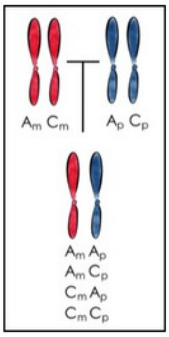
Science Highlight

Characterizing Parent of Origin Effects in the Hutterite Population

by Sahar Mozaffari

Each of us has two copies of each gene in our genome; we inherit one from our father and one from our mother. In most cases, each of our genes or genetic regions from each parent are expressed and contribute equally to the genetic component that makes us who we are. However, there are some genes that have an imbalance of parental contribution because the gene from one parent is silenced and only the gene from the other parent is expressed.

Genes that are silenced in this manner are referred to as imprinted. The genes or regions that are imprinted depend on the parent that passed them down, such that paternally imprinted genes are different from maternally imprinted genes. Imprinted regions generally have epigenetic marks that control whether they are silenced or expressed. While few imprinted genes have been well characterized, there are still many imprinted regions in humans yet to be discovered, and we have yet to learn how these regions are marked in different cells.



Many studies of imprinting have focused on large families in which we can test for parent of origin effects on different diseases or phenotypes, or on gene expression, to uncover new imprinted loci. Parent of origin effects flag potentially imprinted regions in which the genetic information behaves differently depending on the parent it is inherited from.

For example, imprinted diseases, such as Prader-Willi and Angelman syndrome, depend on from parent the mutated gene is inherited. In normal individuals, due to imprinting, only the paternally inherited copy of some genes on chromosome 15 are expressed, whereas only the maternally inherited genes are silenced. If the paternally expressed genes are mutated, the individual will have Prader Willi syndrome because the paternal (normally expressed) copy is silenced. However, if the maternally expressed gene is mutated, a different disease called Angelman syndrome will result since the maternal copy (normally silenced) is now also expressed.

Figure 1. Each individual inherits one maternal chromosome and one paternal chromosome (m refers to maternal, and p to paternal). If the parents have both alleles at the SNP, or are heterozygous, the child can have one of four possible genotypes if we can identify parent of origin.

We are working toward uncovering genetic variation that contributes to parent of origin effects on gene expression and common disease-associated traits.

Our group has been studying the genetics of complex traits in the Hutterites, a founder population of European descent. The approximately 1500 Hutterites in our studies are related to each other in a 13-generation pedigree including more than 3,671 individuals. For each individual, for as many as 5 million genetic variants, called SNPs, we can determine which allele was inherited from the father and which from the mother. We can use this information to test for association with common quantitative traits that are associated with cardiovascular disease (e.g. BMI, LDL-cholesterol, HDL-cholesterol, Triglycerides) and asthma (e.g. IgE levels, blood eosinophil count, fev1 (forced expiratory volume in one second), feNO (fraction exhaled nitric oxide)).

We test for association of the maternal alleles and paternal alleles separately for each trait. Some variants impact triglyceride levels, age of menarche, LVMI (left ventricular mass index), fev1, and cimt (carotid intima media thickness) only when inherited from the mother. In contrast, other variants affect blood eosinophil count, fev1, lymphocytes, systolic blood pressure, and total cholesterol only when inherited from the father.

We are working on characterizing these further with parent of origin specific gene expression understand by what means and by how much these novel effects can contribute to our phenotypes.

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Figure 2. A Hutterite family in South Dakota that participate in our studies.

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