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Beckwith-Wiedemann Syndrome in Diverse Populations

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Abstract

Beckwith-Wiedemann syndrome (BWS) is the most common epigenetic overgrowth disorder and presents with patients affected by a variety of clinical features. Although genotype-phenotype correlations have been demonstrated in BWS and although BWS has been reported to occur equally among racial and ethnic backgrounds, no study to date has evaluated the frequency of findings in different backgrounds. In this study, we evaluated the incidence of clinical features and molecular diagnoses among patients with BWS in Caucasian, Mixed, and non-Caucasian groups. These results suggest that clinical features and molecular diagnoses differ between race/ethnicity groups and raise the possibility of race and ethnicity effects on genotype-phenotype correlations in BWS.

Keywords

Beckwith-Wiedemann Syndrome; Race; Ethnicity; Diverse populations; Overgrowth; Methylation; Imprinting

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) (OMIM #130650) is the most common epigenetic overgrowth disorder, affecting at least 1 in 10,540 live births (Mussa, Di Candia, et al., 2016). Patients with BWS can present with a spectrum of clinical features, including macroglossia, abdominal wall defects (omphalocele, umbilical hernia, diastasis recti), ear creases/pits, organomegaly, macrosomia, and lateralized overgrowth (a more accurate term than the previously used "hemihypertrophy") (Brioude et al., 2018; Kalish et al., 2017). Patients also have a predisposition to embryonal tumors, most commonly Wilms tumor and hepatoblastoma.

Molecular testing has led to the classification of subtypes of patients with BWS due to alterations on chromosome 11: loss of methylation at KCNQ1OT1:TSS differentially

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molecular testing were excluded as these patients without a clear molecular result may represent a less well-defined group beyond the scope of this analysis. For monozygotic twins with positive molecular testing and phenotypic discordance, only the more affected twin was included. All families provided consent for the study.

Medical records were reviewed for information on diagnosis, characteristics of pregnancy and birth, as well as presence of clinical features. Demographic information regarding race and ethnicity was ascertained from available pedigrees and medical records, which in turn were obtained by family report. Patients were clustered into three groups based on race and ethnicity: Caucasian, Mixed, non-Caucasian. For the purposes of this paper, Hispanic ethnicity was defined based on the U.S. Office of Management and Budget (OMB) as non-Hispanic/Latino or Hispanic/Latino. The Caucasian group was defined as patients who identified as Caucasian and were non-Hispanic/Latino. The Mixed group was defined as patients who identified as two or more races, or those who identified as one race in addition to Hispanic/Latino ethnicity. The non-Caucasian designation was defined as patients who identified as one race other than Caucasian only, or those who defined themselves as Hispanic/Latino only.

Literature review

A literature search was conducted in PubMed to identify patient cohorts in which (epi)genotype-phenotype correlations were evaluated in patients with BWS between January 2000 and July 2017. Studies with patient cohorts in which the incidence of clinical features in molecularly-confirmed patients and/or the molecular subtypes of patients were reported were included, and ten cohorts were identified (Brioude et al., 2013; DeBaun et al., 2002; Ibrahim et al., 2014; Lin et al., 2016; Luk, 2017; Maas et al., 2016; Mussa et al., 2016a, 2016b; Sasaki et al., 2007; Weksberg et al., 2001). Several additional studies were identified that included data from earlier publications, so the earlier publications were excluded to avoid duplicating patients.

The included references were reviewed for information about molecular diagnosis and clinical features in patients and were grouped based on the location of the reporting institutions to develop two cohorts: the European/North American cohort and the Asian cohort. The number of patients presenting with each clinical feature and the total number of patients evaluated for the presence of each feature was recorded from each source as available. If the source included data from other included sources or from patients with negative molecular testing, these patients were not included in the analysis. The total percentage of each feature was calculated to determine the expected incidence for patients from the European/North American cohort and the Asian cohort and used for clinical feature comparisons. The number of patients presenting with each molecular subtype were also recorded from each source and combined to calculate the incidence within the European/North American cohort and the Asian cohort and used for molecular subtype comparisons. Based on the available information, not all ten references were used for the clinical feature and/or molecular subtype comparisons and the specific references included for each are described in the Results section.

Statistical Analysis

Data were analyzed using SPSS Statistics (version 24.0). Descriptive statistics were used to summarize the mean and standard deviation for continuous variables and the frequencies for nominal/categorical variables. Differences between the clinical features in race/ethnicity groups within the cohort were tested with Chi-squared test statistics and Fisher's exact test when appropriate. One-way t testing was performed to compare the incidence of clinical features in the overall current cohort and within subgroups to expected values based on the literature cohorts. Pearson chi-squared testing was used to evaluate overall differences in molecular subtype incidence between the cohorts and column proportion testing (z-test) with adjusted p-values using the Bonferroni method was used to evaluate for differences between the cohorts in regard to each molecular subtype. Significance was set at $p < 0.05$.

RESULTS

Characteristics of the Current BWS Cohort

A total of 139 patients were included for analysis. To our knowledge, only 32 of these patients have previously been reported (Kalish et al., 2016; MacFarland et al., 2018; MacFarland et al., 2017; Peterson et al., 2016; Tong et al., 2017). Characteristics about diagnosis including the age at diagnosis and indications for diagnosis were evaluated for differences between the three groups (Caucasian, Mixed, non-Caucasian) within the current cohort. Facial photographs of representative patients within the cohort are shown in Fig 1.

Age at Diagnosis—The age at diagnosis was grouped into three categories: Prenatally confirmed (9.5%); Diagnosed in the neonatal period (less than 28 days) (45.3%); and Diagnosed after the neonatal period (45.3%). No significant difference was found in the age categories between the race/ethnicity groups by Pearson chi-square analysis ($p=0.377$), however a trend was observed with Caucasian patients being diagnosed younger than Mixed and non-Caucasian patients. More than half of the patients in the Mixed and non-Caucasian groups were diagnosed after the neonatal period (52.2% and 54.5% respectively), while more than half of the Caucasian patients were diagnosed either prenatally (12.0%) or in the neonatal period (46.7%). Among patients diagnosed after the neonatal period, no significant differences were found between the groups in the mean or median age at diagnosis (months) by Kruskal-Wallis ($p=0.545$) and median ($p=0.913$) testing.

Indications for Diagnosis—The indications for diagnosis, representative of what brought these patients to medical attention, were grouped into four categories: typical BWS clinical features (79.1%); first presenting with hyperinsulinism (10.1%); first presenting with tumor (9.4%); and incidentally diagnosed (1.4%). The indications for diagnosis did not differ significantly between the race/ethnicity groups by Pearson chi-square analysis ($p=0.352$). A trend was observed with a higher incidence of patients diagnosed after first presenting with hyperinsulinism among the Mixed and non-Caucasian patients (12.5% and 18.2% respectively) compared to the Caucasian patients (7.5%).

Clinical Feature Comparisons in the Current Cohort and in Literature Cohorts

Seven literature cohorts were included for clinical feature analysis. Among the ten identified cohorts, some were excluded if no clinical features were reported (Sasaki et al., 2007), or if it was not possible to determine the incidence of clinical features in the patients with positive molecular testing (DeBaun et al., 2002; Lin et al., 2016). In the Mussa et al. (2016a) cohort, reported incidence of features as percentages, and it was assumed that all patients were evaluated and the percentage was used to calculate the number of patients affected by each feature (Mussa et al., 2016a). Although overlapping cohorts existed between the Mussa et al. (2016a) and (2016b) cohorts, only the data about birth was included from the Mussa et al. (2016b) reference and these features were not recorded from the Mussa et al. (2016a) reference. For this analysis, the European/North American cohort was composed of patients reported from the Netherlands (Maas et al., 2016), France (Brioude et al., 2013), Italy (Mussa et al., 2016a, 2016b), United Kingdom (Ibrahim et al., 2014), and Canada (Weksberg et al., 2001). The Asian cohort was composed of patients reported from China (Luk, 2017) and Korea (Lee et al., 2013).

Significant differences and trends in the incidence of clinical features were found between the subgroups within the current cohort (Table I) and between the current cohort compared to the European/North American cohort (Table II) and Asian cohort (Table III). Notable differences and trends are summarized by clinical feature below:

Macroglossia—Macroglossia incidence did not differ significantly between the groups within our cohort. A trend towards Caucasian patients receiving a tongue reduction more frequently than Mixed and non-Caucasian patients was observed. Macroglossia occurred significantly more frequently in patients from the European/North American cohort compared to patients in our overall cohort and the Caucasian group within our cohort.

Omphalocele—A significant increase in the incidence of omphalocele was observed for Caucasian patients compared to the Mixed and non-Caucasian patients in the current cohort. A significantly lower omphalocele incidence was observed for our overall cohort and within each subgroup compared to the European/North American cohort, although this difference was less significant for the Caucasian patients. A significantly higher incidence in Caucasian patients and significantly lower incidence in Mixed patients from this cohort was found compared to the Asian cohort, however no significant difference was found overall between the literature cohorts.

Organomegaly/Nephromegaly—The overall incidence of organomegaly did not differ significantly between subgroups within our cohort. Compared to the European/North American cohort, our non-Caucasian patients had a significantly higher frequency of organomegaly. The Asian cohort had a significantly higher frequency of organomegaly compared to our overall cohort and the Caucasian and Mixed groups, but not compared to the non-Caucasian patients in our cohort. Nephromegaly was significantly increased in the non-Caucasian patients within our cohort and compared to the European/North American cohort.

Hypoglycemia—The overall incidence of hypoglycemia did not significantly differ between the groups within the current cohort, however incidence was significantly increased for our overall cohort and Caucasian patients compared to the European/North American and Asian cohorts. Among patients with hypoglycemia in our cohort, the degree of hypoglycemia (transient versus hyperinsulinism) was found to differ significantly between the groups. Caucasian patients had a significantly higher frequency of transient hypoglycemia, while non-Caucasian patients had a significantly higher frequency of hyperinsulinism. Although not significant, a trend in hyperinsulinism requiring a partial pancreatectomy was found to be higher in patients in the Mixed and non-Caucasian groups compared to the Caucasian group.

Facial Nevus Simplex—No significant difference in the incidence of facial nevus simplex (FNS) was found between subgroups within the current cohort, although a trend was observed in that Caucasian patients were noted to present with FNS more frequently than the non-Caucasian patients and the frequency in the Mixed group was between these two groups.

Compared to the Asian cohort, the entire current cohort and the non-Caucasian subgroup had a significantly lower incidence of FNS. No other significant differences were found between the European/North American cohort and within our own cohort. Although not significant, a lower incidence was observed in our non-Caucasian patients compared to the European/North American cohort, while the other groups had similar frequencies.

Tumor Development—No significant difference in tumor development was found between the race/ethnicity groups in the current cohort. A significantly higher incidence of tumors was demonstrated in our overall cohort compared to both the European/North American cohort and the Asian cohort. Caucasian and non-Caucasian patients in our cohort similarly had a significantly higher incidence compared to the European/North American and Asian cohorts, and no significant difference was demonstrated in Mixed patients compared to these cohorts.

Birth Characteristics—No significant difference in prematurity (defined as <37 weeks) was found between the groups within our cohort, although Caucasian patients tended to be premature more often than the Mixed or non-Caucasian patients. Caucasian patients were found to be premature significantly more frequently than the European/North American cohort, and the incidence of prematurity was significantly higher in our overall cohort compared to the European/North American cohort. Patients in the Asian cohort were premature more frequently than the Mixed patients in our cohort.

Within our cohort, no significant differences in regard to large for gestational age (LGA), defined as >90%ile, were found, although frequency was higher in the Mixed and non-Caucasian patients compared to the Caucasian patients. Our cohort had a significantly higher incidence of LGA overall and within each group compared to the Asian cohort. Compared to the European/North American cohort, only the Mixed patients had a significantly higher incidence, and all other comparisons were not significant.

Molecular Subtype Comparisons in Our Cohort and in Literature Cohorts

No significant differences in molecular etiology between the race/ethnicity groups within the current cohort were found by Pearson chi-square analysis ($p=0.693$). The most frequent molecular subtype in the Caucasian and Mixed groups was IC2 LOM, while the most frequent subtype in the non-Caucasian group was pUPD11 (Table IV). IC1 GOM was observed slightly more frequently in the Mixed and non-Caucasian patients.

Nine patient cohorts reporting the molecular subtypes of BWS patients were compared. The cohort reported by (Mussa et al., 2016b) was not included, as it overlapped with the included cohort by (Mussa et al., 2016a). The European/North American cohort was composed of patients reported from the Netherlands (Maas et al., 2016), France (Brioude et al., 2013), Italy (Mussa et al., 2016a, 2016b), United Kingdom (Ibrahim et al., 2014), Canada (Weksberg et al., 2001), and the United States (DeBaun et al., 2002). The Asian cohort was composed of patients reported from China (Luk, 2017), Japan (Sasaki et al., 2007), Korea (Lee et al., 2013), and Taiwan (Lin et al., 2016).

There was a significant difference between molecular subtypes between our overall cohort, the European/North American cohort, and the Asian cohort by Pearson chi-square analysis ($p<0.001$) (Table V). Column proportion testing demonstrated a higher incidence of 11p15.5 anomalies in our cohort and the Asian cohort compared to the North American/European cohort and a lower incidence of *CDKN1C* mutations in the North American/European cohort compared to the Asian cohort. There was a significantly lower incidence of IC2 LOM in our cohort compared to the North American/European cohort.

There was a significant difference ($p<0.001$) in the molecular subtypes between the race/ethnicity groups within our cohort, the European/North American cohort, and the Asian cohort (Table VI). Column proportion testing demonstrated a significantly higher frequency of pUPD11 and lower frequency of IC2 LOM among non-Caucasian patients in our cohort compared to the North American/European and Asian cohorts. Patients in the Caucasian group also had a significantly lower frequency of IC2 LOM compared to the European/North American cohort. There was a significantly higher incidence of 11p15.5 anomalies among Caucasian patients in our cohort and Asian patients compared to the European/North American cohort. Patients in the Asian cohort had a significantly higher incidence of *CDKN1C* mutations compared to the groups within our cohort and the European/North American cohort.

DISCUSSION

In this work, we reviewed differences in clinical features and molecular subtypes in racial and ethnic subgroups using a cohort from an emerging registry as well as several previously published cohorts. We noted significant differences and trends between the race/ethnicity groups in regard to both clinical features and molecular subtypes. Caucasian patients appear to be more frequently diagnosed with outwardly recognizable features of BWS (omphalocele, macroglossia, FNS) while non-Caucasian patients appear to be more prone to less visually apparent features (hyperinsulinism, nephromegaly). This difference in phenotype may be due to a combination of recognition bias and referral bias. Recognition

bias is due to the possibility that facial features are distinct in different populations as has been demonstrated in other syndromes [Kruszka et al., 2017a; Kruszka et al., 2017b; Kruszka et al., 2017c; Kruszka et al., 2018] and as such the facial gestalt in BWS may be under-diagnosed in non-Caucasian groups. Secondly, referral bias may exist in that non-Caucasian patients with BWS may be less frequently referred to a tertiary care center due to socioeconomic stratification and/or other barriers to care and follow-up, resulting in only the extreme cases such as hyperinsulinism being referred. Unfortunately, our data do not dissect the severity of each finding, just its presence. With regard to molecular subtype differences, in the current cohort, non-Caucasian patients had a remarkably lower incidence of IC2 LOM and higher incidence of pUPD11 compared to literature cohorts. In addition, the trends noted in our data suggest that IC1 GOM is more common in Mixed and non-Caucasian patients. It may be possible as well, that these findings are reflective of socioeconomic status, in that IC2 LOM is seen more commonly in IVF pregnancies, which often incur significant out of pocket expenses. Nonetheless, these correlations are consistent with the fact that classic BWS features of omphalocele and macroglossia, which most often correlate with IC2 LOM, are more common in Caucasian patients while severe HI more common in non-Caucasian patients, most often correlates with pUPD11. Finally, these findings may in fact reflect bonafide background variation and there may be specific racial or ethnic differences or modifiers that predispose to different epigenetic/genetic alterations in BWS.

The current cohort had a significantly higher incidence of hypoglycemia and tumors compared to both the European/North American and Asian cohorts. Approximately one-fifth of the patients included in this cohort first presented with hyperinsulinism or tumors. As a result, the patients included in this cohort are likely more representative of the broader Beckwith-Wiedemann spectrum (Brioude et al., 2018).

These differences in molecular subtypes may reflect the differences in clinical features observed between the groups. Caucasian patients were found to have a higher frequency of omphalocele, which is most common in the IC2 group (Brioude et al., 2013; Ibrahim et al., 2014; Mussa et al., 2016a). Similarly, among patients with omphalocele in the general pediatric population, Caucasian was found to be the most common race/ethnicity (Corey et al., 2014), suggesting a background predisposition whereas umbilical hernias are more common in African American patients (Marinkovic & Bukarica, 2003). The non-Caucasian patients were found to have a higher frequency of nephromegaly and hyperinsulinism, which in some cases required partial pancreatectomy. (Epi)genotype-phenotype correlations found nephromegaly to be most common in IC1 GOM and pUPD11 (Goldman et al., 2002; Ibrahim et al., 2014; Mussa et al., 2012). In addition, hyperinsulinism and partial pancreatectomies are most common in patients with pUPD11 (Flanagan, Kapoor, Smith, Hussain, & Ellard, 2011; Hussain et al., 2005; Kalish et al., 2016; Laje et al., 2013; Meissner et al., 2001). There is a trend in IC1 GOM, which can also account for the trend in LGA being observed in Mixed and non-Caucasian patients (Brioude et al., 2013; Mussa et al., 2016b).

These findings raise the question of whether race/ethnicity affects the molecular type of BWS or whether it affects phenotypic features that result from each molecular etiology. We propose that if (epi)genotype-phenotype correlations predominate, then it is likely the

molecular subtype affecting the various race groups is responsible for the differences in clinical features observed. If the race/ethnicity of the patient is driving the clinical features, then currently understood (epi)genotype-phenotype correlations may not be entirely accurate, but may be confounded by race/ethnicity. A larger dataset is required to investigate for (epi)genotype-phenotype correlations within racial groups.

Limitations

Certain differences in the current cohort compared to the literature cohorts can be explained by patient ascertainment. Due to the tertiary referral nature of our institution, approximately one-fifth of patients in this cohort were diagnosed with BWS after presenting with hyperinsulinism or a tumor, instead of the classic BWS features. Although these patients had positive molecular testing in one or more tissues, they did not always exhibit some of the classic BWS features, thus affecting the results. These patients highlight the need to detect more subtle BWS features and perform testing in affected tissues when available (Brioude et al., 2018).

Due to the heterogeneity of this group and small numbers of specific racial groups, we were unable to further subclassify the Mixed and non-Caucasian groups. To achieve this, larger data sets are needed to group patients by geographic origin (African, Asian, Latin American, etc.) and to evaluate whether significant differences occur within groups. Additionally, for the literature cohorts, we made assumptions that patients from the European/North American cohort were predominantly Caucasian as no demographic information was reported. This provides a limitation in that the cohort may be more diverse than was assumed in this analysis.

CONCLUSION

In summary, BWS is a heterogeneous syndrome with a spectrum of clinical features. While a racial/ethnic predisposition has not been previously reported, these data suggest that race/ethnicity may play a role in both phenotypic manifestation of BWS and epigenetic/genetic cause. This leads to a potentially distinct phenotype-(epi)genetic correlation within different races or ethnic groups which need to be considered in making the diagnosis.

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Figure 1 –.

Facial photographs of patients with BWS demonstrating features in Caucasian, Mixed, and Non-Caucasian patients. Abbreviations: IC2 (imprinting center 2 loss of methylation); pUPD (paternal uniparental disomy of chromosome 11); GWpUPD (genome wide paternal uniparental disomy)

Top Row Caucasian patients: **A)** pUPD, 1 month old **B)** IC2, 5 months old **C)** pUPD, 15 months old **D)** IC2, 3 years old

Middle Row Mixed patients: **E)** IC2, 2 months old **F)** pUPD, 9 months old **G)** IC2, 2 years old **H)** GWpUPD, 3 years old

Bottom Row Non-Caucasian patients: **I)** IC2, 1 month old **J)** pUPD, 3 months old **K)** pUPD, 8 months old **L)** IC2, 14 months old

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Table I.

Incidence of Clinical Features in the Current Cohort and Comparisons Between Race/Ethnicity Groups

Feature	Total (n=139)	Caucasian (n=93)	Mixed (n=24)	Non-Caucasian (n=22)	p-value ^a
Macroglossia	72.7%	71.0%	79.2%	72.7%	0.724
Tongue Reduction ^b	48.4%	56.5%	42.1%	21.4%	0.050
Abdominal Wall Defects	65.5%	66.7%	62.5%	63.6%	0.912
Omphalocele	20.9%	26.9%	4.2%	13.6%	0.034 [*]
Umbilical Hernia	37.7%	31.5%	50.0%	50.0%	0.108
Diastasis Recti	18.4%	18.7%	26.1%	9.1%	0.336
Organomegaly	45.3%	41.9%	36.4%	68.2%	0.055
Hepatomegaly	24.6%	22.8%	27.3%	30.0%	0.758
Nephromegaly	26.9%	22.8%	22.7%	50.0%	0.041 [*]
Splenomegaly	13.4%	13.0%	9.1%	20.0%	0.574
Lateralized Overgrowth	82.5%	82.4%	79.2%	86.4%	0.814
Hypoglycemia	64.5%	67.4%	58.3%	59.1%	0.602
Transient hypoglycemia ^c	62.9%	71.0%	57.1%	30.8%	0.021 [*]
Hyperinsulinism ^c	38.6%	31.1%	42.9%	69.2%	0.035 [*]
Pancreatectomy ^d	47.1%	36.8%	66.7%	55.6%	0.371
Ear creases/pits	70.4%	71.1%	69.6%	68.2%	0.960
Facial nevus simplex	49.3%	52.7%	47.8%	36.4%	0.383
Tumor	23.4%	22.8%	17.4%	31.8%	0.509
Placentomegaly	17.7%	18.2%	14.3%	19.0%	0.901
Polyhydramnios	25.4%	27.3%	9.5%	33.3%	0.161
Preterm Birth (<37 weeks)	44.2%	48.4%	33.3%	38.1%	0.345
LGA ^e	65.2%	60.0%	79.2%	71.4%	0.174

* significant at $p < .05$

^a P values refer to the frequency of each feature between the three subgroups (Caucasian, Mixed, non-Caucasian), so all subgroups are compared at the same time

^b Percentages reported among just those patients with macroglossia

^c Percentages reported among just those patients with hypoglycemia

^d Percentages reported among just those patients with hyperinsulinism

^e Large for gestational age (>90%ile)

Table II. Comparison of Clinical Features in Current Cohort to the European/North American Cohort

Feature	European/North American Cohort		Current Cohort						
	%	Overall		Caucasian		Mixed		Non-Caucasian	
		p-value	%	p-value	%	p-value	%	p-value	%
LGA ^a	53.6%	0.006**	60.0%	0.221	79.2%	0.006**	71.4%	0.093	
Preterm Birth (<37 weeks)	32.0%	0.005**	48.4%	0.002**	33.3%	0.893	38.1%	0.581	
Polyhydramnios	30.7%	0.168	27.3%	0.475	9.52%	0.004**	33.3%	0.805	
Macroglossia	83.4%	0.005**	71.0%	0.010	79.2%	0.622	72.7%	0.285	
Ear creases/pits	51.0%	<0.001***	71.1%	<0.001***	69.6%	0.072	68.2%	0.106	
Facial Nevus Simplex	51.0%	0.687	52.7%	0.746	47.8%	0.768	36.4%	0.178	
Abdominal Wall Defect	62.3%	0.435	66.7%	0.377	62.5%	0.984	63.6%	0.900	
Omphalocele	37.7%	<0.001***	26.9%	0.021*	4.17%	<0.001***	13.6%	0.004**	
Umbilical Hernia	32.5%	0.213	31.5%	0.841	50.0%	0.107	50.0%	0.124	
Diastasis Recti	29.4%	0.001**	18.7%	0.011*	26.1%	0.727	9.1%	0.004**	
Organomegaly	46.2%	0.825	41.9%	0.409	36.4%	0.359	68.2%	0.042*	
Nephromegaly	23.8%	0.427	22.8%	0.825	22.7%	0.908	50.0%	0.034*	
Hepatomegaly	18.4%	0.098	22.8%	0.317	27.3%	0.372	30.0%	0.284	
Splenomegaly	9.5%	0.186	13.0%	0.318	9.1%	0.949	20.0%	0.267	
Hypoglycemia	47.6%	<0.001***	67.4%	<0.001***	58.3%	0.307	59.1%	0.296	
Lateralized Overgrowth	40.8%	<0.001***	82.4%	<0.001***	79.2%	<0.001***	86.4%	<0.001***	
Tumor	10.3%	<0.001***	22.8%	0.005**	17.4%	0.390	31.8%	0.046*	

* significant at p < .05

** significant at p < .01

*** significant at p < .001

^a Large for gestational age (>90%ile)

Table III.

Comparison of Clinical Features in Current Cohort to the Asian Cohort

Feature	Asian Cohort		Current Cohort							
	%	p-value	Caucasian		Mixed		Non-Caucasian			
			%	p-value	%	p-value	%	p-value		
LGA ^a	38.6%	<0.001***	60.0%	<0.001***	79.2%	<0.001***	71.4%	0.004**		
Preterm	54.5%	0.017	48.4%	0.244	33.3%	0.042*	38.1%	0.146		
Polyhydramnios ^b	18.5%	0.075	27.3%	0.070	9.5%	0.187	33.3%	0.175		
Macroglossia	79.5%	0.074	71.0%	0.075	79.2%	0.969	72.7%	0.494		
Ear Creases/Pits	61.4%	0.025*	71.1%	0.046*	69.6%	0.414	68.2%	0.512		
Facial Nevus Simplex ^b	59.3%	0.020*	52.7%	0.207	47.8%	0.293	36.4%	0.040*		
Omphalocele ^b	14.8%	0.082	26.9%	0.010*	4.2%	0.018*	13.6%	0.878		
Umbilical Hernia	52.3%	0.001**	31.5%	<0.001***	50.0%	0.827	50.0%	0.835		
Organomegaly ^b	77.8%	<0.001***	41.9%	<0.001***	36.4%	0.001**	68.2%	0.355		
Hypoglycemia	45.5%	<0.001***	67.4%	<0.001***	58.3%	0.224	59.1%	0.219		
Lateralized Overgrowth	45.5%	<0.001***	82.4%	<0.001***	79.2%	0.001**	86.4%	<0.001***		
Tumor	9.1%	<0.001***	22.8%	0.002**	17.4%	0.316	31.8%	0.036*		

* significant at p < .05

** significant at p < .01

*** significant at p < .001

^aLarge for gestational age (>90%ile)

^bData only from Chinese cohort (not included in Korean)

Table IV.

Incidence of Molecular Subtypes within Our Cohort

Molecular Type	Total	Caucasian	Mixed	Non-Caucasian
	%	%	%	%
IC1 GOM ¹	10.8%	9.7%	12.5%	13.6%
IC2 LOM ²	48.2%	51.6%	50.0%	31.8%
pUPD11 ³	29.5%	25.8%	29.2%	45.5%
<i>CDKN1C</i> mutation	3.6%	4.3%	4.2%	0%
Chromosome 11p15 abnormality	7.9%	8.6%	4.2%	9.1%

¹Imprinting center 1 gain of methylation²Imprinting center 2 loss of methylation³Paternal uniparental disomy of chromosome 11

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Table V.

Incidence of Molecular Subtypes between Cohorts

Molecular Type	Our Cohort	European/North American Cohort	Asian Cohort
	%	%	%
IC1 GOM ¹	10.8% ^a	8.6% ^a	6.1% ^a
IC2 LOM ²	48.2% ^a	62.2% ^b	60.6% ^{a,b}
pUPD11 ³	29.5% ^a	24.4% ^a	20.2% ^a
<i>CDKN1C</i> mutation	3.6% ^{a,b}	3.2% ^a	7.1% ^b
Chromosome 11p15 abnormality	7.9% ^a	1.7% ^b	6.1% ^a

¹Imprinting center 1 gain of methylation²Imprinting center 2 loss of methylation³Paternal uniparental disomy of chromosome 11^{a, b} Subset of cohort categories whose column proportions do not differ significantly from each other at the 0.05 level

Table VI.

Incidence of Molecular Subtypes within our Cohort and Literature Cohorts

Molecular Type	Our Cohort			European/North American Cohort	Asian
	Caucasian	Mixed	Non-Caucasian		
	%	%	%	%	%
IC1 GOM ¹	9.7% ^a	12.5% ^a	13.6% ^a	8.6% ^a	6.1% ^a
IC2 LOM ²	51.6% ^{a,b}	50.0% ^{a,b,c}	31.8% ^b	62.2% ^c	60.6% ^{a,c}
pUPD11 ³	25.8% ^{a,b}	29.2% ^{a,b}	45.5% ^b	24.4% ^a	20.2% ^a
<i>CDKN1C</i> mutation	4.3% ^a	4.2% ^a	0% ^a	3.2% ^a	8.5% ^b
Chromosome 11p15 abnormality	8.6% ^a	4.2% ^{a,b}	9.1% ^{a,b}	1.7% ^b	7.3% ^a

¹Imprinting center 1 gain of methylation²Imprinting center 2 loss of methylation³Paternal uniparental disomy of chromosome 11^{a, b} Subset of cohort categories whose column proportions do not differ significantly from each other at the 0.05 level

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