1971; Cohen et al. 1971; Lee 1972; Reddy et al. 1972; Kosseff et al. 1976; Chemke 1976; Best and Hoekstra 1981). Seven recent studies have reported normal chromosome studies in 32 cases of WBS using banded chromosomes (Saal et al. 1984; Martinez et al. 1985; Turleau and de Grouchy 1985; Hadro et al. 1985; Olney et al. 1985; Niikawa et al. 1986; Winter et al. 1986). However six reports of eight abnormal karyotypes in WBS are published (Table 8). Ruffie et al. (1966) first reported a reciprocal translocation between a C and D group chromosome. An X;1 reciprocal translocation in skin fibroblasts was reported in another WBS child (Punnett et al. 1974). Healy et al. (1984) reported a duplication of the distal 2/3 of 8q and a deletion of the upper half of 12p in a WBS patient. Particular interest in relating this syndrome to a specific chromosome anomaly first came from Waziri et al. (1983) who reported two unrelated patients with an 11p duplication. Turleau et al. (1984) also reported two unrelated patients with WBS anomalies and dup (11)(p15). Pueschel and Padre-Mendoza (1984) reported a balanced t(11p;22q) translocation in a child with this disorder.

On the other hand, there have been patients reported with duplications of 11p who do not have the syndrome but have anomalies similar to those found in WBS syndrome (Waziri et al. 1983). The results of examination of 13 cases with dup(11p) for clinical similarities to WBS are presented in Table 9. The most common clinical findings present are mental retardation, macroglossia, abdominal wall defects, renal and heart defects. The other congenital anomalies found in dup(11p) which are not commonly present in WBS probably result from rearrangements, deletions, or duplications involving other chromosomes.

Although chromosome analysis has been performed on a few sporadic WBS cases, banded chromosome studies have not been carried out on relatives in familial cases. In the two

Table 9. Clinical findings present in patients with 11p duplications[a]

	Duplications						Total
	pter→p14				p13→15		
	pter-p14	p12-q11	pter-p11	p14-12	del (q23-25)[b]	p15[b]	
No. of reported cases	1	1	4	3	1	3	13
Mental retardation	+	+	++++	+++	+	+++	13/13
Macroglossia	+	+	++++			+++	9/9
Abdominal wall defect	−		++	−	+	+++	6/8
Renal defect	+	+	+	++		++	7/7
Heart defect	+		−− +	+ +		++	6/8
Large nose	+	+	++++			+	7/7
Cleft lip			+	++			3/3
Cleft palate		+	+	++		+	5/5
Down slanting palpebral fissures	−		++++	−		++	6/8
Hypertelorism			−++	− +		++	5/7
Prominent forehead	−		++	+	+		4/5
Nevus flammeus					+	− +	2/3
Abnormal ears or creases					+	−	1/2
Growth retardation			++	+	−	−−	3/6
Visual defect	+		++	+			4/4
Seizures	+	+	+				3/3
Genital hypoplasia		+	+ +		+	+	5/5
Gut malrotation		+	+				2/2
Polyhydramnios				+	+	+−	3/4
Hypoglycemia						+	1/1

[a] Schinzel (1984)
[b] Diagnosed as BWS

families with two and three affected sibs in this study, normal chromosomes were present. These results suggest that familial WBS does not result from an inherited chromosome anomaly. While these findings and previous reports do not suggest that there is a specific chromosome abnormality associated with WBS, it does appear that duplication of the terminal portion of 11p produces anomalies similar to those seen in WBS syndrome.

Mental retardation has ocurred in both chromosome defects of 11p and WBS. Retardation probably occurs in WBS because of hypoglycemia since retardation is rare in WBS individuals with normal chromosomes who have not experienced hypoglycemia. On the other hand, one would expect mental deficiency to be associated with 11p abnormalities. In light of the reported chromosome abnormalities in WBS, chromosome studies should be carried out on any child with this syndrome and unexplained mental retardation.

The short arm of chromosome 11

The observation that a duplication in 11p can give rise to a phenotype similar to WBS and recent gene mapping data have led us to speculate that this chromosome region may be involved in WBS. Gene mapping data indicate that the short arm of chromosome 11 contains genes coding for beta-globins, parathyroid hormone (PTH), lactate dehydrogenase (LDH)-A, insulin-like growth factors (IGF II – also called somatomedins), insulin, and the oncogene HRAS-1 (Brissenden et al. 1984; Lebo et al. 1985). The insulin gene is of great interest since a large number of WBS infants develop hypoglycemia. Both the insulin gene and IGF II are also of particular interest in considering pathogenesis of WBS since both genes have been considered to be responsible for various forms of gigantism (Spencer et al. 1980). Increased circulating somatomedin (IGF II) activity has been reported in a child with WBS and this high somatomedin activity has been suggested as at least one of the causative factors of this condition (Spencer et al. 1980). Higher levels of somatomedin might result from hepatomegaly or a defect in gene regulation. Also consistent with a disturbance in the metabolic pathways under growth hormone-like regulation are changes in polyamines (raised putrescine and low spermidine ratios) which have been reported in seven infants with WBS (Barlow 1980).

Two other deficiencies reported in some cases of WBS may also be related to genes on 11p. Beta-globin, a component of the complement system needed for activation of the immune system, is located at 11p. Immunodeficiency has been associated with WBS in at least one case (Greene et al. 1973). A few WBS infants have manifested problems in calcium metabolism implicating possible PTH abnormalities, the gene for which also has been mapped to 11p (Lebo et al. 1985).

The concordance between chromosome localization of oncogenes and chromosome aberrations with various forms of cancers has become apparent. Wilms tumor, which may be associated with the deletion of 11p13, is occasionally diagnosed in WBS. The oncogene HRAS-1 has been localized near this region (de Martinville and Francke 1983) and within the regions of duplication present in some cases of WBS. However,

molecular studies using DNA probes for the insulin gene and HRAS-1 have shown no evidence for increased dosage of either gene in chromosomally normal patients with WBS (Saal et al. 1984; Jeanpierre et al. 1985). On the other hand, loss of the HRAS oncogene has been determined in three cases involving Wilms tumor (Eccles et al. 1984; Reeve et al. 1984). These observations, along with the relationship of genes mapped to 11p and the clinical manifestations of WBS appear to suggest that this chromosome region may be implicated in the pathophysiology of this syndrome.

Inheritance

The incidence of WBS has been estimated to be 1:13,700 births (Thorburn et al. 1970). Although most (85%) cases cited in the literature are reported to be sporadic, a significant number of familial cases have been published suggesting some form of inheritance. Since Wiedemann's (1964) initial report of an affected mother with three affected sibs, there have been at least 29 other familial reports. In addition, other relatives often have shown one or more clinical manifestations of WBS, leading to much speculation on the inheritance of WBS.

Beckwith (1969), and Filippi and McKusick (1970) first suggested that WBS is determined by an autosomal recessive gene. Because of a consanguineous mating which produced eight affected infants, Chemke (1976) also suggested autosomal recessive inheritance, although he did not discard the possibility of modifying genes or environmental factors influencing clinical features.

Kosseff et al. (1972) first suggested that the transmission of WBS was not consistent with autosomal recessive inheritance in some families. Forrester (1973) suggested autosomal dominant inheritance in another family with four siblings and two first cousins with WBS. In reporting four other families, Lubinsky et al. (1974) implied an autosomal dominant sex-dependant model of transmission of a wbs+ gene through male or female carriers with the affected being born only to the females. Hadro et al. (1985) also proposed the transmission of WBS through ovum-mediated autosomal dominant inheritance in a large three generation family with 11 affected individuals.

Evidence for transmission as an autosomal dominant gene with incomplete penetrance and variable expressivity has been proposed by a number of authors (Irving 1970; Sommer et al. 1977; Ben-Galim et al. 1977; Grace et al. 1977; Best and Hoekstra 1980; Puissan et al. 1980; Niikawa et al. 1986). Sommer et al. (1977) studied a family where eight affected infants were born to three normal sisters and suggested that inheritance may be due to a delayed mutation of an autosomal dominant gene. Further evidence supporting autosomal dominant inheritance can be seen in the transmission of WBS from mother to son in three families (Ben-Galim et al. 1977; Grace et al. 1977; Best and Hoekstra 1980). We also know of one family in which there is mother-to-son transmission (P. Dignan, personal communication). In addition, Best and Hoekstra (1980) reported WBS to be present in a mother, her brother, and two of her children. Other relatives also were identified with various WBS manifestations suggesting that the trait in this family was an autosomal dominant condition with variable expressivity. Niikawa et al. (1986) recently described five unrelated families with 18 individuals expressing variable clinical manifestations of WBS. Segregation analysis of their families and some others from the literature suggested that WBS was inherited as an autosomal dominant with variable expressivity.

Of the 16 extended pedigrees reported in the literature, 15 exhibit transmission of WBS through the mother (Irving 1970; Grunt and Enriquez 1972; Kosseff et al. 1972; Forrester 1973; Chemke 1976; Ben-Galim et al. 1977; Grace et al. 1977; Sommer et al. 1977; Hadro et al. 1985; Niikawa et al. 1986). Partial manifestations of WBS also predominate in the maternal side (Chemke 1977; Sommer et al. 1977; Best and Hoekstra 1980; Niikawa et al. 1986). Matsuura et al. (1975) and Ben-Galim et al. (1977) reported the only families in which affected children were related through their father. Even when we consider the complete pathway from the affected individuals in each family back to their common ancestors, in 10 families transmission is entirely through females. In another three families transmission occurs through both males and females. In the current study, four of eight families have presumed inheritance through the maternal family if we consider partial manifestations as an indication of the WBS gene.

Four sets of monozygotic twins discordant for WBS have been reported (Benke 1978; Berry et al. 1980; Olney et al. 1985). Berry et al. (1980) suggested that WBS was inherited multifactorially. Six additional sets of twins are reported in the 226 cases reviewed, including one from our records, although none are monozygotic (Beckwith 1969; Moncrieff et al. 1970; Grunt and Enriquez 1972; Kosseff et al. 1976; Piussan et al. 1980). We know of four other sets of discordant twins with the syndrome (A. Olney, K. Jones, and E. Ives, personal communication). Our findings and the data from the literature would suggest that twining may be associated with WBS, although this could be reporting bias.

Segregation analysis suggests that autosomal dominant inheritance of WBS is more likely than autosomal recessive inheritance. If it is inherited as an autosomal dominant condition the penetrance would be quite low, about 35% in males and 45% in females. This does not consider the variable expressivity if partial manifestations are considered an expression of the WBS gene. We are currently examining the multifactorial model in which more than one gene as well as environmental factors may interact to express WBS. This may more adequately explain the predominance of presumed maternal transmission and the variable expressivity.

The problem of inheritance in WBS is complex. Although an autosomal recessive inheritance is unlikely in most cases, it cannot be ruled out in others. At present, there is no definite evidence of heterogeneity for the disorder. Closer examination of extended pedigrees may be useful for quantification of the variable expressivity and molecular genetic techniques may aid in the consideration of other genetic models and in the understanding of the genetics this syndrome.

Acknowledgements. We would like to thank Drs. M. E. Hodes, T. Reed, N. A. Heerema, D. Goldstein, P. M. Conneally, and J. C. Christian for their valuable discussion and assistance on various portions of this project.

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Received April 9, 1986 / Revised June 5, 1986