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Inheritance Pattern of Beckwith–Wiedemann Syndrome Is Heterogeneous in 291 Families with an Affected Proband

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familial aggregation; causal heterogeneity

Introduction

Beckwith–Wiedemann syndrome (BWS) is a congenital overgrowth syndrome whose molecular etiology is related to a cluster of imprinted genes on 11p15 (OMIM 130650) [Lee et al., 1997, 1999; DeBaun et al., 2002]. A number of complex genetic and epigenetic abnormalities have been demonstrated in patients with BWS. Approximately 42% of the patients have abnormal methylation of LIT1 (OMIM 604115), an untranslated RNA of unknown function [Lee et al., 1999; DeBaun et al., 2002]. Another 11% of the patients have abnormal methylation of H19, an untranslated RNA involved in the expression of insulin-like growth factor 2 (IGF2) (OMIM 103280) [DeBaun et al., 2002]. Approximately 13% of the patients have abnormal methylation of an extensive region of 11p which includes both H19 and LIT1, and of these, 75% have uniparental disomy (UPD) while another 25% have an imprinting disturbance in the region whose etiology is unknown. Point mutations in p57KIP2, also on 11p, appear to account for 5% of the cases of BWS. Finally, less than 1% of the patients have chromosomal abnormalities detectable by cytogenetic analysis, although more subtle chromosomal rearrangement may occur in a larger proportion of the patients [Reish et al., 2002]. The known molecular lesions account for approximately 70% of cases of BWS with the remaining 30% unknown [DeBaun et al., 2002].

The majority of cases of BWS appear to be sporadic, but a substantial proportion of cases are familial [Pettenati et al., 1986; Elliott et al., 1994], and a number of studies have described familial BWS characterized by pedigrees which appear autosomal dominant. One previous study using segregation analysis performed on a small cohort of 21 families suggested autosomal dominant inheritance with incomplete penetrance when considering family members with any feature of BWS as affected [Pettenati et al., 1986]. In addition, a number of reports have presented family pedigrees suggestive of an autosomal dominant mode of inheritance including three families in which parametric linkage analysis assuming autosomal dominant inheritance was successfully applied to identify 11p15 as the BWS

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locus [Sommer et al., 1977; Best and Hoekstra, 1981; Niikawa et al., 1986; Koufos et al., 1989; Ping et al., 1989; Barr et al., 2001]. An alternative mode of inheritance was suggested by an examination of several family pedigrees more consistent with sex-dependent autosomal dominant inheritance [Lubinsky et al., 1974]. This concept was further supported by the elucidation of the epigenetic etiology of many cases of BWS and a report of familial BWS in families with an epigenetic etiology [Bliek et al., 2001].

The mode of inheritance of familial BWS has been difficult to delineate because of variable expressivity, lack of uniform diagnostic criteria, and lack of knowledge of which molecular defects underly cases of familial BWS. No comprehensive study using genetic epidemiology in a large number of patients to evaluate the inheritance pattern of BWS has been carried out. Based on previous studies of familial cases of BWS, we proposed to test the hypothesis that familial cases of BWS were transmitted through an autosomal dominant pattern of inheritance.

Materials and Methods

Study Population

This study was approved by the Institutional Review Board (IRB) at the National Cancer Institute (NCI) and at Washington University School of Medicine. In 1994, the BWS Registry began at the NCI [DeBaun et al., 1996; DeBaun and Tucker, 1998]. The Registry was moved to Washington University School of Medicine in 1999. The ascertainment strategy for this study was single ascertainment for a child meeting the criteria of BWS. No consideration of family history was made in recruitment or diagnosis. Patients were recruited to the registry through referral from physicians and contact with the BWS support network. Informed consent was obtained for all patients. Patients were recruited from January 1994 to the present.

Questionnaire

A questionnaire was completed for each case of BWS in the Registry including an extensive family history. The questionnaire included specific reference to the phenotypic features of BWS in the proband and the parents, siblings, avuncular, and grandparents of the proband.

Definitions

The proband of the family was defined as the individual with BWS who was initially recruited to the Registry. The proband of the family was considered to have BWS if they had two or more of the five major features, and had a diagnosis of BWS by a physician. Individuals in the family were considered to have BWS if they had two or more of the five major features of the syndrome reported in the questionnaire [DeBaun et al., 2002]. These five features are ear pits or creases, macroglossia, macrosomia, hypoglycemia in the first month of life, and abdominal wall defects such as umbilical hernia, diastasis recti, or omphalocele. The parents of the proband provided information on the presence of each feature as well as the date of diagnosis and physician contact information. Macrosomia was determined from birth weights reported using over 90th centile as the cutoff [Battaglia and Lubchenco, 1967; Walli et al., 1980].

Statistical Analysis of Demographics

Statistical analysis was performed in SPSS 10.0 (Statistical Package for the Social Sciences, Chicago). The χ^2 test and Fisher's Exact test were applied to evaluate the significance of differences in proportion. The 95% confidence interval of proportions was calculated using the method for independent proportions [Newcombe, 1998].

Segregation Analysis

Segregation analysis was performed using the pedigree analysis package (PAP) [Hasstedt, 2002]. PAP was parameterized for a discrete trait with a known prevalence (1 in 12,000) through the selection of the appropriate subroutines [Hasstedt, 1993]. This model assumed the disease trait was determined by independent contributions of a single major effect and a polygenic residual heritability. The major effect was assumed to result from the segregation of two alleles (A and a) at a single locus in Hardy–Weinberg Equilibrium. Each model in the analysis was described by seven parameters: the frequency of the A allele (p); the displacement in liability of disease between the two homozygotes, AA and aa (t); the relative position of the heterozygote Aa in liability with respect to the homozygotes, or dominance (d); the polygenic residual heritability describing familial similarity not due to the major effect (H); and the transmission probabilities for the major effect (τ_{AA} , τ_{Aa} , τ_{aa}). The transmission probabilities described the pattern of inheritance of the modeled major effect. The three transmission probabilities were the probability of transmitting the A allele to offspring for that genotype. Under Mendelian transmission, the values of τ_{AA} , τ_{Aa} , τ_{aa} are 1, 0.5, and 0, respectively. Models differed in terms of which of these parameters are fixed to a certain value versus being estimated using an algorithm for likelihood maximization [Lalouel, 1979].

Two major classes of models were tested in the analysis, models with Mendelian transmission probabilities, and models in which the transmission probabilities were estimated from the data. In the first class of Mendelian models in which $\tau_{AA}=1$, $\tau_{Aa}=0.5$, $\tau_{aa}=0$, the models tested included: sporadic inheritance ($P=1$, $d=0$, $t=0$, $H=0$), polygenic inheritance without a major effect ($P=1$, $d=0$, $t=0$), Recessive with ($d=0$) and without ($d=0$, $H=0$) polygenic effects, Additive with ($d=1/2$) and without ($d=1/2$, $H=0$) polygenic effects, Dominant with ($d=1$) and without ($d=1$, $H=0$) polygenic effects, and a General Mendelian Model with and without ($h=0$) a polygenic effect. Hypothesis tests for the Mendelian Models were carried out with respect to the General Mendelian Model with the polygenic effect. In the second class of models in which the transmission probabilities were estimated, an environmental model ($P=\tau_{AA}=\tau_{Aa}=\tau_{aa}=0$), and the most general model were tested. In this analysis the full general model did not converge properly, and a revised general model was tested in which $\tau_{AA}=1$ and $\tau_{Aa}=0.5$. Hypothesis tests overall were carried out with respect to this revised general model.

The models tested were evaluated in terms of their goodness of fit to the data and their parsimony. Goodness-of-fit was evaluated using the likelihood ratio test (LRT) which is the difference between minus two times the natural log of the likelihood ($-2\ln L$) between two models. This difference is distributed approximately as a χ^2 test with a number of degrees of freedom equal to the difference in the number of parameters estimated (as opposed to set at certain values) between the two models. A P -value of <0.05 in the LRT was taken to indicate a model that represented a significantly worse fit to the data than the general model and which should be rejected. The parsimony of each model was evaluated using Akaike's information criterion (AIC) which is the $-2\ln L$ plus twice the number of estimated parameters in a given model. The most parsimonious model is that which has the lowest AIC [Akaike, 1974]. Likelihood values of models are difficult to interpret when one or more of the parameters takes on a boundary value (the maximum or minimum solution allowed for that parameter), therefore we followed a defined procedure for evaluating boundary solutions. In cases in which a parameter (F) took on a boundary solution, the procedure was as follows: (1) F was fixed to the boundary and the other parameters in the model were estimated, (2) the other parameters were fixed at their values in the first step and the likelihood was estimated at values of F in and around the boundary. (3) If the lowest value of $-2\ln L$ was obtained when F was at the boundary then this solution was accepted as the

best solution. Three conditions were considered necessary to infer Mendelian transmission of the disease, (1) the sporadic model ($P=1$, $d=0$, $t=0$, $H=0$) was rejected; (2) one or more Mendelian models was not rejected ($\tau_{AA}=1$, $\tau_{Aa}=0.5$, $\tau_{aa}=0$); (3) the environmental model was rejected ($P=\tau_{AA}=\tau_{Aa}=\tau_{aa}=0$).

Results

Patient Demographics

A total of 291 families selected for having a child with BWS were included in the analysis. Of these, 84.9% (247 of 291) were white not Hispanic, 2.7% (8 of 291) were black not Hispanic, 4.1% (12 of 291) were Hispanic, 1.4% (4 of 291) were Asian or Pacific Islander, and 6.5% (19 of 291) reported “other” ethnicity. A total of 52.6% (153 of 291) of the probands were male.

Recessive and Additive Models Are Most Parsimonious Mendelian Models of Familial BWS

The results of a formal segregation analysis in which models of inheritance were tested suggested that additive and recessive modes of inheritance were the most likely fit to the pedigrees in our cohort, (Tables I and II). A total of 1,219 individuals from the 291 nuclear families were included in the analysis. The sporadic inheritance model and the multifactorial model in which no major effect was present were both rejected ($\chi^2=1,426.043$, $df=4$, $P<0.0001$ and $\chi^2=19.568$, $df=3$, $P=0.0002$), respectively. Dominant inheritance of the major effect was rejected both with ($\chi^2=8.644$, $df=1$, $P=0.0033$) and without ($\chi^2=6.589$, $df=2$, $P<0.0001$) a polygenic residual. However, both recessive and additive models of inheritance of the major effect were equally parsimonious with a polygenic residual ($AIC=2,708.713$). The value of the likelihood was identical for the Recessive, Additive, and General Mendelian models ($-2\ln L=2,702.713$). A grid search revealed little change in the likelihood occurred for values of the dominance parameter (d) between 0.0 and 0.8, but that values above 0.8 led to substantially higher values of $-2\ln L$ suggesting both additive and recessive models were equally likely, but that the dominant model was significantly less likely.

Familial BWS Is Consistent With Mendelian Inheritance under Additive or Recessive Modes

Our cohort met the criteria for Mendelian transmission based on a Revised General model (Tables I and II). The sporadic inheritance model was rejected ($P<0.0001$), the General Mendelian model was not rejected ($P=1.0$), and the Environmental model was rejected ($P=0.0052$). Therefore, the results of the segregation analysis met the three conditions required to infer Mendelian inheritance, although these results should be interpreted with caution because the General Model was revised during the analysis and included a boundary value. The full General Model failed to converge, as did models in which the values of τ_{AA} and τ_{Aa} were estimated. A model in which τ_{aa} was estimated converged, but included the boundary solution $\tau_{aa}=0$, and this solution was confirmed to be the best solution by a grid search procedure. Examination of the pedigrees in our cohort suggested a small proportion of pedigrees were inconsistent with autosomal recessive inheritance and more consistent with autosomal dominant, although additive inheritance is also possible (Fig. 1). Although the segregation analysis underscored the importance of recessive or additive inheritance of BWS, our cohort appeared to be consistent with a heterogeneous group of inheritance patterns. We attempted to better define this heterogeneity with segregation analyses in subgroups of patients based on the features of the proband. However, we were unable to converge key models in these analyses and hypothesis testing was not possible (data not shown).

Discussion

BWS is a complex genetic and epigenetic disease in which the inheritance pattern of familial disease is unclear. The incidence of the syndrome, and the complexity of the molecular abnormalities observed in BWS have led to ambiguity in interpreting familial cases of BWS [Wiedemann, 1997]. In the largest cohort of children with BWS assembled to date, we have used family history information to describe the risk to family members of different classes. In our cohort, approximately 8% of families have familial disease. Our findings suggest, new approaches are needed to identify which families are at risk for familial disease.

Despite numerous case reports in the literature suggesting that autosomal dominant inheritance is the primary pattern of familial BWS, we found no evidence for dominant transmission as the primary mode of inheritance. Our results most likely reflect heterogeneity of familial BWS. The results of a segregation analysis were suggestive of recessive or additive modes of inheritance rather than dominant. Our findings do not exclude the possibility that some proportion of familial cases may have autosomal dominant modes of inheritance, as some family pedigrees in our cohort are consistent with autosomal dominant or other transmission patterns (Fig. 1). Overall our results support the hypothesis that there are heterogeneous subgroups that comprise familial cases of BWS.

Our study design had some inherent limitations. Our assertion of the possibility of recessive or additive inheritance may not be correct if common environment such as shared intrauterine conditions contribute to the similarity between siblings, although no biological basis for this possibility in BWS is known. Quite possibly incomplete penetrance rather than recessive inheritance accounts for the lower prevalence of disorder in the parental generation, as previously suggested [Pettenati et al., 1986]. Further studies in which molecular genotyping is combined with inheritance modeling is necessary to distinguish between these possibilities. We relied on self-reported questionnaire data for the presence or absence of features in family members, a strategy which has associated in accuracy. However, unlike studies with more common features such as high blood pressure or obesity, the features of BWS such as macroglossia and omphalocele are distinctive. In addition, the questionnaire was generally completed by a parent who would generally have accurate knowledge of phenotypic features of their children and other family members. Our findings on children with BWS with cytogenetic abnormalities were limited to those reported, and so we cannot rule out the presence of more subtle translocations, deletions, or duplications among the familial group. Finally, the results of our segregation analysis are based on a revised General model and so should be interpreted with caution.

Autosomal dominant inheritance does not appear to be the primary mode of inheritance of familial BWS. No common mode of inheritance for familial cases of BWS was identified, although the family structure with affected siblings from unaffected parents appears to be most common. The presence of an array of molecular lesions underlying familial BWS now seems plausible. Molecular studies are necessary to clarify which specific molecular abnormalities associated with BWS tend to lead to familial disorder and how those lesions are inherited.

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Figure 1.
 Family pedigrees from the Beckwith–Wiedemann syndrome (BWS) registry suggesting paternal dominant (A) sex-dependent (Maternal) (B) recessive (C) and additive (D) transmission of BWS.

Table 1
Segregation Analysis of Beckwith–Wiedemann syndrome (BWS) in 291 Nuclear Families

Model	df	-2ln L	χ^2	P	AIC
Sporadic ($P = 1$, $d = 0$, $t = 0$, $H = 0$)	4	4,128.757	1,426.043	<0.0001	4,128.757
Multifactorial ($P = 1$, $d = 0$, $t = 0$)	3	2,722.282	19.568	0.0002	2,724.282
Recessive without polygenic residual ($d = 0$, $H = 0$)	2	2,709.348	6.634	0.0363	2,713.348
Recessive with polygenic residual ($d = 0$)	1	2,702.713	0.0	1.0	2,708.713
Additive without polygenic residual ($d = 1/2$, $H = 0$)	2	2,709.348	6.634	0.0363	2,713.348
Additive with polygenic residual ($d = 1/2$)	1	2,702.713	0.0	1.0	2,708.713
Dominant without polygenic residual ($d = 1$, $H = 0$)	2	3,905.659	1,202.946	0.0001	3,909.659
Dominant with polygenic residual ($d = 1$)	1	2,711.358	8.644	0.0033	2,717.358
General Mendelian without polygenic residual ($H = 0$)	1	2,709.303	6.589	0.0103	2,715.303
General Mendelian with polygenic residual	—	2,702.713	—	—	2,710.713
Non-Mendelian tau's					
General Mendelian with polygenic residual ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$)	1	2,702.713	0.0	1.0	2,710.713
Environmental ($P = \tau_{AA} = \tau_{Aa} = \tau_{aa}$)	1	2,710.531	7.818	0.0052	2,718.531
Revised general ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$)	—	2,702.713	—	—	2,712.713

Table II
Parameter Estimates for Segregation Analysis of BWS in Nuclear Families

Model	A allele frequency <i>P</i>	Three transmission probabilities			Dominance <i>D</i>	Displacement <i>t</i>	Heritability <i>H</i>
		τ_{AA}	τ_{Aa}	τ_{aa}			
Sporadic ($P = 1, d = 0, t = 0, H = 0$)	[1]	[1]	[1/2]	[0]	[0]	[0]	[0]
Multifactorial ($P = 1, d = 0, t = 0$)	[1]	[1]	[1/2]	[0]	[0]	[0]	0.5472
Recessive without polygenic residual ($d = 0, H = 0$)	0.7915	[1]	[1/2]	[0]	[0]	7.000	[0]
Recessive with polygenic residual ($d = 0$)	0.7391	[1]	[1/2]	[0]	[0]	8.464	0.4415
Additive without polygenic residual ($d = 1/2, H = 0$)	0.7916	[1]	[1/2]	[0]	[1/2]	7.320	[0]
Additive with polygenic residual ($d = 1/2$)	0.7391	[1]	[1/2]	[0]	[1/2]	17.095	0.4415
Dominant without polygenic residual ($d = 1, H = 0$)	0.9952	[1]	[1/2]	[0]	[1]	13.071	[0]
Dominant with polygenic residual ($d = 1$)	0.8517	[1]	[1/2]	[0]	[1]	15.940	0.4771
General Mendelian without polygenic residual ($H = 0$)	0.8088	[1]	[1/2]	[0]	0.5916	4.973	[0]
General Mendelian with polygenic residual	0.7391	[1]	[1/2]	[0]	0.4981	15.940	0.4416
Environmental ($P = \tau_{AA} = \tau_{Aa} = \tau_{aa}$)	0.5126	[1]	[1/2]	[0]	0.0398	5.013	1 ^a
Revised General ($\tau_{AA} = 1, \tau_{Aa} = 0.5$)	0.7391	[1]	[1/2]	0 ^a	0.1951	9.811	0.4416

[] Denotes a fixed parameter.

^a Denotes boundary solution verified to be the best solution by a grid search procedure.