the new editorial team proved problematic, also from a financial and organizational point of view. In 1983, in agreement with Prof. Ferrata's heirs, Prof. Storti set up the Fondazione Ferrata-Storti and became its first President. One of the Foundation's principal objectives was to strengthen Haematologica's profile. The Ferrata family donated the Journal to the Foundation, making it the new owner.

In 1990, Prof. Storti stood down as the Journal's Editor and Prof. Edoardo Ascari took his place while Prof. Mario Cazzola became Assistant Editor and later Co-Editor. Since 1992, the Journal also published supplements, mainly consisting of the proceedings of hematology meetings and congresses.

In addition to its link with the Italian Hematology Society, Haematologica became also the official journal of the Spanish Hematology Society in 1997, and a few years later, the Foundation moved all its editorial operations to Pavia and a bigger production office was set up.

Prof. Edoardo Ascari was made Chairman of the Board of Directors of the Fondazione Ferrata-Storti in 2002, a position he continues to hold today, and Prof. Mario Cazzola became the Journal's Editor-in-Chief. The Impact Factor continued to grow and in 2006 had reached 5.032 (Figure 2). In 2005, on the request of the European Hematology Association (EHA), Haematologica now became also the official journal of this prestigious society that brings together most of the European hematology community. The name of the Journal was changed to Haematologica/the Hematology Journal in order to incorporate the name of the Hematology Journal of the EHA. The President of the EHA, Prof. Robin Foà, was chosen to be Co-Editor to work with Prof. Mario Cazzola.

Prof. Cazzola stood down as Editor-in-Chief in 2012 in order to take on new responsibilities on the international stage. The new Editor-in-Chief was to be nominated by the EHA while the role of Deputy Editor would be chosen by the Ferrata Storti Foundation. Since 2012, the Editor-in-Chief is Prof. Jan Cools and the Deputy Editor is Prof. Luca Malcovati.

These last eight years since the agreement with the EHA have seen a further increase in the Journal's editorial achievements. Figures for 2013 show that 1017 original articles were submitted of which 190 were accepted (18% acceptance rate), and there were 3566 subscription holders. This high level has been maintained in 2014. Since 2010, Haematologica has been within the top 10 of hematology journals, with a stable Impact Factor around 6 (most recent IF: 5.868 for 2013). Haematologica is currently ranked 5th among international hematology journals.

The Haematologica website has been managed by Bench-Press (University of Stanford, CA, USA) since 2008. It has a Facebook page since 2012 and an App since July 2014. In the first six months of 2014, the Home Page of the Journal's website has had an average of 56,163 visitors a month.

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Red cells in post-genomic era: impact of personalized medicine in the treatment of anemias

Achille Iolascon, Immacolata Andolfo, and Roberta Russo

Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli Federico II, Napoli; and CEINGE Biotecnologie Avanzate, Napoli, Italy

E-mail: achille.iolascon@unina.it *doi:10.3324/haematol.2014.120733*

Over many years of research on pharmacogenetics and pharmacogenomics, we are now aware that the genetic variability among individuals is able to explain the remarkable diversity of either the therapeutic or the adverse effects observed during drug treatment. The term pharmacogenomics refers to the study of variations in the characteristics of DNA and RNA related to the drug response, while the pharmacogenetics is a subset of pharmacogenomics, and is defined as the influence of variations in DNA sequence on the drug response.[1] The response to drug treatment, as well as the occurrence of adverse events, is complex, involving multiple genetic and environmental factors and their interactions. Indeed, it is conditioned either by non-genetic factors, such as environment, diet, age, sex, lifestyle, or socio-economic rank, or by genetic variations in genes codifying proteins involved in drug metabolism and delivery. Thus, personalized medicine is based on the understanding of genomic, epigenomic, environmental and pathophysiological factors as well as on drug interactions.

In the past years, genome-wide association studies (GWAS) have identified a lot of common genetic variants underlying susceptibility, most of them with only small effects, to the complex response to drug treatment. The availability of genetic and genomic data is considered an important advance towards characterizing and explaining

the variability in treatment response. This knowledge is mainly translated into clinical application by the introduction of pharmacogenomic labels into product descriptions, which state whether predictive genotyping of the patient's DNA is mandatory, highly recommended or informative. At present, 176 drugs approved by the US Food and Drug Administration contain pharmacogenomics information, while for the European Medicines Agency, the current number of approximately 130 labels is increasing rapidly.[2]

Since the drug response is complex, no single molecular event is expected to fully unravel the mechanism of its variability among individuals. Conversely, multiple molecular levels can contribute to define different situations. In this context, the development of high-throughput technologies

Table 1. SNPs associated with altered response to drugs used for the treatment of hereditary anemias.

Disease	Gene/genomic region	SNP ID	Drug	Effects	PubMed ID
SCD sickle cell disease	*CYP2D6*	rs16947; rs1135840 rs28371706; rs16947 rs3892097; rs4001467	Codeine/hydrocodone	Increased enzyme activity Decreased enzyme activity Absent enzyme activity	23619115
SCD sickle cell disease	*BCL11A*	rs1427407; rs766432; rs4671393; rs11886868	Hydroxyurea	Influence the base-line %HbF	21876119
SCD sickle cell disease	*ARG2*	rs2295644	Hydroxyurea	Modulation of %HbF after treatment	21876119
SCD sickle cell disease	*ARG1*	rs17599586	Hydroxyurea	Modulation of %HbF after treatment	21876119
SCD sickle cell disease	*HBE1*	rs7130110	Hydroxyurea	Influence the base-line %HbF	21876119
SCD sickle cell disease	*XmnI*	rs7482144	Hydroxyurea	Influence the base-line %HbF	21876119
β-thalassemia major	*UGT1A6*	rs2070959	Deferiprone	Drug responsiveness	24036429
β-thalassemia major	*UGT1A6*	rs6759892	Deferiprone	Adverse drug reactions	24036429

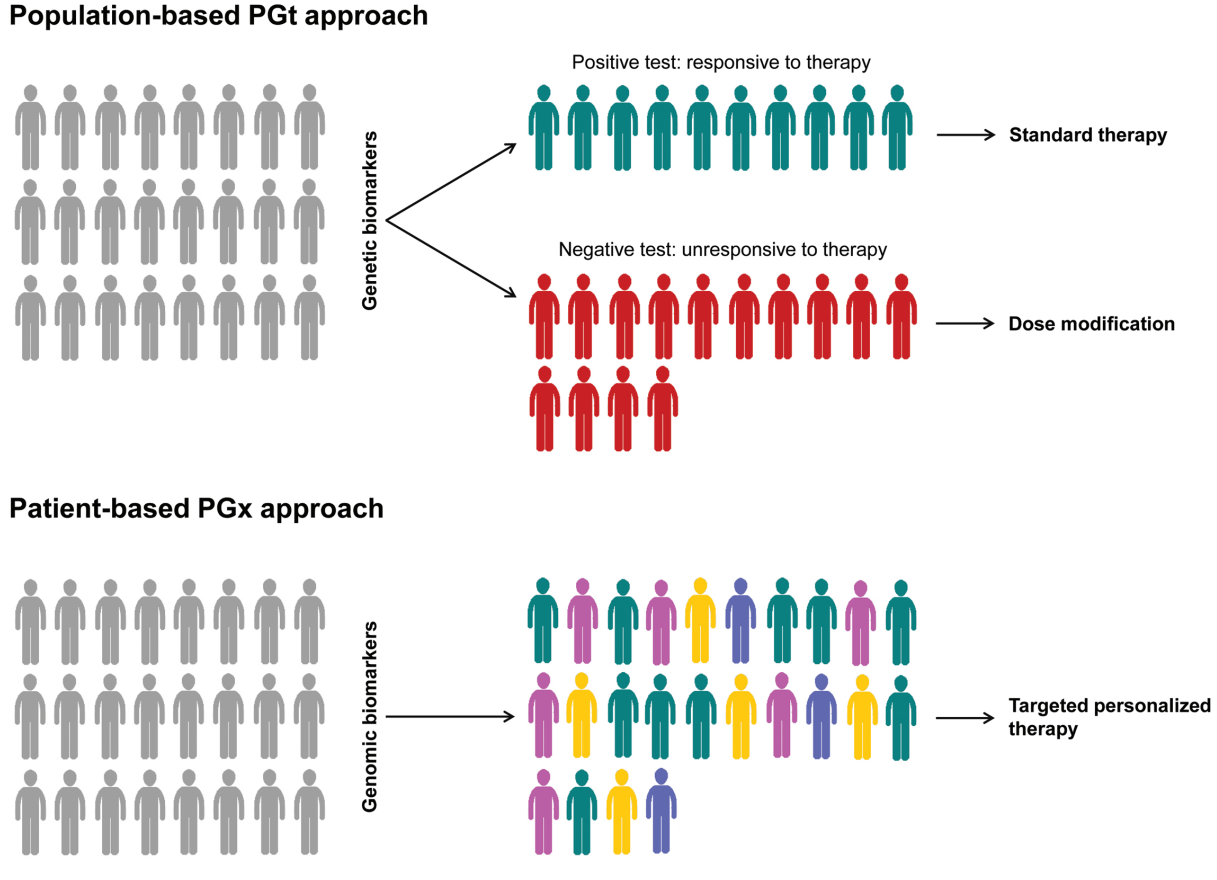

Figure 1. Patient stratification using genetic and genomic biomarkers. Top panel shows the classical framework of a population-based pharmacogenetic (PGt) study. It involves the identification of genetic biomarkers which are able to classify the cohort of patients in different genetically determined populations, in which each patient is phenotypically overlapped to each other. Bottom panel shows a single patient-based pharmacogenomic (PGx) approach, in which the integration of data from multiple '–omics' technologies could allow the definition of individual genomic signatures which will be able to create a targeted personalized therapy for each patient.

to detect genetic variation and gene expression certainly marked the opening of a new era for genetic and clinical research. Massively parallel DNA sequencing technologies, termed next generation sequencing (NGS), have rendered the whole-genome resequencing of each individual more and more practical. The increased knowledge of genetic and genomic differences among individuals has enhanced the attention given to the individual response, leading to a transition from population-based dosing and prescriptions to patient individualization both in drug development and in clinical practice (Figure 1). This could improve the probability of achieving desired treatment outcomes and/or reduce the risk of adverse effects.[3] However, there is still a need for new integrative approaches that are able to combine data from the different '-omics' technologies, in order to infer the causality relationship between genotype and phenotype.

Anemia affects approximately 1.6 billion people, 25% of the world population, mainly due to iron deficiency.[4] However, secondary anemia, i.e. the anemia of chronic disease or anemia due to surgical blood loss, is the most common form of anemia in hospitalized patients and the second most prevalent worldwide after iron deficiency.[5] Moreover, anemia is the most common side effect of a wide range of pharmacological treatments for very different conditions. A paradigmatic example of this concept is represented by glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is associated with development of acute hemolytic anemia (AHA) induced by a number of drugs, the best known of which is the antimalarial primaquine. Recently, the list of drugs leading to AHA in G6PD-deficient subjects has been extended and the effects of each drug have been classified into two groups: i) predictable hemolysis, which means that AHA can be expected in a G6PD-deficient patient; ii) possible hemolysis, which means that AHA may or may not take place, depending on dosage, other concomitant drugs, co-morbidity and other factors.[6]

Another example is represented by the treatment with ribavirin (RBV), which is the standard of care therapy for chronic hepatitis C virus (HCV) infection in combination with pegylated interferon (peg-IFN)-alpha, and which is associated with a range of treatment-limiting adverse effects. One of the most important of these is RBV-induced AHA, which affects most HCV patients and often requires dose modification in up to 15% of patients. It has been demonstrated that genetic variants leading to inosine triphosphatase (ITPA) deficiency, which seems to be a benign condition, are a major protective factor against RBV-induced AHA in HCV-infected patients receiving standard care therapy.[7] This knowledge is particularly important if we consider that various genetic predictors of response to standard treatment of chronic HCV infection has been already described, for example IL28B and SOCS3 single nucleotide polymorphisms (SNPs).[8,9] Moreover, since ITPA deficiency seems to be a benign condition, it would be possible to envisage protection against RBV-induced anemia by pharmacological intervention against ITPA.

Genetic variations play a major role also in phenotypic variability in Mendelian diseases. The overwhelming majority of these are caused by rare mutations that affect the function of individual proteins. While the identification of such genetic variants has informed our knowledge of the etiological bases of diseases, there continues to be a substantial gap in our understanding of the factors that modify disease severity. Monogenic diseases provide an opportunity to identify modifiers as they have uniform etiology, detailed phenotyping of affected individuals, and familial clustering.[10]

Hereditary anemias represent a substantial and heterogeneous group of anemias in which the identification of genetic variants is crucial for appropriate treatment. Examples of studies of pharmacogenetics in hereditary anemias have been conducted on sickle cell disease (SCD) and β-thalassemia major (Table 1). Hydroxyurea therapy has been shown to improve signs and symptoms of SCD, primarily by increasing the level of fetal hemoglobin (HbF). Hydroxyurea, especially when escalated to the maximum tolerated dose (MTD, defined by moderate suppression of circulating neutrophils and reticulocytes), can consistently and significantly increase the percentage of HbF (%HbF) level in infants, children and adults with SCD.[11] In spite of the clinical benefits from hydroxyurea treatment, extensive phenotypic variation is observed. For example, the %HbF achieved in young patients at hydroxyurea MTD ranges from a low %HbF (10-15%) to a high %HbF that occasionally exceeds 40%.[12] Pharmacogenetics analysis highlighted the role of several SNPs influencing either the base-line %HbF (including 4 SNPs within *BCL11A*, one in Hb Epsilon and one in XmnI γ-globin promoter region) or the variation of %HbF between baseline and MTD; this is the case of the 2 SNPs located in *ARG1* and *ARG2* genes.

Another example of pharmacogenetics analysis in SCD is the study conducted for the opioid medications codeine and hydrocodone, commonly prescribed for the treatment of mild to moderate vaso-occlusive crisis. Both drugs require metabolic conversion by cytochrome P450 2D6 (CYP2D6) to morphine and hydromorphone, respectively, to exert their analgesic effects. The CYP2D6 gene is highly polymorphic, with variant alleles that result in decreased, absent, rapid or ultra-rapid enzyme activity. Several variants have been analyzed in SCD patients showing correlation with increased, decreased or absent enzyme activity (Table 1).[13]

In β-thalassemia the only treatment to sustain life is regular transfusions which inevitably lead to iron overload, thus iron chelation is necessary to prevent the multiple organ dysfunction and/or failure and decrease the mortality. For this reason, oral iron chelators like deferoxamine, deferiprone and deferasirox have been introduced into clinical practice. UGT1A6 is responsible for glucuronidation of deferiprone. In the study by Gunaseeli *et al.*, serum ferritin levels were estimated periodically in β-thalassemia patients to evaluate iron overload and the patients were grouped into responders and non-responders depending on the ferritin levels. A significant difference in the genotypic distribution and allelic frequencies of UGT1A6*2 Thr181Ala (rs2070959) between responders and non-responders was observed. Conversely, there was no significant difference in the genotypic distribution of UGT1A6*2 Ser7Ala (rs6759892) between responders and non-responders; however, this SNP showed a significant difference between responders with adverse drug reactions and responders without adverse drug reactions.[14]

Currently, there are no pharmacogenetics studies exploring the correlation of drug responsiveness to genetic variants for

many other hereditary anemias. Undoubtedly, several data will come from NGS studies on genetic variations in modifier genes that affect the clinical phenotype and are thus relevant for prognosis, follow up and for personalized treatment. Furthermore, new avenues are now opening up in the study of human induced pluripotent stem cells (iPS), derived from human somatic cells through the ectopic forced expression of OCT4 and SOX2 with either the combinations of KLF4 and MYC or NANOG and LIN28. The potential applications of iPS are enormous. Indeed, since these cells are derived from the patients themselves, they represent a true *in vitro* model of that particular disease, such as hereditary anemias, and reflect the same pathological features as in *in vivo* conditions. Thus, iPS could be considered the best candidate model to use in pharmacogenetics studies.

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