Title : **Disease mapping and linkage disequilibrium based approach**

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Abstract :

While linkage studies have been very efficient for the mapping of Mendelien disease (or monogenic disease), genetic association studies are considered as more promising in the context of complex inheritance. There is complex inheritance when a combination of genes and/or environmental condition is necessary to create a phenotype.

Linkage disequilibrium (LD), or allelic association, is defined as the preferential association (non-random) of several alleles from different loci on the same chromosome. There is a strong relationship between the physical distance between markers and their level of association. Methods based on linkage disequilibrium are at present considered as highly performant for the mapping of diseases showing a complex inheritance. When a new mutation appears on a chromosome, there is initially full linkage disequilibrium between the mutation and the alleles present on the other loci of this chromosome. With time, recombination, mutation, selection and drift will tend to reduce the size of this chromosomal region, which is in linkage disequilibrium. The older the mutation is, the shortest the region showing LD around the mutation of interest will be. If the mutation of interest is related to the disease, it is possible to localise it by studying the LD profile of the region with the markers studied. We will present 2 approaches actually used in LD based mapping studies: 1) Candidate gene based approach; 2) Whole genome association study. We will present a multilocus-based association method based on the Malecot model of isolation by distance. We will discuss issues of power, choice of markers (SNPtag), correction for multitest and problem of replication.
We will take the example of the AMD study recently published in Science, were 3 groups have found the same causal mutation using 3 different study designs.