Increased power for detection of parent-of-origin effects via the use of haplotype estimation

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Introduction
• In genetic studies, parent-of-origin (imprinting) effects can be considered as the phenomenon whereby an individual's phenotype depends on the parental origin of the alleles that make up the individual's genotype.
• The power to detect parent-of-origin effects would be increased if the true parental origin of the alleles could be determined with a higher degree of certainty.
• We present here an extension1 to the method for detection of parent-of-origin effects implemented in the PREMIM/EMIM2,3 software, which uses external estimates of haplotypes for the mother, father and child provided by the program SHAPEIT2, thereby using surrounding SNP information to help better estimate the parental origin of alleles at a given test SNP.

Simulated Data
• 1000 replicates of pedigree data consisting of 1500 case/parent trios (or 1500 case/mother duos) and 200 SNPs were simulated.
• The type I error of PREMIM/EMIM to detect imprinting effects remains at the expected level when using trios phased with SHAPEIT2.
• However, for duos there may be an inflation in the type I error if SHAPEIT2’s initial parent-of-origin estimates are used.
• It is possible to adjust the parent-of-origin estimates to lower this inflation by recognizing that most SNPs will not be associated with an imprinting effect.

Imprinting
• From father
• From mother
• Unknown parent-of-origin

Specific Language Impairment
• Specific language impairment (SLI) is a neurodevelopmental disorder that affects linguistic abilities when development is otherwise normal.
• In a recent genome-wide association study using PREMIM/EMIM of 297 affected children in 278 pedigrees, Nudel et al.4 found a region of interest on chromosome 5 with SNP rs10447141 giving a minimum p-value 1.29 × 10^{-7} (OR 0.326) of association with maternal imprinting.
• Analysis using the latest version of PREMIM/EMIM with SHAPEIT2 gave a less significant p-value 6.16 × 10^{-6} (OR 0.494) providing weaker evidence of association with maternal imprinting.

Summary
1. Haplotype estimation increases the power to detect imprinting effects.
2. This method is available in the PREMIM/EMIM software: http://www.staff.ncl.ac.uk/richard.howey/emim/

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References

pie chart
• The p-value 10^{-6} was used to calculate the powers in the line plot.

data table
• The table below shows the (estimated) cell counts for the number of risk alleles at SNP rs10447141 for the ambiguous scenario where all individuals are heterozygous, thus providing extra information on the parent-of-origin.

Maternal imprinting, EMIM

Maternal imprinting, EMIM with SHAPEIT2

Maternal imprinting, EMIM with SHAPEIT2

Maternal imprinting, EMIM

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