Silver Russell and Beckwith-Wiedemann syndromes: Mosaic distribution of epigenetic anomalies

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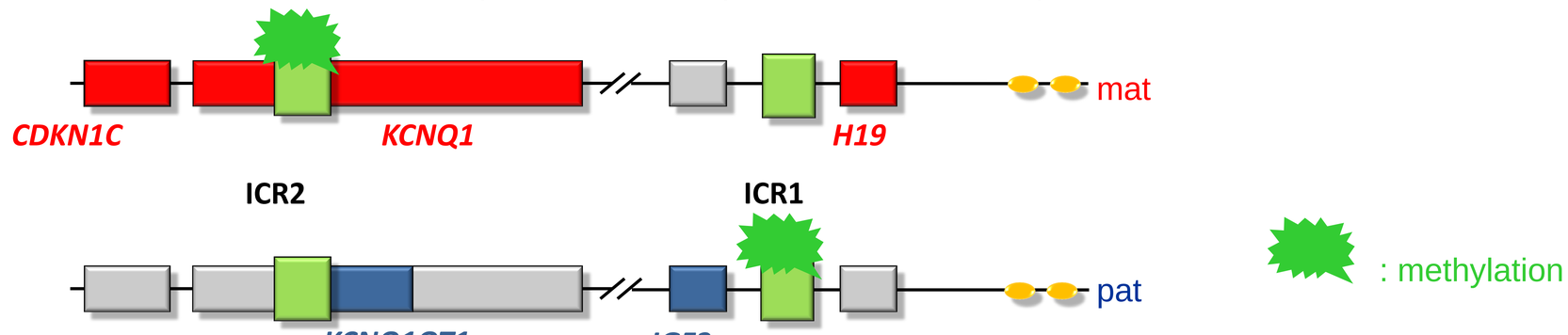
Background

Genomic imprinting is an epigenetic mechanism referring to the monoallelic silencing of genes according to their parental origin. Human chromosome 11p15.5 encompasses **two imprinted domains (ICR1 and ICR2**) playing an important role in controlling fetal and postnatal growth. Genetic (uniparental disomy or gain/loss of function mutations) or epigenetic alterations at the 11p15.5 imprinted region (loss or gain of DNA methylation) are associated with two clinical disorders with opposite phenotypes: **Silver-Russell syndrome** (SRS, growth restriction, pubertal and metabolic disturbances) and **Beckwith-Wiedemann syndrome** (BWS, overgrowth with enhanced tumor risk during childhood). These epigenetic anomalies are thought to occur in a mosaic manner, postzygotically. Therefore, recent consensus about SRS and BWS highlighted the usefulness of testing alternative tissues in case of a normal molecular test in leucocytes. However, only few data have been reported in Human.



Methods

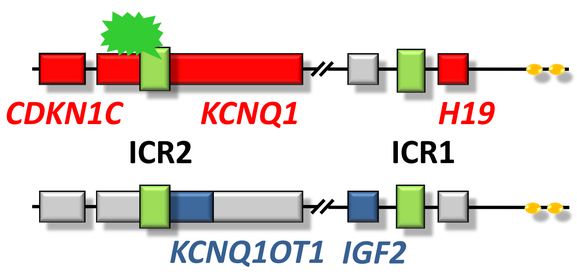
Allele-Specific Methylated Multiplex Real-Time Quantitative PCR was performed in **fibroblasts** for patients with a clinical diagnosis of SRS (score ≥4/6 in Netchine-Harbison clinical scoring system) or meeting the clinical criteria for BW spectrum (because of the presence of lateralized overgrowth) in which 11p15.5 molecular testing was normal in blood samples.

Results

Ten patients (three SRS and seven BWS) have been detected with **normal methylation in leucocytes and abnormal methylation in fibroblasts**.

SRS patients

The three SRS patients scored the six criteria of the Netchine-Harbison clinical scoring system. They all had an 11p15 ICR1 lost of methylation (LOM) in skin fibroblasts. One patient had a multi-locus imprinting disturbance (MLID) : methylation analysis showed lost of methylation at regions other than 11p15 ICR1.

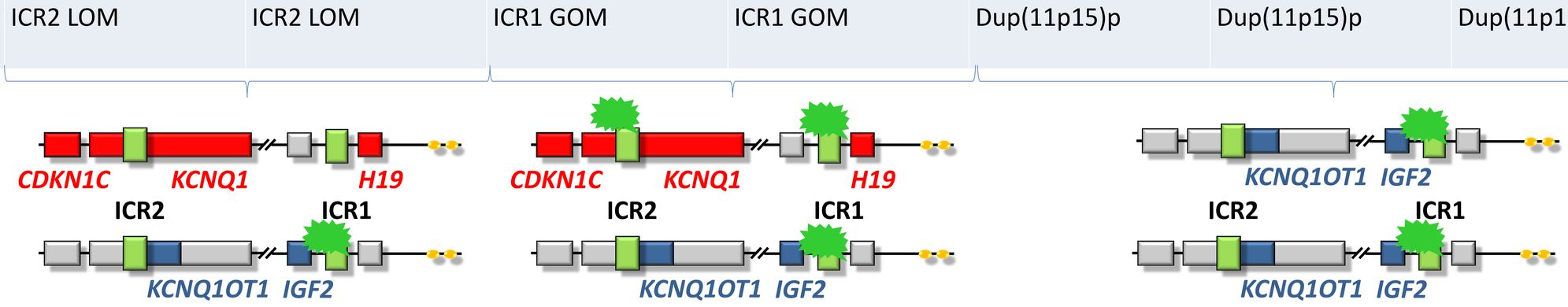


	Patient 1	Patient 2	Patient 3
Small for gestational age	+	+	+
Postnatal growth failure	+	+	+
Relative macrocephaly at birth	+	+	+
Protruding forehead	+	+	+
Body asymmetry	+	+	+
Feeding difficulties and/or low BMI	+	+	+
Molecular defect in skin fibroblasts	ICR1 LOM	ICR1 LOM	ICR1 LOM MLID

BWS patients

All seven BWS patients had lateralized overgrowth (LO). **Embryonal tumors occured in two BWS patients** : one bilateral Wilms tumor and one hepatoblastoma. Two BWS patients had an 11p15 ICR2 lost of methylation (LOM), two patients an 11p15 ICR1 gain of methylation (GOM) and two patients an 11p15 uniparental paternal disomy in skin fibroblasts.

	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Cardinal features	LO	LO	LO, macroglossia	LO	LO	LO	LO
Suggestive features	Facial naevus simplex	Facial naevus simplex	Facial naevus simplex, ear pits	Facial naevus simplex, umbilical hernia	Hepatoblastoma	Facial naevus simplex, hepatomegaly	Wilms tumor
Clinical score	3	3	6	4	3	4	3
Molecular defect in skin fibroblasts	ICR2 LOM	ICR2 LOM	ICR1 GOM	ICR1 GOM	Dup(11p15)p	Dup(11p15)p	Dup(11p15)p



Conclusion

11p15 methylation patterns may vary between different tissues. This can explain some cases of a negative molecular diagnosis when tested in blood samples for SRS and BWS. This is indeed in favor of a tissue **mosaic distribution** of these epigenetic anomalies and their postzygotic onset, and reinforces the usefulness of testing alternative tissues in case of clinical suspicion of BWS/SRS.

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57ESPE 180--P1

Growth and syndromes (to include Turner syndrome)

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Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018

PosterSessionOnline.com