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Review Article

Genes in Serious Adverse Drug Reactions

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ABSTRACT

Since long it has been postulated that various ADRs have some genetic determinants.To the date various genes have been identified and studied. Presence of particular gene determines individual susceptibility for adverse drug reaction for a particular drug. Genome-wide association studies and HLA genotyping have detected novel associations for serious, idiosyncratic and adverse drug reactions. This review article highlights genes involved in serious adverse drug reactions for drugs which are widely prescribed and occasionally give rise to serious ADR and newly licenced drugs or drugs still in development with liability to give rise to serious ADR as detected during clinical trials based on genome wide association studies, candidate gene analysis and HLA genotyping. Pharmacogenomics haspotential role in reducing the incidence of ADRs. Targeting susceptiblegenes may potentially allow for reintroduction of some valuable drugs that have been withdrawn previously and may also help to avoid some of the serious adverse drug reactions seen with licenced drugs.

Key words: Drugs, Genome wide association Study, Ximelagatran, Flucloxacillin, Lumiracoxib, Amoxicillin-Clavulunate

1. INTRODUCTION

A serious adverse drug reaction is defined as an undesirable experience concerned with a particular type of drug and that lead to any of the following: death or life threatening events, hospitalization, disability or permanent damage, congenital abnormality or birth defect [1-3]. In the period of 1976-2005, 28 different drugs were withdrawn from the market in US as a result of idiosyncratic reactions [4, 5].

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Reactions include cadiotoxicity, hepatotoxicity, nephrotoxicity, rhabdomyolysis, skin rashes and haemolytic anemia. These type of serious side effects results in withdrawal of otherwise valuable drugs. In the market, many example of licenced drugs available which occasionally gives risesimilar type side effects, often label on drug narrating the possibilities of serious side effects. This type of drug still continues to be prescribed and available might be because of non-availabilities of better effective alternatives. Researchers are interested in developing screening test that predicts which patients are at high risk of developing serious side effects. This type of approach may potentially allow for reintroduction of some valuable drugs that have been withdrawn previously and may also help to avoid some of the serious adverse drug reactions seen with licenced drugs.

In past 20 years, attempts are made to develop genetic test for susceptibility of individuals for adverse reactions [5]. Now it become very clear that certain genetic factors contributes to susceptibilities to these reactions along with other factors [5, 6]. The development of genome-wide association studies and their successful application to the identification novel susceptible gene for several complex polygenic diseases [7] resulted in application of genome-wide association studies in areas of serious adverse drug reactions [8].

Table 1: Summary of published genome-wide association studies on serious adverse drug reactions.

Type of toxicities	Drug involved	Genes implicated	Reference
DILI (Drug induced liver injury)	Flucoxacillin, Amoxicillin-Clavulunate, Lumiracoxib, Ximelagatran, Carbamazepine plus miscellaneous	*HLA classes I & II*	(9-12)
Skin and Hypersensitivity		*HLA-A*	(13-15)
Myotoxicities	Simvastatin	*SLCO1B1*	(16)
QT prolongation	Iloperidone	*CERKL*	(17)
Osteonecrosis of jaw	Pamidronate & Zoledronic acid	*CYP2C8*	(18)

2. DRUG INDUCED LIVER INJURY (DILI)

Single-center study in India shows DILI results in significant overall mortality of (17.3%). Anti-tubercular drugs, anti-convulsants, sulphonamides, and olanzapine are the leading causes of DILI, common in males but more females developed fulminant hepatic failure [19]. In US, drug-induced hepatic injury accounts for more than 50 percent cases of acute liver failureand more than 75 percent of idiosyncratic drug reactions result in liver transplantation or death [20].Most common cause for idiosyncratic DILI is associated with use of antimicrobial agents and NSAIDs [21-23].

20 years ago genetic susceptibility study showed in certain human leucocyte antigen (HLA) class II serotype, frequency and incidences of DILI cases were higher as compare to control group [24]. A number of reports of further association particular to HLA were studied. Two independent studies suggesting that the HLA class II allele DRB1*1501 was risk factor for DILI induced by antimicrobial agent, amoxicillin – clavulenic acid [25, 26]. This form of DILI has been related predominantly to the clavulenic component of the drug though this has not been demonstrated directly [27].

Table 2: Genome-wide association study on DILI

Drug	Gene allele tagged by SNP	Reference
Ximelagatran	HLA-DRB1*701-DQA1*0201	(9)
Flucloxacillin	HLA-B*5701	(10)
Lumiracoxib	HLA-DRB1*1501-DQB1*0602	(11)
Amoxicillin-Clavulunate	HLA-DRB1*1501-DQB1*0602 and HLA-A*0201	(12)

Ximelagatran direct thrombin inhibitor, which was developed as potential replacement for warfarine and other comurine anticoagulant but was withdrawn by manufacturer in 2006.The drug was associated with raised ALT levels in some patients. In various studied, direct HLA typing confirmed a significant association

between the level of ALT increase and *HLA-DRB1*701*[9].

Flucloxacillin commonly prescribed drug worldwide, occasionally associated with DILI (in<1in 10,000 prescribed flucloxacillin).DNA samples studied were from 51 patients of Northern European ethinic origin who had suffered mild to moderate DILI with clear cut causal link to flucloxacillin. Genome-wide association studies and direct HLA typing confirmed that carriage of HLA-*B*5701* was strong risk factor for flucloxacillin induced DILI [10, 13]. analysis suggested gene that has possible role in B cell immune response and is expressed in liver, ST6 β-galactosamide α-2,6-sialyltransferase 1(ST6GAL1), also contributed to DILI for flucoxacillin [28].

Lumiracoxib, NSAID group of drug in phase III clinical trials in many countries was withdrawn from market owing relatively high incidences of raised ALT levels among users. Genome-wide association studies and direct HLA typing confirmed that carriage of *HLA-DRB1*1501- DQB1*0602* was strong risk factor for lumiracoxib induced DILI. The overall HLA association of lumiracoxib DILI is less strong than flucloxacillin DILI. 34% Europeans are positive for *HLA-DRB1*150*. Typing for particular HLA allele might be considered as interesting approach for reintroduction of lumiracoxib worldwide [11, 29]

Amoxicilin-Clavulenic acid is another example of widely prescribed drug, showing occasional liver toxicity. Amoxicilin-Clavulenic acid related DILI has number of features in common in terms of frequency and type of liver injury. One of the largest genome-wide association studies in Europe shown genome-wide significance in MCH region [12].The most significant SNPs localized to both HLA class I and class II regions. Detailed HLA typing provided evidence that both HLA-*DRB1*1501- DQB1*0602 and A*0201* were risk factor for development of DILI(25, 26). The HLA-*DRB1*1501- DQB1*0602* association was in agreement with previous reports, but *A*0201* association was novel [12].

Lapatanib anticancer drug, initial study fails to detect any genome wide association but in candidate gene analysis significant association found in HLA class II allele DQA1*0201[30].

The mechanism for underlying the HLA association seen in DILI remains unclear. GWA studies have covered number of genetic markers across MCH regions, and localized strongest associations to specific class of HLA class I and II genes. Still there is no direct evidence of these gene products are causal. To the date GWA studies on DILI have focused either on drugs which are widely prescribed and occasionally give rise to DILI (flucoxacillin and augmentin) or either newly licenced or still in development with liability to give rise to DILI as detected during clinical trials (Ximelagatran and lumiracoxib). Assembling NSAIDs, statins and other antimicrobials induced DILI case for GWA study with strong statistical power seems to be more challenging, though achievable through international collaboration. Whether the HLA genotype will be the strongest risk factor for DILI linked to these other drug is still unclear.There are evidences linked to drug metabolizing genes contribute to susceptibility to some form of DILI ,for example NAT2 in case of isoniazide related DILI [31].

3. HYPERSENSITIVITY AND SKIN REACTIONS

Hypersensitivity is an inappropriate immune reaction to an otherwise nontoxic agent, manifestations are broad. Skin reactions, which may involve other organs like liver, lungs, kidneys, are the most common type of drug induced hypersensitivity reactions [32.]

Abacavir is commonly prescribed antiretroviral drug. In 8% individuals' treatment of abacavir is associated with fever, malaise, GI disturbances and other organ involvement. Candidate gene analysis in abacavir

suffered hypersensitivity patients are positive for HLA-B*5701 [33].However result of GWA still missing for abacavir.

Carbamazepine, widely used anticonvulsant, in 10 % case causes skin rash occasionally this may progress to hypersensitivity syndrome [34-36]. Study in patients of Taiwan shows strong association for allele HLA-B*1502 and carbamazepine induces Stevens-Johnson syndrome [37] but no such association seen in Europeans [38, 39] and Japanese [40]. In list of hypersensitivity reactions other agents are phenytoin, lamotrigine, allopurinol and antimicrobials. Strong association found between gene HLA-B*5801 and allopurinol induced Stevens-Johnson syndrome (SJS) / Toxic epidermal necrolysis (TEN) by candidate gene studies [39, 41].These findings are also of considerable interest in terms of the biological basis for hypersensitivity reactions [42].

4. DRUG INDUCED MYOPATHY

A manifestation of myopathy includes muscle weakness, myalgia, an increase in CPK level or myoglobinuria. Most cases are reversible by drug withdrawal, but severe form of disease is rhabdomyolysis followed by death which seenrarely [43]. Despite statin being very effective and successfully used worldwide, can cause muscle toxicity. Mechanism by which statins gives rise to toxicity still not completely clear, but increasing evidences indicates an induction of expression of the protein atrogin-1 in affected muscle tissue leading to muscular atrophy, possibly because of inhibition of geranylgeranyl isoprene unit transfer by statins [44]. Despite these, drug interactions, genetic polymorphism relevant to their metabolism and transport [16] and gene encoding proteins relevant to muscular function are important predictor in susceptibility to toxicity [45]. Understanding of genetic basis for simvastatin induced myopathy was greatly increased by GWA study of 85 cases of myopathy and 90 simvastatin exposed control without evidence of myopathy [46]. SNP of SLCO1B1 was found to be significantly associated which encode an anionic drug transporter located on sinusoidal face of hepatocyte, which is main inward transporter for number of different statins [16]. There is need for further larger study with power to detect smaller effects to explain higher proportion of risk for this toxicity. The association of muscle injury with SLCO1B1*15 has recently been confirmed for milder toxicity and several different statins in a candidate gene study [47].

5. DRUG INDUCED LONG QT SYNDROME

Cardiotoxicity is the most common reason for withdrawal of licensed drugs from market. In susceptible individual it is associated with delay in cardiac repolarization as detected by prolongation of QT interval on ECG, onset of form of ventricular tachycardia named torsades de pointes, which can lead to ventricular fibrillation and death. QT interval prolongation is imperfect marker for the arrhythmogenic potential of drug as many drugs prolong QT interval but do not progress to arrhythmia but it is currently only available measure. There are considerable evidences suggesting drugs prolonging QT interval affect cardiac ion channels [48]. To the date GWA study have focused on factors affecting QT length in populations, not drug induced long QT [49-51]. Finding from these studies resulted in identification of SNPs in more than 10 different genes including the nitric oxide synthase 1(NOS1) regulator, NOS1AP, sodium and potassium channel gene including SCN5A and KCN72 and other genes as important genetic predictors. The only GWA study on drug induced QT prolongation thus far reported involved a phase III clinical trial of the antipsychotic drug iloperidone [17]. No genome wide significant signals were detected but low p value was obtained for several loci including the CERKL gene and SLCO2A1.

Bisphoshonate induced osteonecrosis of jaw (BONJ)

Bisphoshonate associated osteonecrosis of jaw is associated with high-dose bisphoshonate therapy primarily in the oncology patient population with an estimated incidence of 1%-12% at 36 months of exposure. Prevention and treatment strategies are currently based on expert opinion and focus on maintaining good oral hygiene and conservative surgical intervention[52]. GWA study in multiple myeloma patients receiving bisphosphonate predicted CYP2C8 (rs1934951) polymorphism and BONJ predisposition [53].

6. CONCLUDING REMARK

Genomic studies have facilitated in understanding of genetic susceptibility to range of serious adverse drug reactions. Most associations detected are strong and highly significant. Larger GWA studies with strong power and whole genome sequencing studies require to detect rare genetic variants. Introduction of genetic screening tests or genotypingfor the risk factors may be value in avoiding or diagnosing serious adverse drug reactions. Potentially, the findings from some of these studies on drug response could be used to develop simple genetic tests to determine the most suitable drug for treatment or the most appropriate dose to use. Genetic screening test may have value in reintroduction of banned drug. The current findings from different studies should also be of the value in the design of better system to detect idiosyncratic adverse drug reactions during drug development.

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