# That is why you are my twin...

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Cliniques Universitaires Saint Luc
GBN - 27/11/2025


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Zwilling
Twins
Tweeling
Jumelles
Jumeaux
Jumelles
Tweeling
Jumeaux
Twins
Zwilling
Jumelles

# So let us start with our case…

Spontaneous pregnancy

Female **monochorionic-biamniotic** twins

Born preterm at 24 3/7 weeks (premature rupture of membranes)

At birth :

- Twin 1 : Birthweight **700g** (birth weight at P70) ; **Hb 10,7 g/dL**
- Twin 2 : Birthweight **910g** (birth weight at P99) ; **Hb 16,3 g/dL**

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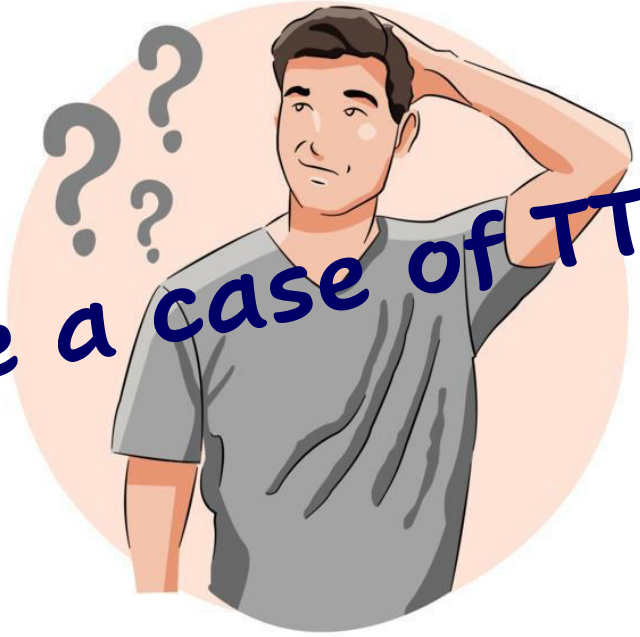
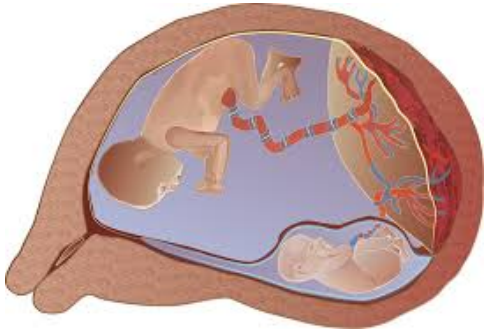
**Twin 1**
700g
Hb 10,7
g/dl



# Could this be a case of TTTS or TAPS ?



**Twin 2**
910g
Hb 16,3
g/dl

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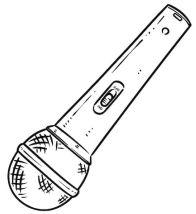

# What do you want to know ?

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# But then...

Meconial ileus with perforation on D15 with twin 2

Suspicion of intestinal occlusion on D22 with twin 1

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# So now...
# Anything else you want to know ?

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# So... to summarize :

Maybe STTT grade 1
Central hypothyroidism in twin 2
Cystic fibrosis excluded in twin 2
(guthrie + genetic)

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# But… Twin 2's evolution challenged us…

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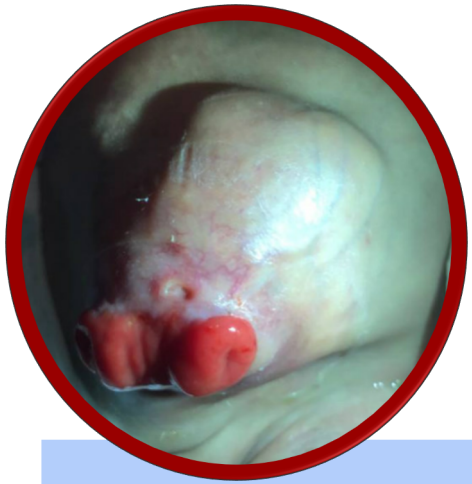
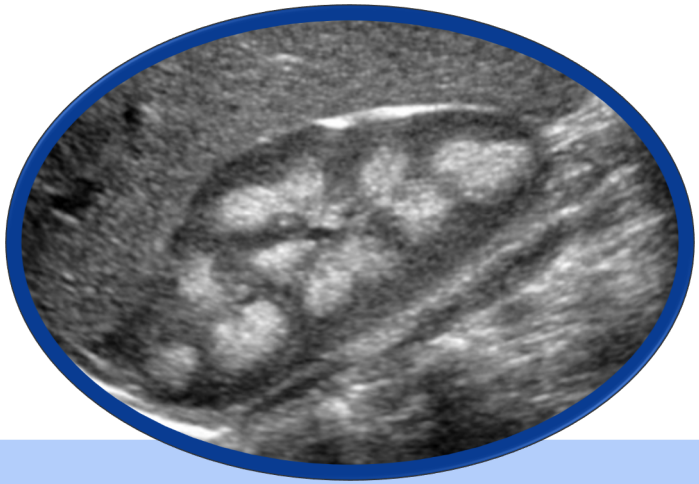




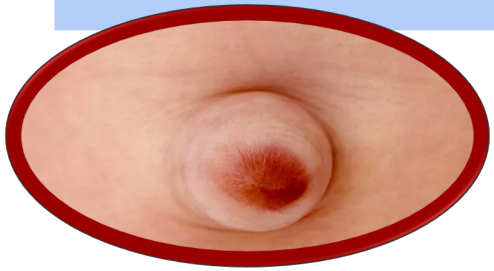
Abdominal wall complications

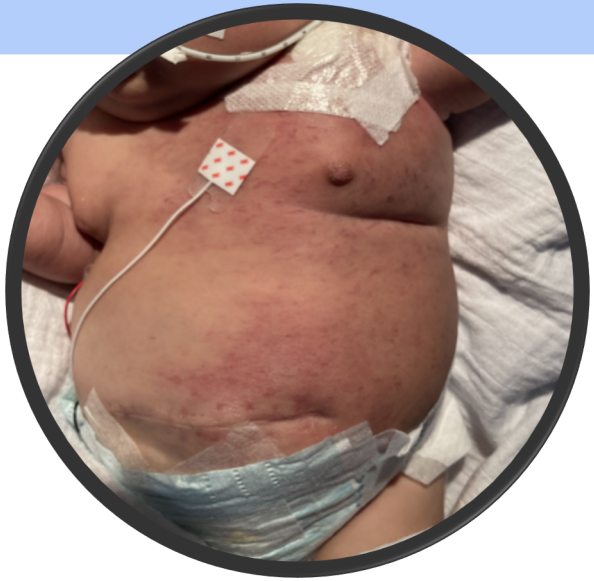
Isolated Left side overgrowth

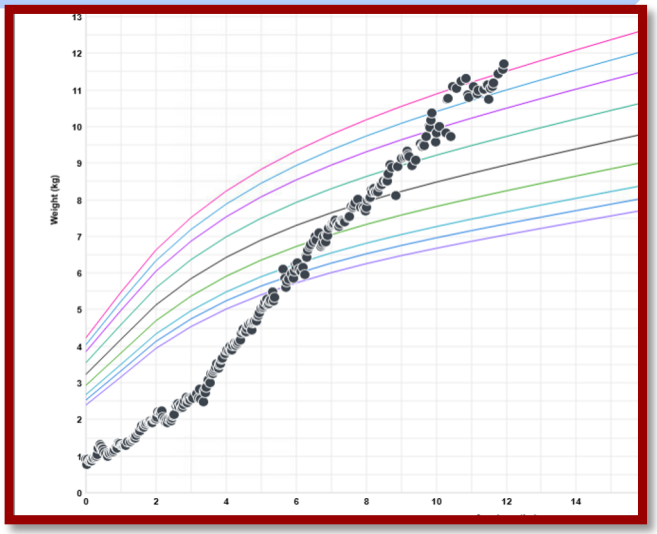
Isolated Left sided telangiesctasia

Nephrocalcinosis

Impressive growth curve







# So what's the diagnosis ?

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# What BIG piece of the clinical puzzle is missing ?

(or that we didn't give to you...🙄)

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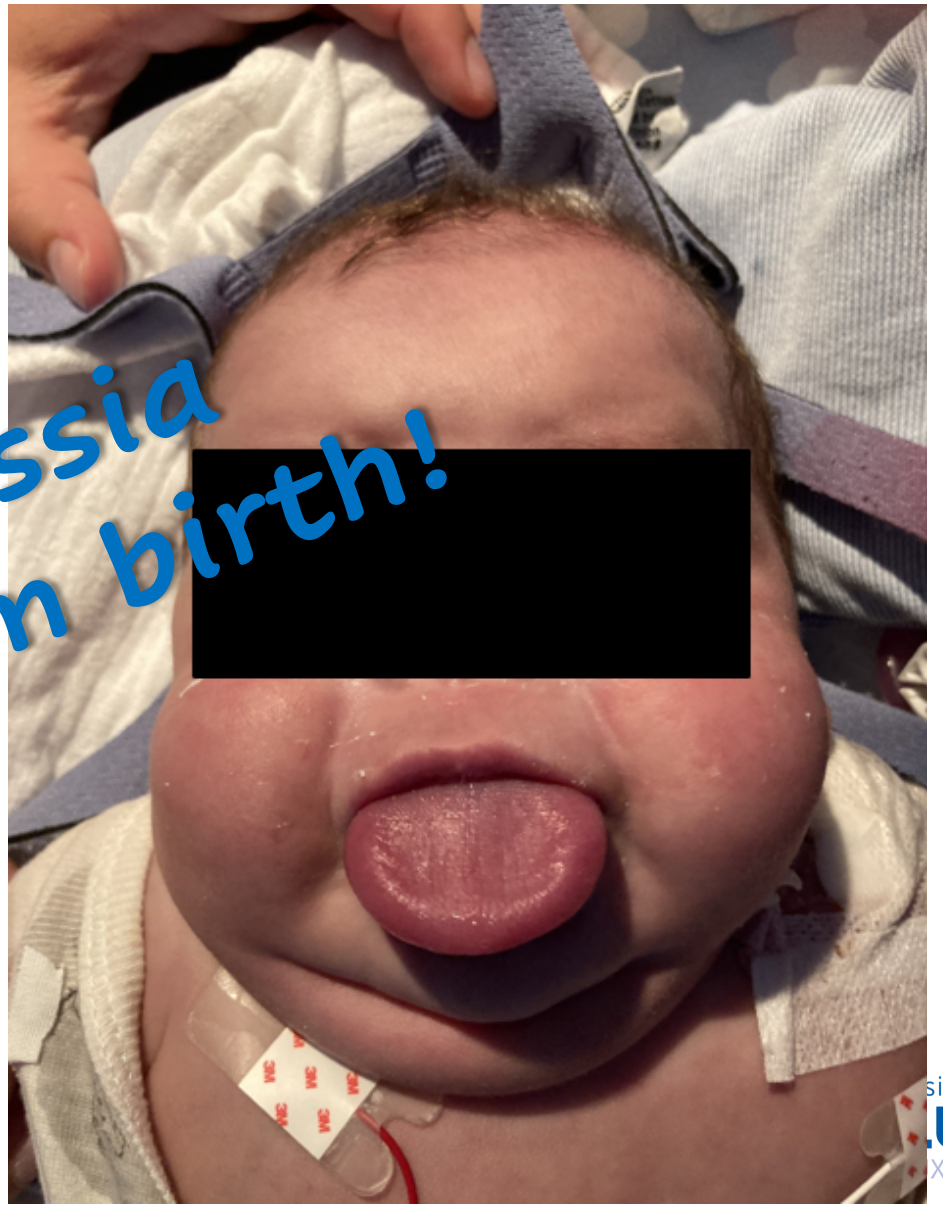
Macroglossia
Present from birth!

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# Clinical diagnosis of Beckwith Wiedemman syndrome

# How to confirm ?

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# CLINICALLY

## with Beckwith-Wiedemann syndrome Score

# AND

# GENETICALLY

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# Clinically => BWS score

| Cardinal features (2 points each) | Suggestive features (1 point each) |
|---|---|
| Macroglossia<br>Exomphalos<br>Lateralized overgrowth<br>Multif[illegible] tumor | Birth weight (>2SDS above the mean)<br>Facial nevus simplex<br>Polyhydramnios and/or placentomegaly<br>Ear creases and/or pits<br>Transient hypoglycemia (lasting < 1 week)<br>Typical BWSp tumors (neuroblastoma, rhabdomyosarcoma, [illegible]nilateral Wilms tumor, hepatoblastoma, adrenocortical [illegible]rcinoma or pheochromocytoma)<br>[illegible]ephromegaly and/or hepatomegaly<br>[illegible]mbilical hernia and/or diastasis recti |

**Twin 2 :**
Macroglossia : 2 points
Lateralized overgrowth : 2 points
Birth weight >2SDS : 1 point
Polyhydramnios : 1 point
Umbilical hernia and diastasis recti : 1 point
**7 POINTS**

[illegible]**core ≥ 4 is required**, and the molecular confirmation of 11p15.5 anomalies

[illegible] required with a score ≥ 2 with further evaluation of a BWS expert.

*Brioude et Al. - Nature reviews. Endocrinology (2018),* Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement.

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Genetically

# MS-MLPA of the specific region

(Methylation-Specific Multiplex Ligation-Dependent Probe Amplification)

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# Genetic results for twin 2

***Hypomethylation of the KCNQ1OT1 TSS-DMR***

***imprinting control region***

*(previously described as ICR2)* ***without apparent mosaicism***

## => Beckwith-Wiedemann Syndrome confirmed

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# What about her twin sibling ?

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# Same genetic...

***Hypomethylation of the KCNQ1OT1 TSS-DMR***

***imprinting control region***

*(previously described as ICR2)* ***without apparent mosaicism***

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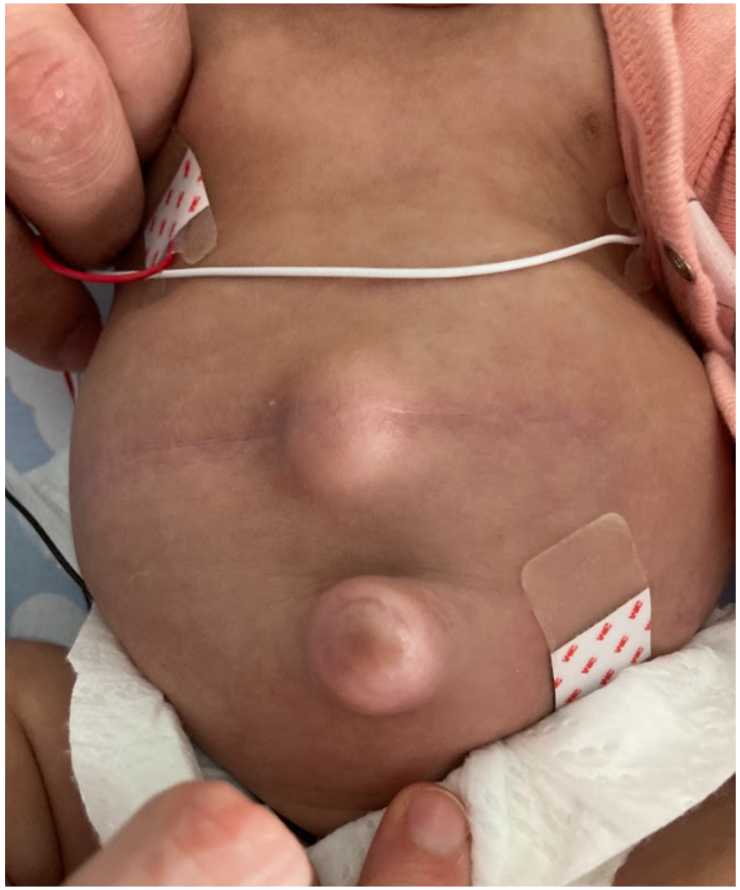
# … but different phenotype !



Only…

- Umbilical hernia
- Abdominal eventration of surgical scar

→ DISCORDANT TWIN

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# BWS score

| Cardinal features (2 points each) | Suggestive features (1 point each) |
|---|---|
| Macroglossia<br>Exomphalos<br>Lateralized overgrowth<br>Multifocal Wilms tumor<br>Prolonged hyperinsulinism | Birth weight (>2SDS above the mean)<br>Facial nevus simplex<br>Polyhydramnios and/or placentomegaly<br>Ear creases and/or pits<br>Transient hypoglycemia (lasting < 1 week)<br>Typical BWSp tumors (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumor, hepatoblastoma, adrenocortical carcinoma or pheochromocytoma)<br>Nephromegaly and/or hepatomegaly<br>Umbilical hernia and/or diastasis recti |

**Twin 1 :**
Umbilical hernia : 1 point
**1 POINT**

**For the clinical diagnosis, a score ≥ 4 is required**, and the molecular confirmation of 11p15.5 anomalies needs to be applied.
A genetic test is also required with a score ≥ 2 with further evaluation of a BWS expert.

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*Brioude et Al. - Nature reviews. Endocrinology (2018),* Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement.

# How is this possible?

What about genetics in BWS ?

What do we know about twins and BWS ?

# What about genetics in BWS ?

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# Some theory...

85% sporadic - 15% familial

Critical genetic region : **11p15.5**

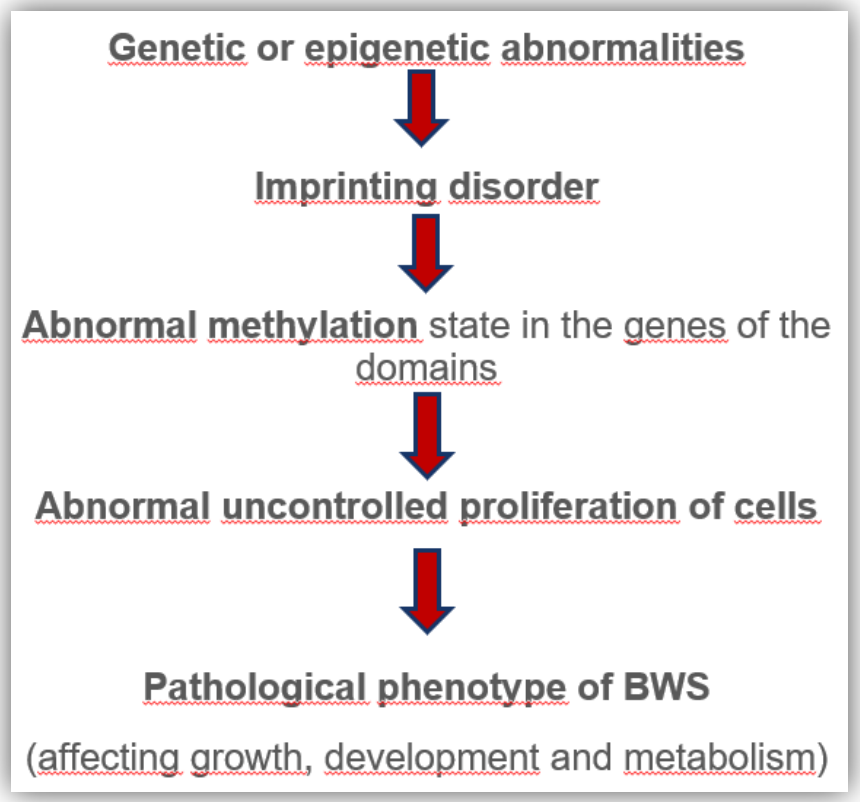
**BWS results from abnormalities of**

**structure or expression**

**of 2 imprinted domains of the region (= imprinting disorders)**

The 2 domains contain growth regulator genes

**The syndrome can also occur in a mosaic fashion → discordance between blood test and tissue test (saliva, buccal, fibroblasts)**

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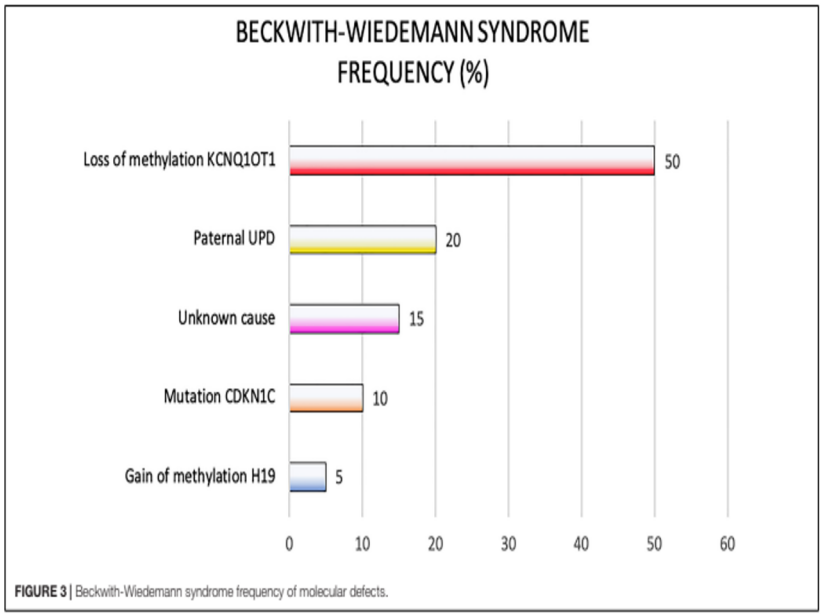
*Papulino et Al. - Frontiers in genetics (2020).* Preclinical and Clinical Epigenetic-Based Reconsideration of Beckwith-Wiedemann Syndrome

# Which genetic tests ? Depends on abnormalities

| Genetic test | Genetic and epigenetic abnormalities |
|---|---|
| MS-MLPA of the specific region | Epimutation<br>(aberrant methylation marks) |
| SNP microarray | Uniparental disomy |
| Sequencing of the specific region | Point mutation in imprinted genes |
| MS-MLPA of the specific region<br>CGH microarray<br>SNP microarray | Copy number variations (CNVs) |




*Papulino et Al. - Frontiers in genetics (2020).* Preclinical and Clinical Epigenetic-Based Reconsideration of Beckwith-Wiedemann Syndrome

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# What do we know about twins and BWS ?

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# Facts

**More frequent in twins** (prevalence Singleton : 1/10000 **><** Twin : 1/1000)

More frequent in **monozygotic twins**

More in MZ **female-female** twin than in male-male twin

Nearly exclusively caused by **hypomethylation in ICR2**

Mostly associated witch **discordance** (one twin affected, one twin less or unaffected)

**→ So is there a link between hypomethylation and twinning ?**

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*Cohen et Al. - American journal of medical genetics (2019).* Diagnosis and management of the phenotypic spectrum of twins with Beckwith-Wiedemann syndrome.

# YES !

## BUT HOW ?

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# A lot of theories…

- **An epigenetic event** (loss methylation on ICR2 in BWS) **prior to twinning leads to the formation of two different clonal populations of cells; these different cell clones repulse one another and trigger the twinning event**
  - → Explains that twinning can result from epigenetic event
  - → Explains the discordance among monozygotic twins

- **Mosaicism**
  - → Explains different phenotypes in singletons and the discordance among monozygotic twins
  - → Explains same blood genetics but different tissue genetic results

- **"Diffuse mosaicism theory" (Cohen et al) : the timing of embryologic twinning is relative to the timing of the epigenetic aberration**
  - → Explains the twinning, the degree of BWS affectedness, and the degree of mosaicism

- **X chromosome inactivation**
  - → Explains higher incidence observed in monozygotic discordant female twins

- **The methylation defect and twinning are so closely correlated that all BWS patients result in twins but sometimes one fetus is resorbed early in pregnancy**
  - → Explains BWS in singletons

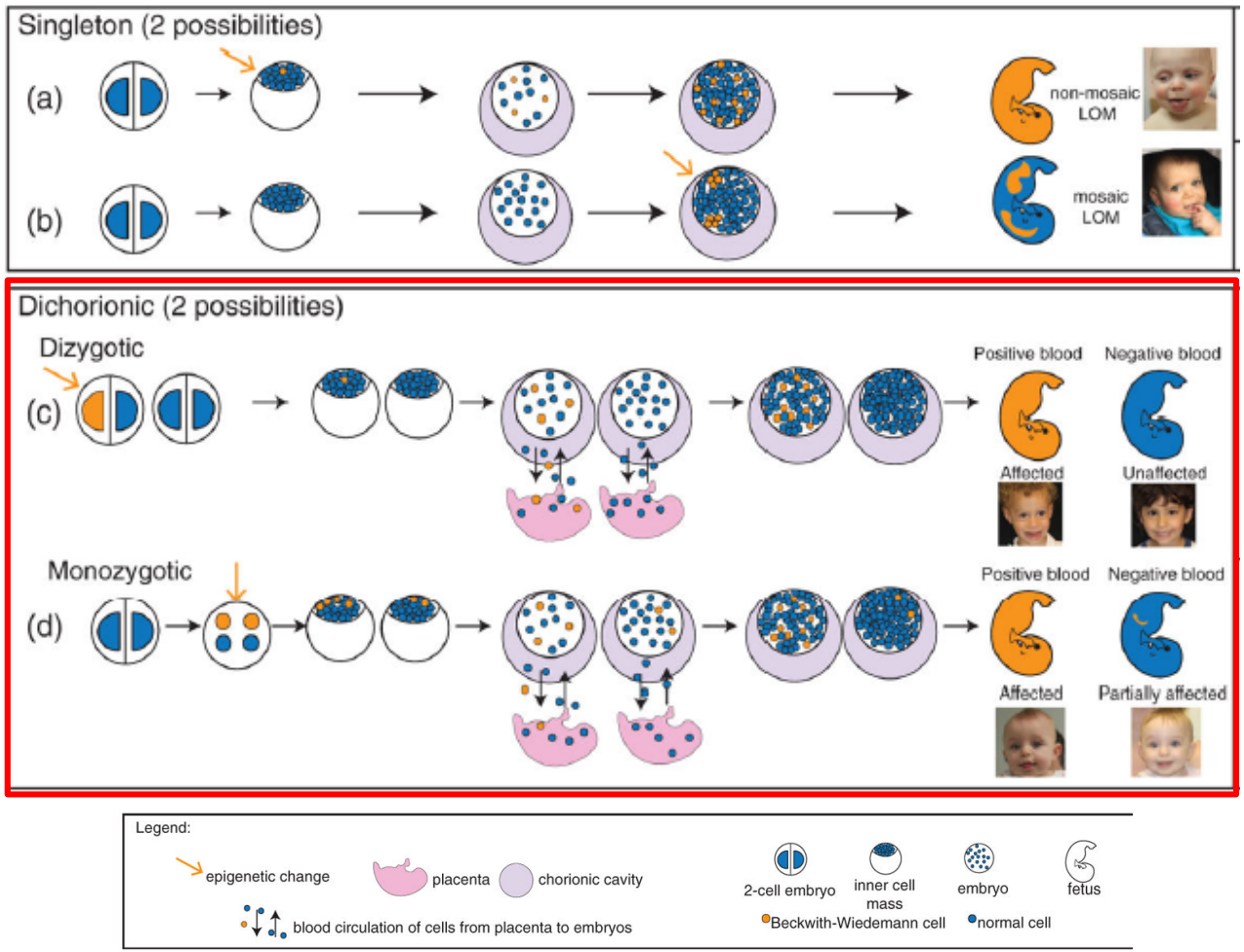
- **Presence of loss of methylation in blood cells can results from placental anastomosis leading to shared blood precursors carrying the epigenetic defects**
  - → Explains same blood genetics results but different tissue genetics results

*Papulino et Al. - Frontiers in genetics (2020).* Preclinical and Clinical Epigenetic-Based Reconsideration of Beckwith-Wiedemann Syndrome
*Cohen et Al. - American journal of medical genetics (2019).* Diagnosis and management of the phenotypic spectrum of twins with Beckwith-Wiedemann syndrome.

# Diffuse mosaicism theory

**<u>In dichorionic gestations</u>, the zygosity determines the timing of the event :**

**Earlier in the dizygotic dichorionic than in the monozygotic dichorionic**




*Cohen et Al. - American journal of medical genetics (2019).* Diagnosis and management of the phenotypic spectrum of twins with Beckwith-Wiedemann syndrome.

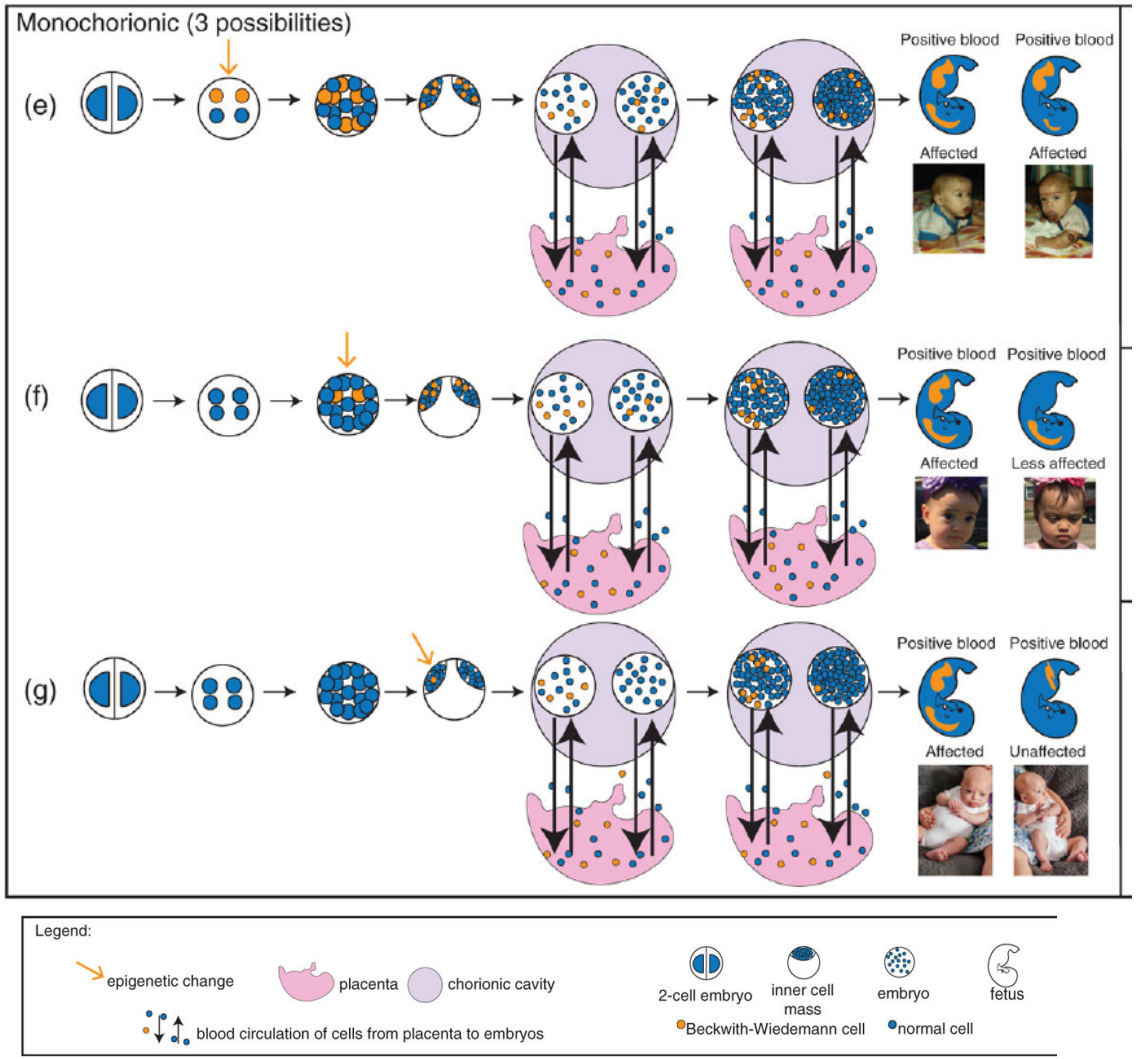
# Diffuse mosaicism theory

**<u>In monochorionic gestations,</u> when the twinning event occurs immediately following the epigenetic event, there is less time for affected cell division and dispersion, leading to two discordant embryos :**

**(e) : a delay between the epigenetic event and twinning allows time for affected cell propagation, leading to 2 concordant embryos**

**(f;g) : when the twinning event occurs immediately following the epigenetic event, there is less time for affected cell division and dispersion, leading to two discordant embryos**

**→ Asymmetric distribution of affected cells among the multiple fetuses in a monozygotic monochorionic pregnancy → spectrum of variably affected phenotypes**




*Cohen et Al. - American journal of medical genetics (2019).* Diagnosis and management of the phenotypic spectrum of twins with Beckwith-Wiedemann syndrome.

# And...

# That is why they were twins !

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# Evolution of our twins...

**Twin 1 : 2,5 yo**

- *Discharge from NICU at day 105 (39+3 weeks)*
- *Disparition of scar eventration, stability of umbilical hernia*
- *Follow up by pediatrician specialized in hematology and oncology :*
  - *No nephrocalcinosis*
  - *No abnormal gain of weight*
  - *No tumor development (screening by abdominal ultrasound)*
  - *Negative aFP screening*

**Twin 2**

- *Never discharged from the NICU due to severe BPD and dependence on respiratory support as well as complicated digestive history (multiples translocations, occlusions/subocclusions, eventration post-operative, infectious complications, enteral feeding failure)*
- *Resuscitation project adaptated*
- *Died at one year old of respiratory failure*

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# TAKE HOME MESSAGES

The disease penetrance is epigenome-regulated

Methylation defect and twinning process are correlated

Hypomethylation can be present in blood cells without pathological phenotype

**If you have a suspicion of BWS in one twin :**

**Ask yourself about the zygosity and chorionicity**

**Clinical Evaluation of both twins (BWS score)**

**Genetic testing on a blood sample AND another sample (buccal, skin fibroblasts, saliva,...) for both twins**

**Follow up often necessary** (according to algorithm) !

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# THANK YOU FOR ATTENTION !

*What's yours is mine, and what's mine is...sometimes yours.*

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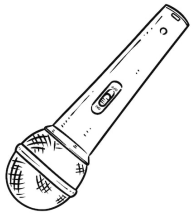

# Questions ?

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# Predisposition in tumor development

Risk depends of molecular defect

Wilms Tumor = most frequent (hepatoblastoma, adrenal carcinoma, neuroblastic tumor, rhabdomyosarcoma)

High risk before first 4 years of life

For high risk : abdominal US /3-4 months during 8-10 yo et aFP /3 month during 30 months

**TABLE 1** | Association of BWS molecular defects in subgroups and tumor risk frequency.

| Molecular defect | Alteration | Frequency of molecular defects | Tumor risk compared with other molecular subgroups |
|---|---|---|---|
| H19/IGF2:IG-DMR HYPERmethylation | Hypermethylation | 5–10% | High risk of Wilms tumor |
| UPD(11)pat | Paternal UPD | 20% | High risk of Wilms tumor and hepatoblastoma |
| KCNQ1OT1:TSS-DMR HYPOmethylation | Hypomethylation | 50% | Tumor incidence is lower than the other molecular subgroups and is very variable |
| CDKN1C mutations | Loss of function mutations | 5–10% (Sporadic cases 5%; Familial cases 40%) | Low risk of Wilms tumor |

*Adapted from Cooper et al. (2005), Eggermann et al. (2014), Maas et al. (2016), Mussa et al. (2016a), and Brioude et al. (2018).*

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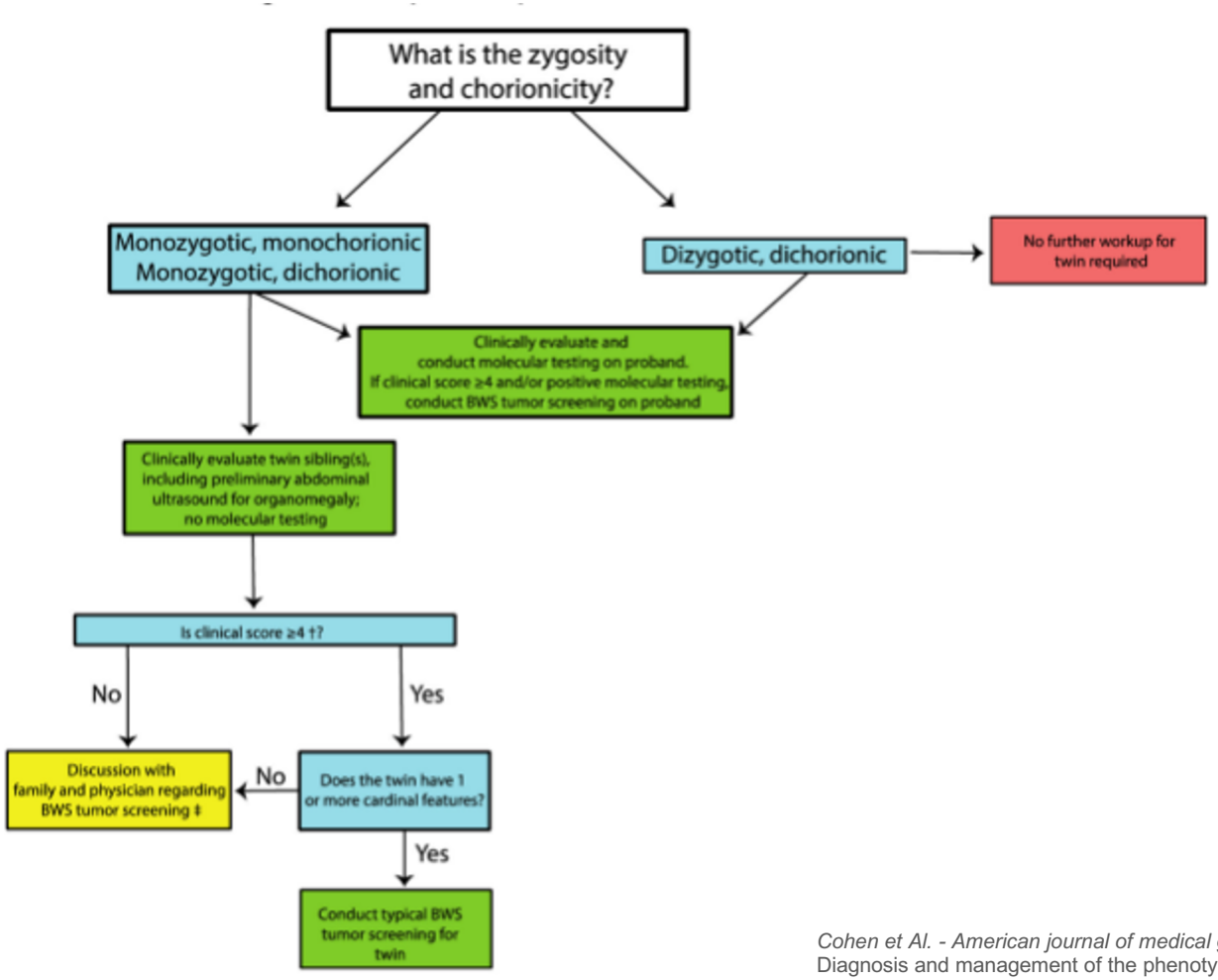
*Papulino et Al. - Frontiers in genetics (2020).* Preclinical and Clinical Epigenetic-Based Reconsideration of Beckwith-Wiedemann Syndrome

# Algorithm for follow up

Screening: abdominal ultrasound and aFP blood testing




*Cohen et Al. - American journal of medical genetics (2019).*
Diagnosis and management of the phenotypic spectrum of twins with Beckwith-Wiedemann syndrome.

**FIGURE 4.**
Proposed algorithm for clinical management of multiple gestations in which at least one child is affected with Beckwith-Wiedemann syndrome. Legend: † Clinical score excluding shared pregnancy factors (i.e., placental mesenchymal dysplasia, placentomegaly, polyhydramnios)‡ No data currently to support or refute the necessity of tumor screening in this instance

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