Group members’ names:

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In-class assignment

**Assigned paper:**

Chiesa *et al*. (2012) The KCNQ1OT1 imprinting control region and non-coding RNA: new properties derived from the study of Beckwith–Wiedemann syndrome and Silver–Russell syndrome cases

**Instructions:**

1. Form a group of 3 - 5 people.
2. Take out the assigned paper (can be on your mobile device, laptop, etc).
3. Discuss the questions below and, as a group, formulate (and type up) answers ensuring that everybody’s input is taken into account.
4. Designate one group member to type the answers into the assignment. At the end of class:
   * type the names of each group member on the assignment;
   * email the assignment (as an attachment, one per group) to Pam **and cc all group members**, so that everybody has a copy;
   * keep in mind that this could be one of your top four assignments for your portfolio!

If you have any questions during the completion of the assignment, please raise your hand and/or ask for help!

**Questions:**

1. The authors report using OMIM to obtain some information for their research. Take a few minutes to look up *Kcnq1ot1* on OMIM (http://www.omim.org) and see what information you get.

Kcnq1ot1 is overlapping the Kcnq1 gene and associated with BWS and SRS.

1. Look at the pedigree in Figure 1.
2. What are a few things that can immediately be concluded about BWS (even without knowing who inherits the mutant allele from whom)?

Effects male and female equally, disease is not lethal and formation is somatic.

1. II-2 and II-4 both have BWS, and both have one child with BWS and one child without BWS. Briefly explain how this is possible.

Because the BWS in II-2 and II-4 is caused by whether the inherited diseased allele is imprinted or not, since they have another WT copy of this allele, it is possible that the offspring can inherit either of those two.

1. Both the BWS and the SRS patients have duplications of parts of the locus being studied, and so does Individual I-4, who has no syndrome. Using the information in Figure 5 and Figure 8, propose a hypothesis that explains the differences in phenotype (both macroscopic phenotype and the DNA methylation pattern phenotype) among the patients with BWS, SRS, and Individual I-4.

-BWS: Duplication causes intermediate methylation within the maternal chromosome

- SRS: Duplication and inversion of the region on the maternal chromosome causes a double dosage of the maternal genes which cancels the silencing effect of the paternal chromosome

- For patients I-1-3 the duplication is within the regulatory sequence that is not transcribed on the maternal chromosome. For patient I-4 the duplication is within the unmethylated regulatory sequence of the gene, that is actively transcribed on the paternal chromosome and repress transcription of the protein coding gene. I-4 does not have symptoms because BWS symptoms occur in patients that have the duplication in the maternal regulatory sequence (Kcnq1ot1)

1. Explain what the data in Figure 7 show, and how you interpret them in terms of the role of *Kcnq1ot1* in the regulation of the imprinted cluster being studied.

Kcnq1ot1 is paternally transcribed and the RNA product acts cis to repress Kcnq1 expression. The figures show that for the BWS patients, we also have maternally expressed Kcnq1ot1, which is not observed for the maternal control. The disease could be caused by this faulty Kcnq1ot1 expression, which also repress the maternal contribution of Kcnq1

1. **Optional/Time permitting:** Take a look at the phenotypes of the SRS and BWS patients. Do you notice any trends? Knowing that all the patients studied in this article have mutations in the same imprinted cluster, what could explain the differences in phenotypes? Knowing the effects at the molecular (DNA methylation/gene expression) of the various mutations, how could these macroscopic phenotypes be explained?