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MUTATIONS OF THE SUBCORTICAL MATERNAL COMPLEX AND IMPRINTING DISORDERS: HOW THE GENOTYPE INTERACTS WITH THE EPIGENOTYPE

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The parent-of-origin-specific expression of the imprinted genes is directed by differential DNA methylation of Imprinting Control Regions (ICRs). Maternal-effect variants of members of the subcortical maternal complex (SCMC) are associated with Multi Locus Imprinting Disturbances (MLID) in the Beckwith-Wiedemann syndrome (BWS) and Silver-Russell syndrome (SRS), and with complete loss of maternal imprints in Biparental Hydatiform Mole (BiHM), indicating a role in both oocyte imprinting establishment and post-zygotic imprinting maintenance. However, the mechanism linking these cytoplasmic proteins to methylation control is unknown. Here we describe several cases with maternal-effect variants of different SCMC genes, in which the analysis of DNA methylation provides new information on the role of these proteins. First, in a case of recurrent BiHM carrying a loss of function variant of KHDC3L in homozygosity, genome-wide DNA methylation analysis demonstrated specific loss of ICR methylation in the molar conceptus, but extensive hypomethylation in oocytes, indicating a role of KHDC3L in de novo DNA methylation in the maternal germline. Second, a woman, who is compound heterozygous for loss-of-function variants of NLRP5, had a child with BWS, multiple miscarriages and a further healthy child. Mosaic MLID including KCNQ1OT1 hypomethylation was demonstrated in both affected and unaffected siblings, suggesting a sort of compensation occurring between demethylated imprinted loci in the healthy child. Third, we demonstrated loss-of function maternal variants of PADI6 in three cases of BWS with MLID, including a family with two affected siblings. These results indicate that maternal loss-of-function variants of SCMC genes may impair DNA methylation with different mechanisms and be associated with extremely different phenotypes in the offspring but high familial recurrence risk. The analysis of larger cohorts of patients is needed to formulate more accurate genotype-epigenotype-phenotype correlations in the case of maternal SCMC variants.

Ruolo delle mutazioni materne nei disordini dell'imprinting: come il genotipo della madre influenza l'epigenotipo dei figli

La sindrome di Beckwith-Wiedemann (BWS) e la Sindrome di Silver-Russell (SRS) sono causate da difetti di geni definiti "imprinted", che hanno la caratteristica di funzionare su una soltanto delle due copie che sono normalmente ereditate dai genitori. Questa particolarità è dovuta alla presenza di segnali di metilazione del DNA diversi sul cromosoma di origine materna e su quello di origine paterna. La BWS e la SRS insorgono quando questi segnali di metilazione sono alterati e questo avviene in genere nei gameti o nell'embrione di pochi giorni di vita. Alcuni pazienti hanno difetti di metilazione su un solo gene, altri li hanno in molti geni presenti su cromosomi diversi. E' stato recentemente dimostrato che questi difetti di metilazioni multipli sono causati da mutazioni materne delle proteine del complesso sub-corticale (SCMC). In questo studio dimostriamo come mutazioni materne delle proteine SCMC possono alterare la metilazione de novo negli oociti o il mantenimento della metilazione nell'embrione precoce e causare fenotipi estremamente diversi nella progenie, che vanno dalla Mola Idatiforme Ricorrente ai disordini dell'imprinting o in alcuni casi essere compatibili

con uno stato apparentemente normale.

1. Monk D, Mackay DJG, Eggermann T, Maher ER and Riccio A*. Genomic imprinting disorders: lessons on how genome, epigenome and environment interact. Nat Rev Genet. 2019 Apr;20(4):235-248. doi: 10.1038/s41576-018-0092-0.
2. Federica Maria Valente, Angela Sparago, Andrea Freschi, Katherine Hill-Harfe, Saskia M. Maas, Suzanna Frints, Marielle Alders, Laura Pignata, Monica Franzese, Claudia Angelini, Diana Carli, Alessandro Mussa, Andrea Gazzin, Fulvio Gabbarini, Basilia Acurzio, Giovanni Battista Ferrero, Jet Bliek, Charles A. Williams, Andrea Riccio*, Flavia Cerrato* Transcription alterations of KCNQ1 associated with imprinted methylation defects in the Beckwith-Wiedemann locus. Genet Med. 2019 Jan 12. doi: 10.1038/s41436-018-0416-7.
3. Sparago A, Cerrato F, Riccio A* (2018) Is ZFP57 binding to H19/IGF2:IG-DMR affected in Silver-Russell syndrome? Clinical Epigenetics 2018, 10:23. Doi: 0.1186/s13148-018-0454-7
4. Freschi A, Hur SK, Valente FM, Ideraabdullah FY, Sparago A, Gentile MT, Oneglia A, Di Nucci D, Colucci-D'Amato L, Thorvaldsen JL, Bartolomei MS*, Riccio A*, Cerrato F. (2018) Tissue-specific and mosaic imprinting defects underlie opposite congenital growth disorders in mice PLoS Genet. 2018 Feb 22;14(2):e1007243. doi: 10.1371/journal.pgen.1007243.
5. Brioude F, Kalish JM, Mussa A, Foster AC, Bliek J, Ferrero GB, Boonen SE, Cole T, Baker R, Bertoletti M, Cocchi G, Coze C, De Pellegrin M, Hussain K, Ibrahim A, Kilby MD, Krajewska-Walasek M, Kratz CP, Ladusans EJ, Lapunzina P, Le Bouc Y, Maas SM, Macdonald F, Õunap K, Peruzzi L, Rossignol S, Russo S, Shipster C, Skórka A, Tatton-Brown K, Tenorio J, Tortora C, Grønskov K, Netchine I, Hennekam RC, Prawitt D, Tümer Z, Eggermann T, Mackay DJG, Riccio A, Maher ER. (2018) Clinical and Molecular Diagnosis, Screening and Management of Beckwith-Wiedemann syndrome: An International Consensus Statement. Nat Rev Endocrinol. 2018 Apr;14(4):229-249. doi: 10.1038/nrendo.2017.166.
6. Mussa A, Molinatto C, Cerrato F, Palumbo O, Carella M, Carli D, Baldassarre G, Peris C, Riccio A and Ferrero GB (2017) Assisted Reproductive Technologies and Risk of Beckwith-Wiedemann Syndrome. Pediatrics. 2017 Jul;140(1). pii: e20164311. doi: 10.1542/peds.2016-4311.
7. Hur SK, Freschi A, Ideraabdullah F, Thorvaldsen JL, Luense L, Hines A, Berger SL, Cerrato F*, Riccio A*, Bartolomei MS*. (2016) Humanized H19/Igf2 locus reveals diverged imprinting mechanism between mouse and human and reflects Silver-Russell Syndrome phenotypes. Proc Natl Acad Sci U S A. 2016 Sep 27;113(39):10938-43. doi:10.1073/pnas.1603066113 *Co-corresponding authors.
8. Riso V, Cammisa M, Kukreja H, Anvar Z, Verde G, Sparago A, Acurzio B, Lad S, Lonardo E, Sankar A, Helin K, Feil R, Fico A, Angelini C, Grimaldi G, Riccio A. ZFP57 maintains the parent-of-origin-specific expression of the imprinted genes and differentially affects non-imprinted targets in mouse embryonic stem cells. Nucleic Acids Res. 2016 Sep 30;44(17):8165-78.
9. Mussa A, Molinatto C, Baldassarre G, Riberi E, Russo S, Larizza L, Riccio A, Ferrero GB. (2016) Cancer Risk in Beckwith-Wiedemann Syndrome: A Systematic Review and Meta-Analysis Outlining a Novel (Epi)Genotype Specific Histotype Targeted Screening Protocol. J Pediatr. 2016 Jun 29. pii: S0022-3476(16)30246-3. doi: 10.1016/j.jpeds.2016.05.038.
10. Boonen SE, Freschi A, Christensen R, Valente FM, Lildballe DL, Perone L, Palumbo O, Carella M, Uldbjerg N, Sparago A, Riccio A*, Cerrato F*. Two maternal duplications involving the CDKN1C gene are associated with contrasting growth phenotypes. Clin Epigenetics. 2016 Jun 16;8:69. doi: 10.1186/s13148-016-0236-z. *Co-corresponding authors.
11. Sanchez-Delgado M, Riccio A, Eggermann T, Maher ER, Lapunzina P, Mackay D, Monk D. Causes and Consequences of Multi-Locus Imprinting Disturbances in Humans. Trends Genet. 2016 Jul;32(7):444-55. doi: 10.1016/j.tig.2016.05.001.
12. Eggermann K, Bliek J, Brioude F, Algar E, Buiting K, Russo S, Tümer Z, Monk D, Moore G,

Antoniadi T, Macdonald F, Netchine I, Lombardi P, Soellner L, Begemann M, Prawitt D, Maher ER, Mannens M, Riccio A, Weksberg R, Lapunzina P, Grønskov K, Mackay DJ, Eggermann T. EMQN best practice guidelines for the molecular genetic testing and reporting of chromosome 11p15 imprinting disorders: Silver-Russell and Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2016 Oct;24(10):1377-87. doi: 10.1038/ejhg.2016.45. IF 2015: 4.580. Citazioni WoS: 0. Scopus: 2
13. Anvar Z, Cammisa M, Riso V, Baglivo I, Kukreja H, Sparago A, Girardot M, Lad S, De Feis I, Cerrato F, Angelini C, Feil R, Pedone PV, Grimaldi G, Riccio A. (2016) ZFP57 recognizes multiple and closely spaced sequence motif variants to maintain repressive epigenetic marks in mouse embryonic stem cells. Nucleic Acids Res. 2016 Feb 18;44(3):1118-32. doi: 10.1093/nar/gkv1059.
14. Mussa A, Russo S, De Crescenzo A, Freschi A, Calzari L, Maitz S, Macchiaiolo M, Molinatto C, Baldassarre G, Mariani M, Tarani L, Bedeschi MF, Milani D, Melis D, Bartuli A, Cubellis MV, Selicorni A, Cirillo Silengo M, Larizza L, Riccio A*, Ferrero GB*. (2016) (Epi)genotype–phenotype correlations in Beckwith–Wiedemann syndrome. Eur J Hum Genet. 2016 Feb;24(2):183-90. doi: 10.1038/ejhg.2015.88. *Co-corresponding authors.
15. Mussa A, Di Candia S, Russo S, Catania S, De Pellegrin M, Di Luzio L, Ferrari M, Tortora C, Meazzini MC, Brusati R, Milani D, Zampino G, Montirosso R, Riccio A, Selicorni A, Cocchi G, Ferrero GB. (2016) Recommendations of the Scientific Committee of the Italian Beckwith-Wiedemann Syndrome Association on the diagnosis, management, and follow-up of the syndrome. Eur J Med Genet. 2016 Jan;59(1):52-64. doi: 10.1016/j.ejmg.2015.11.008.
16. Eggermann T, Perez de Nanclares G, Maher ER, Temple IK, Tümer Z, Monk D, Mackay DJG, Grønskov K, Riccio A, Linglart A and Netchine I (2015) Imprinting disorders: a group of congenital disorders with overlapping patterns of molecular changes affecting imprinted loci. Clin Epigenetics. 2015 Nov 14;7:123. doi: 10.1186/s13148-015-0143-8.

Sindrome di Beckwith-Wiedemann, Sindrome di Siver-Russell

Coordinator: Andrea Riccio
Durationg (N. Years): 3
Starting year: 2016

Telethon Project (nr):

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Disease Name:

Beckwith-Wiedemann Syndrome/Siver-Russell Syndrome

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