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Ethnicity and adverse drug reactions

Personalised drug treatment is getting closer but will not replace good clinical judgment

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Whether ethnicity is an important contributor to the variable outcome of drug treatment is still a matter of debate. Research evidence on such associations is limited in quantity and variable in quality. Too often patients' ethnicity is classified by using poorly defined criteria or an inadequate scientific basis.[1] Indeed, both skin colour and self identification of ethnic origin seem to be poorly correlated with molecular genetics, and most genetic variability is found within, rather than among, continental populations.[2] In addition, ethnic differences in drug response might originate from cultural or environmental factors.

In a meta-analysis on p 1177 McDowell and colleagues systematically reviewed the literature and summarised consistent findings about ethnicity and adverse drug reactions to cardiovascular drugs.[3] They found, among other interesting results, a threefold higher risk of angioedema in black compared to non-black patients when taking angiotensin converting enzyme inhibitors as well as a doubled risk of intracranial bleeding from thrombolytic therapy. A simple message to doctors in clinical practice must be an increased awareness of these adverse drug reactions in black patients (although with the caution that ethnicity was inconsistently defined in different studies). This might contribute to more accurate risk assessment in individual cases.

The reported differences in risk of adverse drug reaction would probably not be enough to justify offering other forms of treatment or information to different ethnic groups. Perhaps the greatest impact of this study will be to direct future research on the underlying mechanisms and pharmacogenetics of these specific adverse reactions. Population based differences in drug response are an adequate basis for extensive molecular comparisons, as exemplified in earlier studies.[4–6]

Optimising dose

Indeed, there is a growing body of evidence from detailed pharmacogenetic studies that various populations may differ significantly in the distribution of allelic variants of important enzymes that determine drug disposition or variants of drug receptors.[7 8] Such information about individual genotype could lead to dose optimisation, thus avoiding concentration dependent toxicity caused by drugs such as oral anticoagulants or antiarrhythmic drugs.[8 9]

Finding genetic markers for severe adverse drug reactions would help to identify patients at high risk before the start of specific treatment. Such findings would also serve as valuable support in establishing causality in complex cases where patients have taken more than one suspect drug.

Genetic markers

Some challenging findings on genetic markers of idiosyncratic drug toxicity have been reported recently. Two years ago, a striking association was described in a Han Chinese population between the human leukocyte antigen HLA-B*1502 and induction of Stevens-Johnson syndrome (a severe skin reaction) by the anticonvulsant carbamazepine.[10]

Every patient in this study with the syndrome carried the *B*1502* allele, compared with less than 5% of those who tolerated carbamazepine. In a smaller follow-up study from Europe, where the allele frequency of *HLA-B*1502* is significantly lower, it became clear that only a minority of patients with Stevens-Johnson syndrome induced by carbamazepine carried that particular haplotype, and interestingly enough, these four patients were of Asian descent.[11] These data might imply that East Asians testing negative for *HLA-B*1502* have almost no risk of Stevens-Johnson syndrome from carbamazepine, whereas the same is not true in Europe—where it might be more relevant to test for other genetic risk markers, unknown at this stage. An analogous situation concerns a relatively frequent general hypersensitivity reaction to the HIV drug abacavir, for which the described risk allele, *HLA-B*5701*, represents a highly specific and more sensitive marker in white people than in black people.[12]

Clinical judgment and deeper knowledge

The discovery of unique markers of adverse drug reactions will require validation in different populations before such evidence can be applied widely to practice. An association found in one population but not in others could be explained by differences in linkage between the marker allele and other alleles that are a more important mechanism in the development of adverse drug reactions. Even deeper knowledge about the mechanisms involved in severe reactions should not only lead to more qualified—and more widely applicable—predictions of which individuals are at increased risk, but also to development of safer drugs.

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It is important to keep in mind, though, that even with improved methods to predict an individual's risk of specific adverse drug reactions, the overall clinical value of patient screening will depend on the frequency and severity of adverse reactions and on other means to estimate and possibly avoid drug toxicity in individual patients. "Personalised" drug treatment will continue, therefore, to rely on good clinical judgment. The meta-analysis by McDowell and colleagues[3] is one more important piece of information to consider in the clinical assessment of the benefits and risks of specific cardiovascular drugs.

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A new human genotype prone to variant Creutzfeldt-Jakob disease

New evidence may rekindle fears of a larger epidemic and greater risk of iatrogenic spread

From the initial discovery of variant Creutzfeldt-Jacob disease (vCJD) in the United Kingdom a decade ago, there has been concern about the ultimate extent and magnitude of the epidemic.[1] Early estimates varied widely, with one model predicting up to 136 000 cases.[2] Fortunately, the magnitude of the epidemic at present seems to match the lower limit of the early estimates, with 161 definite or probable cases in the United Kingdom. However, the article by Ironside and colleagues on p 1186 may rekindle fears that a larger epidemic is an ongoing threat.[3]

The study reports a genotype analysis that identified the presence of the homozygous valine (VV) genotype in two samples of appendix tissue that harboured prion proteins. The implication of this finding of most concern is that it raises the possibility that ongoing iatrogenic transmission of vCJD may sustain the epidemic.

Why are the findings from this study worrisome? The current estimates of the prevalence of vCJD have primarily been restricted to populations with one specific genotype (MM), and all clinical cases have occurred in these individuals. This study is the first report of infection in individuals with the VV genotype. One case of infection, but not clinical disease, had been identified in one person with a heterozygous genotype (MV).[4] The fear is that the 60% of people with non-MM genotypes may be at risk of developing the condition, possibly with longer incubation periods.[5] Alternatively, these people may be asymptomatic carriers who might transmit the condition to other susceptible individuals.

It is important to be cautious in interpreting the results of this study. The study shows the existence of the prion protein in two tissue samples, not clinical evidence of vCJD in two patients. The study also provides no evidence to suggest that tissue from these two people could transmit vCJD to others.

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Policy implications

Nevertheless, there are compelling reasons why health officials should take notice. It is conceivable that, having jumped the species barrier, transmission of the prion within the species becomes easier. This is supported by case reports, which suggest that vCJD, unlike classic CJD, can be transmitted through blood transfusion.[4 6 7] Given that long incubation periods (up to 30 years) have been described in cases of iatrogenic transmission of classic CJD,[8] it is reasonable to consider that there are people in an extended preclinical stage of vCJD during which their tissue, in particular their blood, may pose an infectious risk to others.

On the basis of this evidence, should health officials take precautionary actions to protect against this risk? Several countries have instituted measures to protect against transmission of vCJD through transfusion and these measures seem to have at least been partly validated as new evidence has emerged.[9]

However, there are real problems with continuing and, in particular, extending this approach. Apart from the financial costs, measures to prevent transmission of vCJD reduce the pool of blood donors. And strategies such as rejecting donors on the basis of their country

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