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Drug-induced hypersensitivity reactions and pharmacogenomics: past, present and future

Drug-induced hypersensitivity reactions represent a major concern for clinicians, patients, regulators and drug developers. Severe hypersensitivity is associated with high morbidity and mortality, it cannot be predicted from the known pharmacology of the drug and it is usually detected post-marketing when a large number of patients have been exposed to a particular drug. Recent success in developing clinically useful genetic tests that have allowed us to predict the risk of abacavir-induced hypersensitivity has helped to pave the path for a pharmacogenetic approach. However, the loop from identifying a genetic association to improving clinical outcome is still lacking for many drugs. In this commentary, we discuss the progress of hypersensitivity pharmacogenomics over the last decade and point out what remains to be done in the future. The current efforts of the international community are focused on the development of consortia, which aim to standardize disease phenotypes, but also to collect larger numbers of well-phenotyped patients and to pool biological samples through these collaborations. In addition, it is necessary to advance our knowledge of hypersensitivity mechanisms through functional studies, which will lead to the development of predictive and diagnostic tests.

KEYWORDS: consortium ■ drug-induced hypersensitivity ■ HLA ■ pharmacogenetics ■ phenotype ■ polymorphism

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Drug-induced hypersensitivity reactions are 'off-target' adverse drug reactions that develop in susceptible patients following exposure to certain drugs [1]. They represent an important health problem and a major concern for clinicians, patients, regulators and drug developers. The exact incidence is unclear, but estimates suggest that they represent anything from 5–15% of all adverse drug reactions, depending on the setting of the study and its design. Severe hypersensitivity can require or prolong hospitalization, it cannot be predicted from the known pharmacology of a drug and it is usually not detected in clinical trials during drug development. Instead, hypersensitivity is reported post-marketing, when a large number of individuals are exposed to a particular drug. The occurrence of hypersensitivity in a patient often leads to the prescription of alternative drugs that may be less effective or more expensive, which is undesirable from both the patient's and the healthcare provider's perspective.

Past

Most of the work in this area in the past was epidemiological and provided valuable data on

drugs associated with hypersensitivity. However, elucidation of the underlying genetic risk factors was hampered by:

- Lack of adequate phenotyping of patients, since the diagnosis of drug-induced hypersensitivity relies on an adequate medical history. There are many different manifestations of drug hypersensitivity, ranging from mild maculopapular exanthema to the more serious blistering skin rashes, such as Stevens–Johnson Syndrome and toxic epidermal necrolysis. Work undertaken by groups such as the European Registry of Severe Cutaneous Adverse Reactions (REGISCAR) has been valuable in developing criteria for diagnosis of blistering reactions [2], but there is still variation in the criteria used by different groups used to define hypersensitivity syndrome;
- Lack of knowledge of the immune mechanisms that were presumed to be the basis of the reactions, largely based on clinical symptomatology. However, more recent studies have now provided exciting data on the role of MHC restriction and drug-specific T cells [3];

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- Lack of genotyping technologies, such that studies were performed using serological typing of *HLA* alleles or on the basis of single genetic variants in candidate pathways, often compounded by the study of small numbers of individuals, which led to weak associations that were not reproducible [1].

Present

With the advent of the Human Genome Project, the availability of better genotyping technologies at an affordable cost and the setting up of consortia to identify, phenotype and recruit patients; there has been a resurgence of interest in the pharmacogenomics of drug hypersensitivity. This has recently led to several independent groups reporting striking associations between different *HLA* alleles and drug-induced hypersensitivity reactions [4–11]. A common characteristic of all of these studies is the large genetic effect size that has been demonstrated, with odds ratios ranging from 20 to 2000. This was unexpected given the postulated multifactorial etiology of hypersensitivity, which has been compared with that of common disease genetics. The paradigm for this is abacavir hypersensitivity, where the clinical utility of testing for *HLA-B*5701* prior to prescription has been demonstrated in a randomized controlled trial [11], is of value in different ethnic groups [12,13], and has been shown to impact on clinical outcome in real-world clinical practice [14–16].

Although the loop from identifying a genetic association to improving clinical outcomes has been closed with abacavir, this is not the case with other drugs where there is a great deal of heterogeneity in the genetic contribution. Thus, while the genetic contribution to hypersensitivity seems to be large for abacavir, carbamazepine and allopurinol [4,9,12,17]; for sulphamethoxazole, lamotrigine and nevirapine, there is no clear evidence that genetic factors dominate over environmental factors, such as concomitant disease [18–20]. The small or absent genetic effects described with these drugs may be either genuine or the consequence of inadequate genotyping or small sample sizes. With respect to genuine drugs, the use of unbiased whole-genome approaches may identify novel associations residing within known immune pathways, as well as in novel ‘nonimmune’ genes. The utility of this approach has been shown recently for flucloxacillin-induced cholestatic hepatitis and its association with *HLA-B*5701* [5]. With respect to the consequence of inadequate genotyping or small sample sizes, the need for larger population

sizes, and the realization that this cannot be achieved in single centers, has led to the development of several international consortia such as the Serious Adverse Event Consortium [101], EUDRAGENE [102] and REGISCAR [103].

Future

‘Prediction is very difficult, especially about the future.’

Niels Bohr (1885–1962)

Where will we be in 2020 in relation to our knowledge base of hypersensitivity pharmacogenomics? With the continued development of genetic technologies and their decreasing cost, taken together with the increasing availability of well-phenotyped patient samples, it is likely that further progress will be made with hypersensitivity pharmacogenomics in the near future. Success, however, will depend on a number of issues, where there needs to be much more attention and research.

It is still unclear what the relationship is between different phenotypic manifestations of drug hypersensitivity. For instance, we do not definitively know that a mild reaction is a different ‘disease’ from the more severe reactions, or whether they represent different ends of the same disease spectrum. Thus, identifying and studying patients with mild reactions, as well as the more severe phenotypes, will be important.

Although much progress has been made with respect to definitions, there is still further work to be done, for example with hypersensitivity syndrome, which is variously known as drug reaction with eosinophilia and systemic symptoms or drug-induced hypersensitivity syndrome [21]. Furthermore, the relationship of reactions involving both the skin and extracutaneous organs and those involving only the extracutaneous organs with the same drug in different patients needs to be better defined in terms of pathogenesis. The work of the Serious Adverse Event Consortium and the phenotype standardization project is a step in the right direction.

The development of consortia is encouraging, but these need to go further; to collect larger number of well-phenotyped patients using innovative approaches such as electronic medical records and adverse event databases, as well as developing precompetitive collaborations that allow pooling of biological samples, even from patients involved in trials of new medicines. This not only needs to happen in Western countries, but also in developing countries, so that the findings can be compared across ethnicities in order to develop predictive tests that are applicable globally.

The current generation of genome-wide association study platforms will undoubtedly improve with the incorporation of data from sequencing initiatives, such as the 1000 Genomes Project. This, however, also needs to be supplemented with the use of next-generation sequencing technologies to identify rare variants that may have large effect sizes. Furthermore, the role of epigenetic changes and microRNA in predisposition to drug hypersensitivity also needs to be defined.

While striking associations have been shown with *HLA* alleles and some forms of drug hypersensitivity, definitive proof that the implicated *HLA* allele is truly the causal variant is still lacking, even with abacavir. The advances in genomic approaches need to be accompanied by advances in functional studies, which will aid our understanding of the prevention of these severe reactions, not only for currently available

drugs but also for future drugs, and will lead to the development of better predictive and diagnostic tests.

In conclusion, therefore, there has been tremendous progress over the last decade, but much still remains to be done. Given the current efforts by the international community, it is likely that the pace of this progress will accelerate to the benefit of patients.

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Websites

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www.saeconsortium.org
- EUDRAGENE
www.eudragene.org
- European Registry of Severe Cutaneous Adverse Reactions
regiscar.uni-freiburg.de