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Review

# Genetic data: The new challenge of personalized medicine, insights for rheumatoid arthritis patients

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ABSTRACT

Rapid advances in genotyping technology, analytical methods, and the establishment of large cohorts for population genetic studies have resulted in a large new body of information about the genetic basis of human rheumatoid arthritis (RA). Improved understanding of the root pathogenesis of the disease holds the promise of improved diagnostic and prognostic tools based upon this information. In this review, we summarize the nature of new genetic findings in human RA, including susceptibility loci and gene–gene and gene–environment interactions, as well as genetic loci associated with sub-groups of patients and those associated with response to therapy. Possible uses of these data are discussed, such as prediction of disease risk as well as personalized therapy and prediction of therapeutic response and risk of adverse events. While these applications are largely not refined to the point of clinical utility in RA, it seems likely that multi-parameter datasets including genetic, clinical, and biomarker data will be employed in the future care of RA patients.



**Contents**



*Abbreviations:* RA, Rheumatoid Arthritis; PM, Personalized Medicine; GWAS, Genome Wide Association Study; NGS, Next generation Sequencing; SNP, Single Nucleotide Polymorphism; eQTLs, Expression quantitative trait loci; ACPA, anti–citrullinated peptide antibodies.

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## 1. Introduction

The previous era of 'blockbuster' drugs is now giving way to an era of stratified medicine in most diseases, with the ultimate goal of delivering the right drug to the right patient at the right time, a task that represents a key objective of the modern translational medicine. To date, only few studies have demonstrated the impact of stratified medicine interventions at population level, probably because of the high costs of studies using proper stratification and tailored interventions directly compared to universal interventions.

Taking rheumatoid arthritis (RA) as an archetype disease, it can be treated with a broad variety of immunotherapeutic agents, and even though outcomes have improved dramatically recently with targeted therapies, few patients are cured and we are still from having sufficient knowledge to allow preventive measures in "at risk" individuals. In RA, further complexity is brought with duration of disease and history of responses to current therapies. Heterogeneity between patients is in fact one of the major features of RA, also reflected in its wide range of responses/non-response to therapeutic agents.

The past decade has seen astonishing progress in our ability to decipher genetic and molecular reasons behind diseases as complex as cancers, obesity, neurodegenerative disorders and autoimmune diseases. Equally exciting, the advances in stem cell manipulation, cellular reprogramming, tissue engineering, and genome editing have offered possible therapeutic solutions to conditions previously considered untreatable. Identifying genetic variants of clinical significance remains however very complex and far from perfect technically but such progress has been made over the past few years that we are now approaching clinical utility.

There are different approaches using detailed knowledge of human genetic variation to tailor treatments to patients. One main approach is to tailor drug treatments based upon genetic variations that may affect the metabolism of the drug itself (pharmacogenomics). Another aims to choose a drug according to the best chances of response to that particular agent (Personalized Medicine). However, it should be pointed that this "personalized medicine" approach does not yet allow treatment to be tailored to the needs of each individual but rather allows patients to be stratified into groups with a better chance to respond to a particular drug before treatment is started.

In this review, we will use the example of RA to discuss many factors shaping the future use of genetic information in personalized medicine, ranging from the discovery of RA-associated variants to the resulting insights into disease biology and the potential for clinical applications of such findings.

## 2. The rapidly changing technologies enable new approaches

The history of modern human genetics research is largely the history of the rapidly changing technologies. Although the vast size of the human genome appeared at first impossible to work with, the development of new analytical approaches has allowed us to reach the point where individual genome sequencing is a feasible task for many laboratories (Kere, 2010). The sequencing of the human genome represents a critical milestone in the scientific landscape and a springboard for genetic studies (International Human Genome Sequencing Consortium, 2001).

The most crucial argument for seeking genetic data is the high heritability of many important medical conditions. The extraordinary technical advances in the field of human molecular genetics over the past few years have led to an explosion of new information about the genetics of complex, multigenic human diseases, notably including autoimmune disorders. The design of genetic studies has relied of three main components: availability of population (with well defined ethnic/racial groups for original and replication studies), technology (with comprehensive coverage of the entire genome) and data (as comprehensive as possible) to be associated with the outcome of interest. Advances in DNA sequencing and genotyping technology have put us in a unique position to consider issues raised by the use of genetics data in personalized medicine.

### 2.1. Genome-wide association studies (GWAS)

During the last decade, many breakthroughs have contributed to the unraveling of the genetic etiology and pathophysiology of complex autoimmune diseases and other genetic disorders. GWAS have uncovered thousands of variants involved in the pathogenesis of many complex human disorders and have proven a powerful hypothesis-free method to identify common disease-associated variants. This method identifies SNPs that are present in the general population, but it cannot predict functional consequences. Such genetic associations identify a region or genetic locus that is associated with disease, but the specific causative mutation within that locus is not immediately identified.

Despite the success of GWAS, a substantial heritability gap remains. GWAS have identified a high number of loci common to several autoimmune diseases, such variants despite being common have a modest-effect size and thus a substantial fraction of heritability remains unexplained and/or hidden (Manolio et al., 2009). Some of this missing heritability should be accounted for by low-frequency and rare variants, which would be expected to have large biological consequences (Zeggini, 2011). Rare variants can be discovered by re-sequencing a small sample size cohort and then genotype the discovered variants in a larger sample set (Rivas et al., 2011; Momozawa et al., 2011). The study of these rare variants can be strengthened by focusing on isolated or well-defined populations, where an appropriate combination of data from whole genome sequencing and GWAS as well as imputation of variants into a reasonable study may lead to the detection of susceptibility loci for complex diseases (1000 Genomes Project consortium, 2010; Holm et al., 2011). GWAS have not yet reached their limits and although the majority of GWAS that have discovered common variants for human diseases were performed using a case–control design, an interest has been expressed in using family-based designs for GWAS. The reason for this new tendency caused by the expansion of new generation sequencing (NGS) methodology, which outlined the importance of the rare variants in disease susceptibility (Ionita-Laza and Ottman, 2011). Also, the use of GWAS to study patient subgroups, comparing patients with different subtypes of a disease has been fruitful recently (Kariuki et al., 2015).

### 2.2. Allelic discrimination by Taqman real time PCR

Real-time PCR is a very popular procedure for the quantification of gene expression (Ponchel et al., 2003). This technique monitors the progress of a PCR reaction as it develops to quantify a relatively small amount of initial sequence (DNA, cDNA or RNA). Quantification is based on the detection of the fluorescence produced by a reporter molecule, which increases as the reaction proceeds. These fluorescent reporter molecules include dyes that bind to the double-stranded DNA (i.e. SYBR® Green) or sequence specific probes (i.e. Molecular Beacons or TaqMan® Probes) (Bustin, 2000). An important application of the TaqMan PCR is the detection of known gene mutations or polymorphisms. This is based on the design of two TaqMan probes, each specific for one allele (A or B) representing the 2 alternative sequences. Both probes are labeled with two different fluorescent tags. The TaqMan probe is then designed to bind the gene sequence flanking the mutation (Livak et al., 1995). TaqMan probe-based assays are widely used in research and medical laboratories for the purposes of SNP genotyping and Pharmacogenomics.

### 2.3. Sequencing — next generation sequencing (NGS)

DNA sequencing and genotyping technologies have advanced quickly over the past decade, with the development of novel methodologies