A Genetic Explanation of RSS 11p15LOM

MAGIC Convention 2008
Taken from "It's in the Genes" By IréneNetchine, MD PHD

In 2008, the MAGIC Foundation was very lucky that IréneNetchine, MD PhD, accepted our invitation to speak at our annual children's convention. Dr. Netchine was an integral part of a European cohort that had just discovered a major genetic cause of Russell Silver Syndrome. Prior to 2007, the only known genetic cause of RSS was MATUPD7, occurring in approximately 10% of clinically diagnosed children.

Genetics are very complicated and explaining them to average every day parents is no easy task. Below are some notes from this presentation to help you understand the genetics behind RSS 11p15 LOM.

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Imagine genetics like this:

- Cell Nucleus = library;
- Chromosomes = bookshelves;
- Genes = books

All of the cells have the same books in their libraries but they use only some of them, and they use different books in different organs – this choice is governed by epigenetic factors (above the genes).

- The epigenetic factors control the "on" or "off" status of the books

Imprinted genes: play an important role in the regulation of fetal growth and development in mammals (only .1 – 1% of all genes are imprinted)

- dad's "books" = increase growth
- mom's "books" = decrease growth

IGF2 on chromosome 11 – produced only from dad's #11 during fetal development

- methylation is the "packaging" of the gene that allows it to be switched on or off
- so when a child is diagnosed with 11p15 methylation, "mom" shut off "dad's" book allowing child to be smaller; this occurs AFTER fertilization-This is a LOSS OF METHELYATION
- methylation doesn't occur in every cell, which is why there is body/limb asymmetry

HOW DO WE DETERMINE METHYLATION?

0% = Complete loss of methylation = (RSS undergrowth)

50% = normal meth

100% = Beckwith Weidemann Syndrome (overgrowth)

Let's say the lab studies a sample of 4 cells:

- if all 4 are normal = 50% methylation
- if ¼ is methylated = 37.5% methylation
- if 2/4 are methylated = 25% methylation
- if ¾ are methylated = 12.5% methylation
- if 4/4 are methylated = 0% methylation

Dr. Netchine's lab studies a sample of cells (more than 4) and then repeats this test an average of 3 times – so they get three scores. Keep in mind that for any given child, there are thousands and thousands of cells, so even a 37.5% methylation will result in the RSS phenotype.

This is one reason there is such a range of affectedness and severity for RSS. The greater the LOM (loss of methylation) the more significantly affected the child.

Eggermann et al (2006) found that of a group of clinically diagnosed RSS subjects 30% were found to be 11p15

Netchine et al (2007) had a more stringent clinical diagnosis coding, so of the group of RSS subjects that they clinically felt looked RSS, 63% turned out to be 11p15

NETCHINE's 2007 STUDY RESULTS:

- Birth weight, birth length and BMI were significantly lower for 11p15 RSS children than for RSS children who were matUPD7 or unknown cause RSS
- And the degree of methylation was correlated to the degree of birth weight and birth length but NOT head circumference; so the greater the degree of methylation (meaning closer to 0%), the more severe the birth weight and birth length retardation

- 24% of Beckwith Weidemann Syndrome children have additional loss of methylation at two or more loci; and 9.5% of the 11p15 kids also had this additional loss of methylation at two or more loci; BUT if you have this extra demethylation, your phenotype is NOT different than if you don't (meaning 11p15+2+ loci == NOT different than 11p15 only)