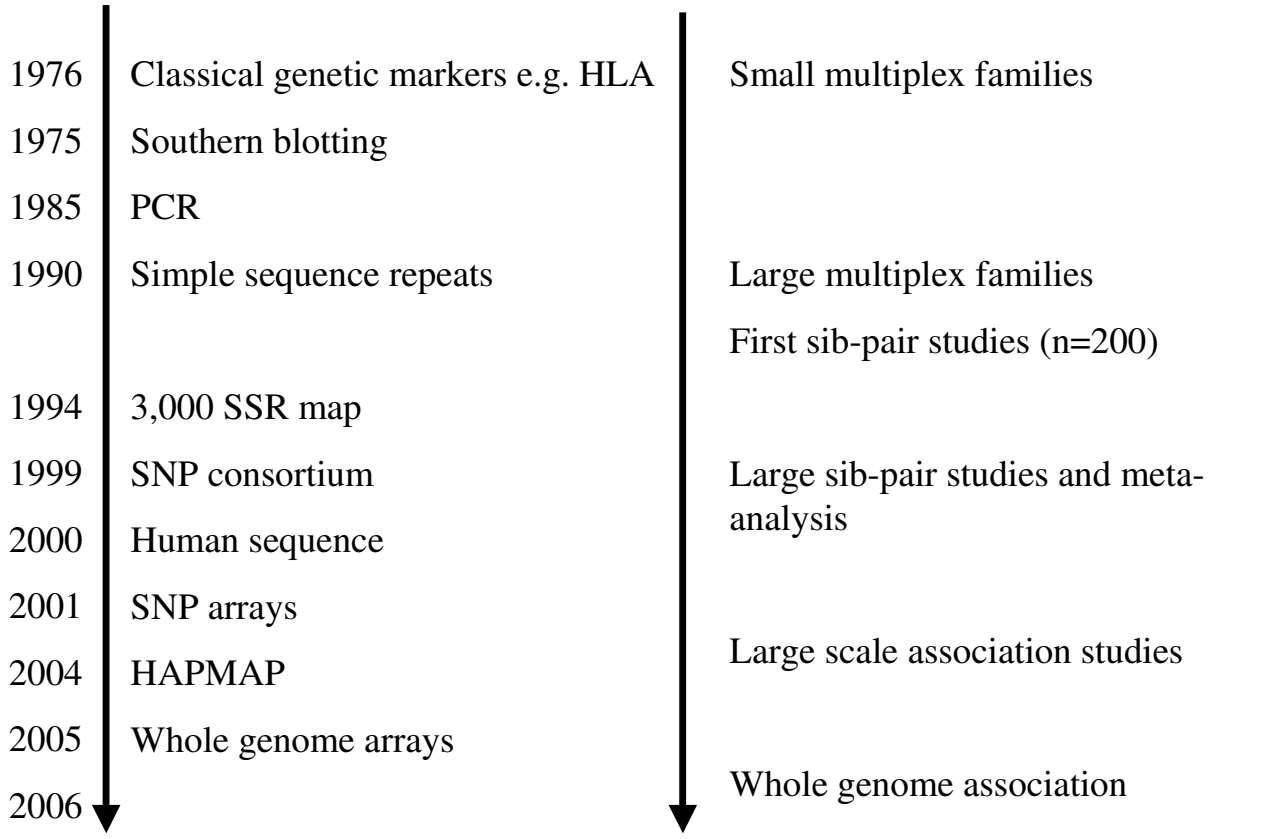

Figure 1
Historical perspective on gene mapping in common disorders. Initial studies, before DNA markers became available, relied on classical genetic markers such as blood or HLA types and therefore provided very limited information on a few regions of the human genome. The early genetic markers that used restriction enzymes to cut DNA at specific DNA sequences could identify sites that differed by one or more DNA bases. These restriction fragment length polymorphisms (RFLPs) were analyzed using a technique called Southern blotting that could identify one or a few markers at a time and was a relatively slow process. Linkage analysis came of age with the identification of another class of genetic variants, the simple sequence repeats (SSRs) that commonly consist of between two to four base pairs that are repeated in variable number tandem sequences (e.g. (AC)n) and are found approximately one every 50 thousand base pairs (Kb) across the genome. Around 3,000 such SSRs were identified for the first major human genome map in the mid 1990's, whereas only 400 of such markers are required for a first pass linkage scan. More recently the SNP consortium was established to identify single nucleotide polymorphisms (SNPs) that occur far more frequently, approximately one every 500 base pairs and are therefore useful for high-density association mapping. These are key to current studies since association, unlike linkage, can only be detected by markers that are correlated with functional variants in the population and are informative over very small distances. The HapMap project was set up to genotype SNPs across the genome in representative populations and establish the structure of linkage disequilibrium. High-density arrays that can be used to genotype between 350,000 – 500,000 SNPs in a single assay are now available and provide between 65–75% coverage for all SNPs with a minor allele frequency greater than 0.05. Further development of 1,000,000 plus arrays will be able to detect all common variation across the genome.

As an example of a haplotype association in ADHD, we can consider recent findings from the analysis of the dopamine transporter gene (DAT1) and ADHD [7]. Several previous studies have documented the association of ADHD with a repeat length polymorphism in the 3'-untranslated region (3'-UTR) of DAT1, although averaged