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Frequent pattern mining of genotypes underlying digenic traits

Jurg Ott
Rockefeller University, USA

Some genetic diseases ("digenic traits") are due to the interaction between two DNA variants. For example, certain forms of Retinitis Pigmentosa occur in the presence of two mutant variants, one each in the ROM1 and RDS genes, while occurrence of only one such variant results in a normal phenotype. Detecting digenic traits by standard genetic methods is difficult but FPM methods offer a solution. Let Y=2 refer to cases (with disease) and Y=1 to control individuals, with X denoting a specific genotype pattern. We need **association rules**, "$X \rightarrow Y$", with high **confidence**, P(Y=2|X), higher than the proportion P(Y=2) of cases. We use *fpgrowth* as the basic FPM engine and built a permutation based framework around it to find significant high-frequency digenic genotype patterns. Application to a published dataset on opioid dependency furnished results that could not have been found with classical genetic methodology. There were 143 cases and 153 healthy controls, each genotyped for 82 variants in eight genes of the opioid system. The aim was to find out whether any of these variants were disease-associated. Single-variant analysis did not lead to significant results. Application of our FPM implementation resulted in one significant ($p < 0.01$) genotype pattern with both genotypes in the pattern being heterozygous and originating from two variants on different chromosomes. This pattern occurred in 14 cases and in none of the controls. Thus, the pattern seems quite specific to this form of substance abuse and is also rather predictive of disease.

Biography

Jürg Ott has completed his PhD from the University of Zürich with postdoctoral studies in Medical Genetics at the University of Washington in Seattle, USA. He is the director of the Laboratory of Statistical Genetics at Rockefeller University, New York. He has published more than 400 papers in reputed journals and is the recipient of various prestigious awards, including the Allan Award from the American Society of Human Genetics.