# A New Zealand platform to enable genetic investigation of adverse drug reactions

Simran DS Maggo, Eng Wee Chua, Paul Chin, Simone Cree, John Pearson, Matt Doogue, Martin A Kennedy


## ABSTRACT

A multitude of factors can affect drug response in individuals. It is now well established that variations in genes, especially those coding for drug metabolising enzymes, can alter the pharmacokinetic and/or pharmacodynamic profile of a drug, impacting on efficacy and often resulting in drug-induced toxicity. The UDRUGS study is an initiative from the Carney Centre for Pharmacogenomics to biobank DNA and store associated clinical data from patients who have suffered rare and/or serious adverse drug reactions (ADRs). The aim is to provide a genetic explanation of drug-induced ADRs using methods ranging from Sanger sequencing to whole exome and whole genome sequencing. Participants for the UDRUGS study are recruited from various sources, mainly via referral through clinicians working in Canterbury District Health Board, but also from district health boards across New Zealand. Participants have also self-referred to us from word-of-mouth communication between participants. We have recruited various ADRs across most drug classes. Where possible, we have conducted genetic analyses in single or a cohort of cases to identify known and novel genetic association(s) to offer an explanation to why the ADR occurred. Any genetic results relevant to the ADR are communicated back to the referring clinician and/or participant. In conclusion, we have developed a programme for studying the genetic basis of severe, rare or unusual ADR cases resulting from pharmacological treatment. Genomic analyses could eventually identify most genetic variants that predispose to ADRs, enabling *a priori* detection of such variants with high throughput DNA tests.


An adverse drug reaction (ADR) is defined by the World Health Organization as any response to a drug which is noxious, unintended, and which occurs at doses used for prophylaxis, diagnosis and therapy.[1] Adverse drug reactions cause significant morbidity and mortality, with up to 100,000 annual deaths reported in the US in 2014, with an additional 800,000 ADRs reported as serious (resulted in hospitalisation, were life-threatening, led to a disability or resulted in a congenital anomaly).[2] In Christchurch ADRs were reported to be primarily responsible for about 19% of admissions to general medicine and partially contribute to a further 9% of admissions.[3] Data from the UK showed that hospitalisations due to ADRs are estimated to cost the health system over £637 million annually,[4] and about half are considered preventable.[5,6] Hence strategies to identify patients at risk of ADRs offer opportunities for both health gains and cost savings.

Some risk factors contributing to the development of ADRs are known, including age, sex, renal function, body composition, co-medications, existing diseases, smoking and/or alcohol consumption. However, these only account for some of the risk and many patients present with idiosyncratic ADRs where the above mentioned factors cannot provide a plausible explanation, and in some cases genetic causes have been identified. A small proportion of ADRs are immune-mediated hypersensitivity reactions often labelled as drug allergies. Some immune-mediated hypersensitivity ADRs have a significant association with particular human leukocyte antigen (HLA) alleles. Examples include an increased risk of abacavir-induced hypersensitivity in patients carrying at least one *HLA-B*57:01* allele,[7] and an increased risk of carbamazepine-induced Stevens-Johnson syndrome (SJS) in patients carrying at least one copy of *HLA-B*15:02*.[8] The association of

*HLA-B*15:02* is reported to be strongest in individuals of Asian ancestry, particularly South East Asians, where this variant is reported as common, ie, occurs at a frequency of >1% in the population.[9] In contrast, carbamazepine-induced SJS is rare in individuals of European ancestry, and is associated with a different HLA allele (*HLA-A*31:01*).[9,10]

Most ADRs are due to the extended or non-specific pharmacological properties of a drug. The risks increase with drug dose and there is substantial inter-individual variability in the pharmacokinetics and pharmacodynamics limiting our ability to predict individual risk. Some ADRs have been found to have significant association with particular genes. Examples include an increased risk of hematopoietic toxicity associated with genetic variants, which reduce thiopurine S-methyltransferase (TPMT) activity, increased risk of simvastatin-induced muscle myopathy with specific variants in the *SLCO1B1* gene and various ADRs related to reduced CYP2D6 activity.[11–13] However, many more ADRs have not been subject to genetic studies.

This report describes a New Zealand initiative to systematically collect samples from people who have had ADRs to characterise known or identify novel genetic variants associated with rare, unusual and severe ADRs. The pilot work described in this report was prompted by the strong genetic component observed for serious ADRs, such as those of abacavir, azathioprine and carbamazepine,[14–17] for which pharmacogenetics has proven clinical utility. Several other observations also informed our study design. First, sequencing of many human genomes has revealed that each individual has a high load of singleton variants, some of which may impact pharmacogenes.[18–20] This suggests that the overall contribution of low frequency gene variants towards inter-individual differences in drug response may be greater than previously thought. Second, international collaborative efforts between multiple centres have emerged as a possible solution to the as yet unresolved questions in pharmacogenomics research. Notable examples are projects hosted by the Pharmacogenomics Knowledge Base (PharmGKB; http://www.pharmgkb.org/page/projects), and the International Serious Adverse Event Consortium (iSAEC; http://www.saeconsortium.org/). To contribute to these important initiatives, the essential prerequisite is an effective means of accruing blood and DNA samples from ADR cases that are phenotypically well characterised. Taking statin-myopathy as an example, it is important to define myopathy using standardised guidelines so that it is not missed, or incorrectly classified as another statin-muscle ADR such as myalgia, rhabdomyolysis or necrotising autoimmune myopathy.[21] Third, high throughput next-generation sequencing technology, which enables simultaneous sequencing of a large number of genes or even entire genomes, has proven to be a powerful tool in the discovery of causal variants for rare diseases.[22,23] The success of this technology in Mendelian disease gene discovery suggests it will have similar value in identifying rare, functionally relevant pharmacogenetic variants.

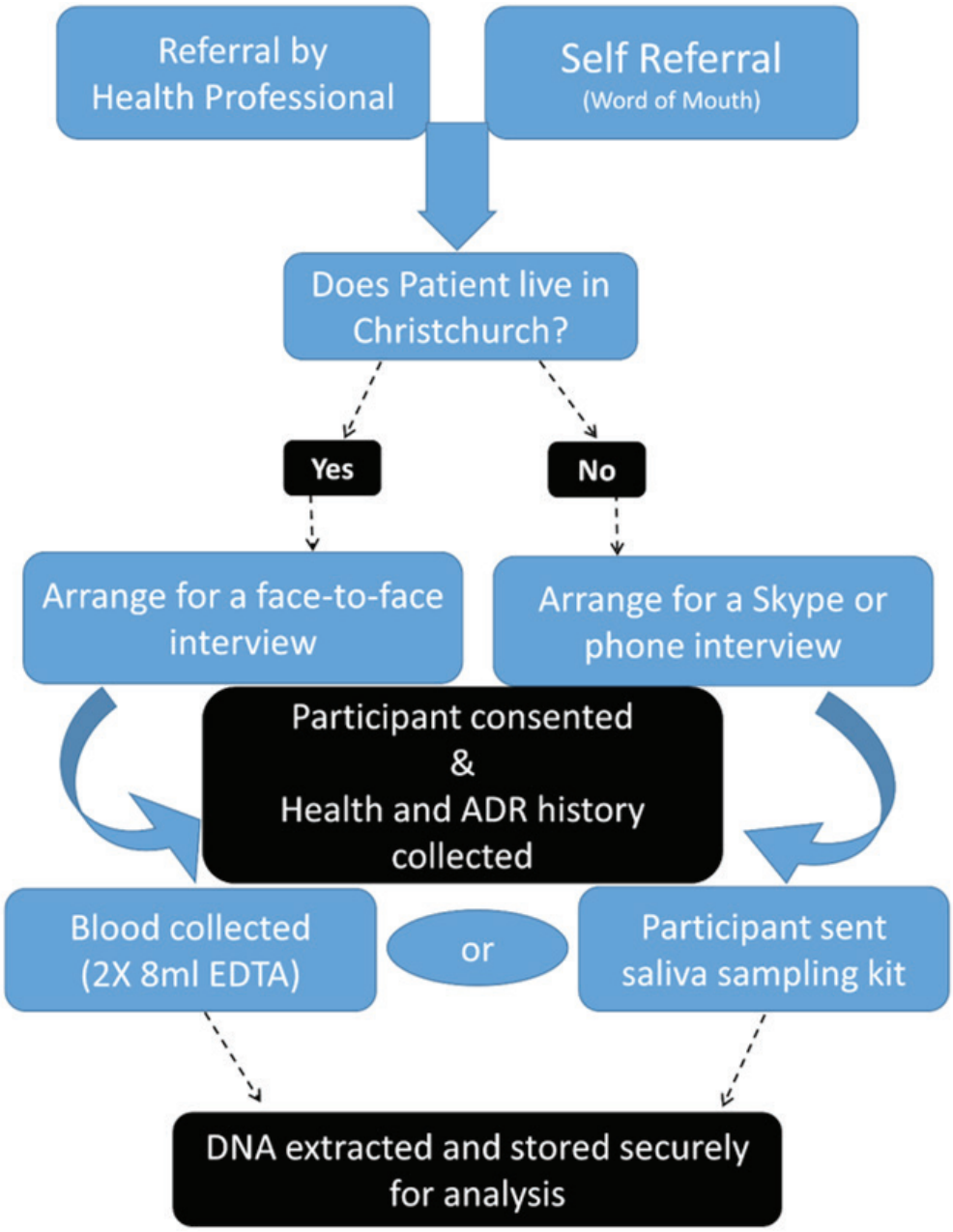
On this background we established a programme called UDRUGS (Understanding Adverse Drug Reactions Using Genomic Sequencing), with two major goals: (1) to establish a DNA bank linked to clinical information of patients who have experienced severe ADRs or exhibited aberrant response to pharmacological treatment, and (2) to explore the range of variations in known pharmacogenes that may contribute to the observed phenotypes.

# Methods

## Patient recruitment

The programme was approved by the Southern Health and Disability Ethics Committee (New Zealand). Participant recruitment is an active ongoing process. Participants are recruited from various sources (Figure 1). To date these have been mainly via referral through clinicians working in Canterbury District Health Board, but also from clinicians in Southern, Capital & Coast, and Auckland District Health Boards. Other sources have been patient self-referrals resulting from word-of-mouth communication between patients. The programme includes studies of specific cohorts, that is, patients who have experienced a specific ADR or unusual drug response. For example, we recruited a group of patients who preferentially methylate thiopurine compounds into 6-methylmercaptopurine (6-MMP), as evidenced by a high 6-MMP/6-TGN ratio (6-thioguanine nucleotides) (>20), and applied various approaches to evaluate possible genetic underpinnings of this phenotype.[24]

**Figure 1:** Patient recruitment into the UDRUGS study.




## Consenting, sample collection and storage

Written consent is sought from all patients referred to the UDRUGS study, and is obtained by a researcher or collaborating clinician. Consent includes provision for extensive whole genome analyses, long-term storage of blood and DNA samples, access to hospital medical records, contact with family members or relatives where necessary, and sharing of research data and samples with local or international collaborators. The possibility of incidental genetic findings is discussed with the patient at time of consenting. For patients unable to attend a face-to-face meeting, a telephone or Skype meeting is arranged to discuss and complete the consent form with a UDRUGS study coordinator. After consent is obtained, peripheral blood in two 8ml EDTA tubes is collected and frozen at -20ºC until required for DNA extraction. If a study participant is unable to provide a blood sample, a saliva sample is collected via an Oragene DNA (OG-500) kit (DNA Genotek Inc.).[25,26] In this case, participants are sent an Oragene kit

via courier, with a return courier envelope to return the saliva kit to the Carney Centre for Pharmacogenomics. Saliva samples are stable at room temperature for at least two years,[25] and on extraction, DNA quantity and quality is sufficient to use in standard polymerase chain reaction (PCR) as well as next-generation sequencing, eg, whole exome sequencing. Extracted DNA is aliquoted and stored at -80 ºC until required for analysis. All samples are assigned a UDRUGS code and spreadsheets linking the codes to participants' details are password protected and stored securely.

### Medical history questionnaire

The questionnaire was designed by adapting the Pharmacist's Workup of Drug Therapy, and is therefore suitable for universal documentation of ADRs.[27] The questionnaire consists of two parts: the first part is answered by the participant at the time of consenting and blood collection with the help of a UDRUGS study coordinator. The second part of the questionnaire is completed by the referring clinician. Participants' demographics, disease and medication histories, detailed account of the adverse drug reaction(s), and objective data (eg, blood test results including concentrations of the suspected drug) are documented. Causality of adverse drug reactions is evaluated using the Naranjo Algorithm.[28] For participants unable to attend a face-to-face meeting, the health questionnaire is completed over the phone by the UDRUGS study coordinator.

### Genetic analysis

Various genetic analysis techniques are employed. Sanger sequencing of candidate genes—those related to drug metabolism in particular—has been the principal route of analysis. Increasingly with multiple candidate genes potentially involved, a more comprehensive approach is adopted. This entails whole exome sequencing (WES), which enables simultaneous sequencing of all protein coding regions (exome) within the human genome. However, whole genome sequencing (WGS) is becoming more tractable and affordable, and we will begin testing this approach for analysis of UDRUGS cases in the near future. Functional effects of novel or rare genetic variants that may be clinically important are analysed using computer prediction algorithms or software such as Annotate Variation (ANNOVAR),[29] Combined Annotation Dependent Depletion (CADD)[30] and the SeattleSeq Annotation server.[31] However, proof of causality would require replication in other cohorts and more extensive laboratory-based studies.

### Long-term storage and contribution to international consortia

Where no immediate genetic analysis is possible because of limitations in current technology or genetics understanding, the participants' blood, saliva and extracted DNA samples are stored at -80 ºC for future analysis or contribution to appropriate international studies.

### Return of results

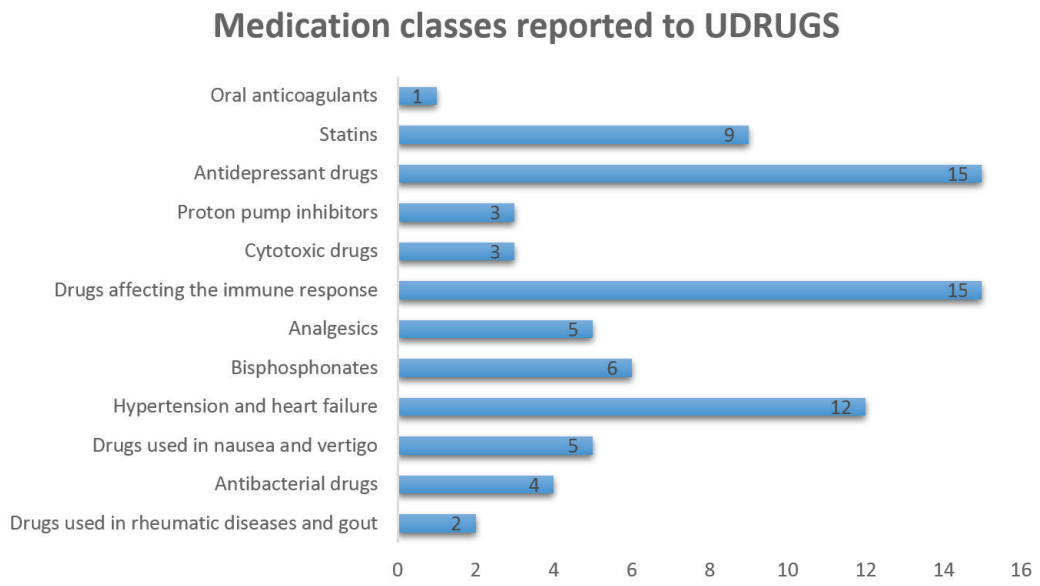
We communicate relevant research findings back to the participants and/or the referring clinician, emphasising that the findings are from a research laboratory. Where requested, we can also provide a list of medications for which genetic findings may be important. This list is largely based on the therapeutic guidelines formulated by Swen et al 2011,[32] and recently, guidelines are available from the Clinical Pharmacogenetics Implementation Consortium (CPIC).[33,34]

## Results and discussion

To date we have collected 80 cases (with stored DNA samples and clinical histories) thus far in the exploratory phase of this study (Figure 2). We utilised broad inclusion criteria and collected ADR cases, which seemed more likely to have a genetic underpinning. We did not exclude patients taking interacting drugs or patients with multiple medical conditions, as these factors need to be taken into account during any genetic association analyses in the future.

In collaboration with clinical colleagues, it has been possible to recruit case series of patients who have had specific ADRs. The first example of this includes the aforementioned whole exome study of 12 patients who exhibited extreme therapeutic resistance to azathioprine or 6-mercaptopurine, termed "extreme shunters".[24] In addition to WES, array-based comparative genomic hybridisation (aCGH) was also carried out to identify potential genes with copy number variations (CNVs). Novel genetic variants

**Figure 2:** Horizontal bars show the current number of UDRUGS cases per medication class.




identified in four genes associated with thiopurine metabolism were considered, but no significant variants were identified as being associated with treatment resistance in this study.[24] Similarly, we have recently recruited eight patients defined as "statin intolerant". These selected patients all have a history of persistent muscle myalgia, even after being challenged on two different statins, at varying doses. It has been previously reported that up to 50% of patients initiated on statin therapy are non-compliant after the first year, and ADRs or fear of ADRs are two of the major reasons associated with this high rate of non-adherence to statins.[35–37] Therefore, identifying genetic variants associated with statin-induced muscle myalgia will allow clinicians to consider a different lipid lowering agent or introduce statin intolerance management strategies earlier.[38,39] We have conducted WES on these eight patients, and these data are currently being analysed. Although these studies are small, the data can ultimately be combined with that from other groups, and underlying genetic patterns relevant to the ADR may become apparent.

Currently we are actively recruiting patients who have a thorough medical history of drug-induced hyponatremia, particularly induced by drugs such as thiazide diuretics, SSRIs and proton pump inhibitors (PPIs). Furthermore, we are looking to recruit patients with a history of PPI-induced hypomagnesemia and/or interstitial nephritis. The aim is to identify genetic variants which predispose to these specific ADRs.

Biobanking of samples is essential for contemporary or future personalised medicine research, and is being carried out elsewhere to facilitate the genetic analyses of ADRs.[40,41] The preliminary findings that we have obtained and reported[24,42] show that this is a viable route towards uncovering novel genetic components of severe ADRs or unusual drug response. Future work with UDRUGS will focus on establishing more systematic processes for patient recruitment, and in this regard, exploring the use of e-prescribing systems that are being introduced into district health boards in this country may be an efficient way to identify rare, severe or unusual ADRs. With the fast developing pace of genomic technologies, we are also trialling new DNA sequencing methods and developing assays that can be efficiently applied to incoming samples. Finally, where possible, studies to evaluate the likely functional effects of any relevant genetic variants identified will be conducted.

## Conclusion

We have developed a programme for studying severe, rare or unusual ADR cases resulting from pharmacological treatment—the high-risk group where genetic factors may be more likely to be implicated. This has entailed recruiting participants via various routes, documenting phenotype data, collecting and storing blood samples, exploring the range of appropriate genetic analyses, assessing the clinical relevance of genetic findings based on *in silico* predictions or available literature, and returning results to participants in an easily understood format. Genomic analyses should eventually identify most genetic variants that predispose to ADRs, enabling *a priori* detection of such variants with high throughput DNA tests. Establishing UDRUGS, a New Zealand DNA bank that can receive ADR samples and associated clinical data, will ensure we contribute to and benefit from such research. We welcome approaches from colleagues with problematic ADR cases that may contribute to this goal.

**Competing interests:**
Dr Doogue reports grants from Health Research Council during the conduct of the study; Dr Doogue is employed by CDHB as a clinical pharmacologist with responsibilities including adverse drug reactions and medicines governance. Dr Doogue's work includes general medicine, and patients with adverse drug reactions are admitted under general medicine. Dr Doogue is a member of the Health Quality and Safety Commission, Medicines Safety Expert Advisory Group.

**Acknowledgements:**
Dr Eng Wee Chua initiated the UDRUGs study as part of his PhD project. Dr Chua and Dr Maggo should be considered joint first authors of this publication.
The Carney centre for Pharmacogenomics and salary for research fellow Dr Simran Maggo is funded by the Jim and Mary Carney Charitable Trust. Work on UDRUGS is also supported by a project grant from the Health Research Council of New Zealand. We thank the clinicians and patients who have supported this work.

**Author information:**
Simran DS Maggo, Research Fellow, Carney Centre for Pharmacogenomics and Department of Pathology, University of Otago, Christchurch; Eng Wee Chua, Lecturer, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia;
Paul Chin, Clinical Pharmacologist, Department of Medicine, University of Otago, Christchurch; Simone Cree, Research Fellow, Carney Centre for Pharmacogenomics and Department of Pathology, University of Otago, Christchurch;
John Pearson, Senior Research Fellow & Biostatistician, Biostatistics and Computational Biology Unit, University of Otago, Christchurch; Matthew Doogue, Clinical Pharmacologist, Department of Medicine, University of Otago, Christchurch;
Martin A Kennedy, Department of Pathology, University of Otago, Christchurch.

**Corresponding author:**
Dr Simran Maggo, Pathology, University of Otago, 2 Riccarton Avenue, Christchurch 8140.
simran.maggo@otago.ac.nz

**URL:**
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