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Pharmacogenetics and target identification in diabetes

For Current Opinion in Genetics and Development

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Figures 1

Abstract

In diabetes, pharmacogenetics can be used both to identify patient subgroups who will have most benefit and/or least harm from a particular treatment, and to gain insights into the molecular mechanisms of drug action and disease aetiology. There is increasing evidence that genetic variation alters response to diabetes treatments – both in terms of glycaemic response and side effects. This can be seen with dramatic impact on clinical care, in patients with genetic forms of diabetes such as Maturity Onset Diabetes of the Young caused by *HNF1A* mutations, and Neonatal diabetes due to activating mutations in *ABCC8* or *KCNJ11*. Beyond monogenic diabetes, pharmacogenetic variants have yet to impact on clinical practice, yet the effect sizes (e.g. for metformin intolerance and *OCT1* variants; or for metformin action and *SLC2A2* variants) are potentially of clinical utility, especially if the genotype is already known at the point of prescribing. Over the next few years, increasing cohort sizes and linkage at scale to electronic medical records will provide considerable potential for stratification and novel target identification in diabetes.

Introduction

Pharmacogenetics is the study of how genetic variation modifies drug action. Drug action here is a broad term that, when considering treatment of patients with diabetes, can include glycaemic response, adverse drug reactions including drug side effects, cardiovascular risk reduction, and reduction in microvascular disease progression. As will be discussed later, it is important to consider these potential drug effects as we aim to better target treatment based upon genetic and non-genetic characteristics of patients, but the focus of this review will be on glycaemic benefit and drug side effects as these have been studied more extensively than longer term outcomes.

Traditionally pharmacogenetics has focused on the goal of identifying patients or patient subgroups who should be targeted with one drug in preference to another, based on a predicted differential response to the two drugs, or predicted likelihood of side effect or harm. However, with increasingly deep phenotyping of patients, including molecular phenotyping, the application of pharmacogenomics can be used as a complementary tool to traditional disease genetics to identify aetiological signatures of disease, as well as molecular signatures of drug action. Both latter approaches can help unravel the biology of disease and disease specific mechanisms of a drug, resulting in the potential for the identification of novel drug targets.

As highlighted in the figure, there are two parallel approaches to pharmacogenetics. One approach focuses initially on disease aetiology, the other on initially on a drug intervention. The aetiological approach uses increasingly large case control studies to investigate the genetic basis of type 2 diabetes. Combined with careful clinical, physiological and molecular phenotyping, this may be used to identify patients who are pathophysiologically distinct from other patients who, therefore, are more likely to respond to a drug that targets that pathophysiology. The alternative approach is to consider how genetic variation is associated with variation in glycaemic response to drugs. In this way groups of patients may be identified who are predicted to respond well or poorly to a drug. These patients may differ by pathophysiology and as such may overlap with patients identified via the disease aetiology route, or they may reflect other differences in drug pharmacodynamics or pharmacokinetics.

Disease aetiology and drug response

The monogenic diabetes paradigm.

Patients with diabetes caused by heterozygous mutations in HNF1A, causing a type of Maturity Onset Diabetes of the Young (MODY), are often diagnosed incorrectly as type 1 or type 2 diabetes and treated with insulin or other type 2 diabetes treatments. HNF1A mutations result in a defect in glycolysis and mitochondrial metabolism resulting in impaired glucose stimulated insulin secretion, yet the K_{ATP} channel which sulphonylureas act to close, and the downstream signalling mechanisms, remain intact. Thus, these patients are exquisitely sensitive to sulphonylurea treatment when compared to age and BMI matched patients with type 2 diabetes { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}, and this sensitivity to sulphonylureas is so marked that patients who have been diagnosed with type 1 diabetes

and insulin treated for up to 35 years could transition off insulin onto oral sulphonylurea treatment { ADDIN EN.CITE

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An even more striking example of disease aetiology altering diabetes treatment can be seen in neonatal diabetes caused by KATP channel gene mutations. Neonatal diabetes presents within the first 6 months of life, with marked hyperglycaemia and often ketoacidosis, requiring insulin treatment. Within the last 10 years, activating mutations in the K_{ATP} channel genes (*ABCC8* and *KCNJ11*) have been identified that account for approximately half of all cases of neonatal diabetes { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. Once the genetic aetiology was determined, it was hypothesised that sulphonylureas might close the K_{ATP} channel and trigger insulin secretion. This was established, albeit with high dose sulphonylureas required to overcome the K_{ATP} channel defect, and patients with lifelong diabetes have been able to successfully transition off insulin on to oral sulphonylurea therapy with improved glycaemic control { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}.

From monogenic diabetes to polygenic disease.

There is some evidence that the monogenic diabetes paradigm does translate to type 2 diabetes but, as could have been anticipated because the effect sizes of the diabetes associated variants are far smaller than seen with mendelian disease, the pharmacogenetic effect size is much smaller and has not yet translated to clinical care. Currently the only

reported diabetes risk gene – drug interactions are in relation to variants in *TCF7L2*, *KCNJ11/ABCC8* and *PPARG*.

The first type 2 diabetes variant established to alter glycaemic response to treatment was at the *TCF7L2* locus, where participants in the GoDARTS study, with type 2 diabetes carrying two risk variants at rs12255372 were more likely not to achieve a treatment HbA1c <7% (53mmol/mmol) (OR 2.16 (1.21- 3.86), p=0.009) than patients with no risk variants at this SNP, in response to sulphonylurea treatment { ADDIN EN.CITE

<EndNote><Cite><Author>Pearson</Author><Year>2007</Year><RecNum>405</RecNum><DisplayText>[6]</DisplayText><record><rec-number>405</rec-number><foreign-keys><key app="EN" db-id="zw5f0wsdb20twnewe2apvf0npx95ttstdzsr" timestamp="0">405</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pearson, E. R.</author><author>Donnelly, L. A.</author><author>Kimber, C.</author><author>Whitley, A.</author><author>Doney, A. S.</author><author>McCarthy, M. I.</author><author>Hattersley, A. T.</author><author>Morris, A. D.</author><author>Palmer, C. N.</author></authors></contributors><auth-address>Division of Medicine & Therapeutics, University of Dundee, UK.</auth-address><titles><title>Variation in TCF7L2 influences therapeutic response to sulfonylureas: A GoDARTs study</title><secondary-title>Diabetes</secondary-title></titles><periodical><full-title>Diabetes</full-title></periodical><pages>2178-2182</pages><volume>56</volume><dates><year>2007</year><pub-dates><date>May 22</date></pub-dates></dates><isbn>0012-1797 (Electronic)</isbn><accession-num>17519421</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17519421 </url></related-urls></Cite></EndNote>; a result that has been subsequently replicated { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. Srinivasan et al. analysed the effect of the *TCF7L2* diabetes risk variant rs7903146 on the acute response to glipizide and to metformin in the SUGAR-MGH cohort { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. This cohort is undertaken in people not known have diabetes, who are given a single dose of glipizide, and on separate occasion a 75g OGTT following 2 days of metformin given 500mg twice daily. In this study, in contrast to the studies reporting reduced efficacy of sulphonylureas in patients with diabetes, the diabetes risk variant is not associated with the glucose lowering achieved by a single dose of glipizide, although the risk variant was associated with lower glucagon prior to and following glipizide dosing. Interestingly the diabetes risk variant was associated with a greater response to metformin, an effect that was not observed in the GoDARTS study in participants with type 2 diabetes { ADDIN EN.CITE

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N. </author></authors></contributors><auth-address>Division of Medicine & Therapeutics, University of Dundee, UK.</auth-address><titles><title>Variation in TCF7L2 influences therapeutic response to sulfonylureas: A GoDARTs study</title><secondary-title>Diabetes</secondary-title></titles><periodical><full-title>Diabetes</full-title></periodical><pages>2178-2182</pages><volume>56</volume><dates><year>2007</year><pub-dates><date>May 22</date></pub-dates></dates><isbn>0012-1797 (Electronic)</isbn><accession-num>17519421</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17519421 </url></related-urls></urls><language>Eng</language></record></Cite></EndNote>}. The difference between these results may reflect that the physiological studies are an acute dosing in people not known to have diabetes compared to chronic dosing in patients with established diabetes. More work is clearly required to establish if and how *TCF7L2* variants alter response to sulphonylureas and metformin in patients with type 2 diabetes.

Secondly, the E23K/S1369A variant at the *KCNJ11/ABCC8* gene was also reported to alter sulphonylurea response. Here in contrast to *TCF7L2*, the diabetes risk variant is associated with greater response to sulphonylureas { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}; this contrast highlights how all beta-cell variants cannot be considered equal and that the site of the defect within the beta-cell determines whether the response to sulphonylureas is increased or reduced. Another replicated finding is the association between the *PPARG* Pro12Ala diabetes risk variant and response to thiazolidinediones. A few studies, albeit each with fewer than 200 participants, have consistently reported that the T2DM risk Pro allele is associated with poor glycaemic response { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}.

Beyond these reported drug-gene interactions, there have been no other reported associations of genetic variants that alter diabetes risk with glycaemic response to any of the diabetes treatments, even though there are now over 400 robustly replicated type 2 diabetes risk variants { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. This probably reflects that the pharmacogenetic community lag the disease genetics community with regards to sample size and available genetic data – most of the risk variants have very small effects and these are unlikely to have a measurable impact on diabetes drug response in the few thousand patients that represent the largest pharmacogenetics cohorts to date. However, it should be noted that in this GWAS of ~900k individuals, the top 2.5% of the genetic risk distribution have a 9-fold increase in risk for diabetes; thus even though individual variants are small, the combined effect can be large. If these genetic variants can be grouped into pathophysiologically similar subgroups, it may be that a genetic risk score of these subgroup variants will impact on glycaemic response to a drug that targets that pathophysiological defect. Furthermore, 14 low frequency and rare variants are identified that have a large effect size (OR for diabetes risk >2). In some populations, large effect variants can be found at relatively high frequency. One potential example that may rapidly translate into a stratified therapeutic approach is the finding that a rare missense variant in *HNF1A* is associated with type 2 diabetes risk in a Latino population { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. The risk variant is present in 2.1% of the population with type 2 diabetes. Given the previously described extreme sensitivity to sulphonylureas in patients with mendelian mutations in *HNF1A*, it seems likely that this subgroup of Latinos will respond well to sulphonylurea therapy although this remains to be established.

Expanding the aetiological subtypes of diabetes

Even though we have long acknowledged that type 2 diabetes is a pathophysiologically heterogeneous disease, there has been little attempt to tease this group apart into pathophysiologically similar groupings. A recent elegant recent study has done just this, using simple clinical (age, BMI, HbA1c), physiological measures (HOMA%B, HOMA%S) and the presence or absence of GAD antibodies to cluster patients with newly diagnosed diabetes into 5 groups { ADDIN EN.CITE <EndNote><Cite><Author>Emma Ahlqvist</Author><Year>2017</Year><RecNum>2445</RecNum><DisplayText>[18]</DisplayText><record><rec-number>2445</rec-number><foreign-keys><key app="EN" db-id="zw5f0wsdb20twnewe2apvf0npx95ttstdzsr" timestamp="1516295864">2445</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Emma Ahlqvist, Petter Storm, Annemari Karajamaki, Mats Martinell, Mozghan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B. Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spegel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Ake Lernmark, Kaj Lahti, Tom Forsen, Tiinamaija Tuomi, Anders H. Rosengren, Leif Groop</author></authors></contributors><titles><title>Clustering of adult-onset diabetes into novel subgroups guides therapy and improves prediction of outcome</title><secondary-title>bioRxiv</secondary-title></titles><periodical><full-title>bioRxiv</full-title></periodical><dates><year>2017</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1101/186387</electronic-resource-num></record></Cite></EndNote>}. The initial clustering was undertaken in the ANDIS cohort from Sweden, with subsequent replication in three independent cohorts. Of the 5 subtypes – one termed ‘Severe Autoimmune Diabetes’ represents type 1 diabetes; the other four are termed ‘Severe Insulin Resistant Diabetes’, ‘Mild Obese Diabetes’, ‘Severe Insulin Deficient Diabetes’ and ‘Mild Age-Related Diabetes’. These have marked differences in their rate of glycaemic deterioration, yet to date how these subgroups respond to different treatments has not been established, but this clustering approach offers potential to identify subgroups who should be best treated with one drug rather than an alternative.

Pharmacogenetics of drug response

Pharmacokinetic variation and efficacy

For a drug to be effective it needs to reach its site of action, in its active form, before being cleared. Variants that alter rate of drug transport or drug metabolism (resulting in activation or inactivation) will potentially alter drug exposure, resulting in increased or decreased efficacy. This has been shown for both sulphonylureas, where loss of function variants in CYP2C9 increase glycaemic response { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} but also increase risk of hypoglycaemia in some studies { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} but not all { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}; and thiazolidinediones where patients with enhanced metabolism (CYP2C8*3 carriers) had reduced glycaemic response to rosiglitazone, whereas those with reduced transport at OATP1B1 had a greater response { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}.

Metformin is not metabolised, but requires to be actively transported into the liver (via the organic cation transporter OCT1) and into the urine (via OCT2, Multidrug and Toxin Extrusion MATE1 and MATE2). Metformin has been traditionally thought to work in the liver to lower hepatic glucose production. Thus, reduced transport via OCT1 should reduce metformin efficacy. Reduced function variants in SLC22A1, that encodes OCT1, have been shown to reduce metformin uptake into the liver (using ¹¹C PET-Metformin tracer) { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} yet in patients with diabetes metformin works to lower HBA1c just as well in the the 8% of the Caucasian population who carry two loss of function variants in OCT1 as those who have normal functioning OCT1 { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. This suggests that either with chronic dosing of metformin, OCT1 is not required for metformin uptake into the liver, or that the liver plays less of a role in metformin action than previously thought.

Pharmacokinetic variation and adverse drug reactions

Metformin causes gastrointestinal side effects in up to 20% of patients treated with this drug. Metformin is transported from the gut lumen by the organic cation transporters OCT1 and PMAT, and metformin is also a substrate for the serotonin transporter (SERT). Reduced function OCT1 transport has been reported to be associated with increased GI intolerance in patients treated with metformin, an effect that is increased in patients taking concomitant medication that inhibits or is transported via OCT1 { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. Thus, patients carrying 2 loss of function OCT1 alleles have an odds ratio for intolerance of 2.41 (95% CI 1.22-2.17) and this increased to an odds ratio of 4.13 (95% CI 2.09-8.16) in those also treated with an OCT1 interacting drug, such as proton pump inhibitors, tricyclic antidepressants and verapamil). The Serotonin transporter also plays a role, with an interaction reported between SERT and OCT1 for metformin intolerance { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}.

Genome wide association studies reveal novel biological mechanisms for metformin

Genome wide association studies are now commonly applied across all disease areas and have provided remarkable insight into the biological mechanism of many diseases. However, there have been limited application of GWAS in pharmacogenetic studies, and in diabetes the only reported GWAS are for glycaemic response to metformin. These studies have established that the chip-based heritability for this trait is high ~34% { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}; all chromosomes contribute equally to this heritability suggesting that there are likely to be multiple common variants with small effect similar to the genetic architecture of diabetes. Thus, large sample sizes will be needed to identify variants associated glycaemic response to diabetes treatments. The initial metformin GWAS included a discovery cohort of ~1024 and a total sample size of 3920 patients with diabetes treated with metformin, and identified a variant associated with treatment success at a locus including the *ATM* gene { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}; this result has subsequently been replicated in some studies { ADDIN EN.CITE

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num></record></Cite></EndNote>}. A subsequent study expanded the initial GWAS
replication cohorts as part of the MetGen consortium ({ HYPERLINK
"http://www.pgrn.org/metgen.html" } } to a total sample size of 13,123 and identified an
additional genome wide significant variant for glycaemic response to metformin { ADDIN
EN.CITE { ADDIN EN.CITE.DATA }}. This variant, rs8192675, was shown to be the top cis-
eQTL (a genetic variant altering mRNA expression) for *SLC2A2* in human liver samples, and
in the Genotype Tissue Expression project database (GTEx) was shown to be associated with
altered expression of *SLC2A2* in the pancreatic islets, the intestine and the kidney { ADDIN
EN.CITE { ADDIN EN.CITE.DATA }}. Obese patients who were C-allele homozygotes at
rs8192675 had a 0.33% (3.6mmol/mol) greater absolute HbA1c reduction than T-allele
homozygotes – equivalent to 500mg difference in metformin dose and at a level that could
be used to guide therapeutic decision making. However, the main implication of these
studies is in highlighting their potential to reveal novel biological mechanism of action for
metformin. Large meta-gwas of glycaemic response are now underway in the MetGen
consortium, expanding the GWAS from ~1000 to more than ~20,000 metformin treated
patients. This has the potential to yield further novel biology and drug targets, but also, by
combining genetic variants, the potential to predict larger drug effects that could be
translated into clinical care.

Beyond glycaemia

As highlighted in the introduction, pharmacogenetics in diabetes should not simply focus on
glycaemic response to drugs but should consider hard outcomes such as cardiovascular
disease risk and mortality. To undertake gene*treatment interactions evaluating such
outcomes will require linkage of large genomic bioresources to electronic health record
data; this is an area of rapid expansion and is a focus of consortia such as the EMERGE
network ({ HYPERLINK "https://emerge.mc.vanderbilt.edu" }). However, genetic studies can
already be used to provide insight into the potential benefit or harm of diabetes drugs, in
the absence of a large drug-outcome database. For example, a recent study { ADDIN
EN.CITE { ADDIN EN.CITE.DATA }} identified that a GLP-1 receptor variant, that is associated
with lower glucose, was associated with reduced risk of cardiovascular disease in large case
control studies suggesting that GLP-1RA should have beneficial cardiovascular outcomes –

an effect now being reported in cardiovascular outcome trials for these drugs { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. In another example, Emdin et al. used genetic variation in the ABCC8 gene to address the controversial question of whether Sulphonylureas cause increase cardiovascular mortality, as has been suggested by observational studies e.g. { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. They used the A1369S variant as a genetic proxy for sulphonylurea action, as functional studies show that the variant reduces K_{ATP} channel function, and establish that people who carry this variant have reduced risk of coronary heart disease suggesting that sulphonylureas should not have adverse cardiovascular outcomes { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}.

Conclusions and future directions

There is increasing evidence that genetic variation alters response to diabetes treatments – both in terms of glycaemic response and side effects. Other than in monogenic diabetes these have yet to impact on clinical practice, yet the effect sizes (e.g. for metformin intolerance and *OCT1* variants; or for metformin action and *SLC2A2* variants) are potentially of clinical utility, especially if the genotype is already known at the point of prescribing. With falling sequencing costs, it is likely that within the next decade individual whole genome or exome data will be embedded within the clinical record making the potential utility of the variants described a reality. Soon, we will also be undertaking much larger pharmacogenetic GWAS with the potential to identify many more variants that will yield more insights into the mechanism of action of diabetes treatments with the potential for novel target identification, and by linkage to large electronic health care record systems, we will be able to link genetic variation to the long-term outcomes of these drugs.

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Figure legend

Figure 1. Pharmacogenetic approaches in diabetes. Two parallel approaches can be used to identify patient subgroups who respond well or poorly to diabetes treatments or to discover novel biological mechanisms of drug action. One approach is to use large scale diabetes case-control cohorts to identify genetic variants associated with disease risk and to then investigate these individually or grouped by shared pathophysiology for drug response. The alternative, classic pharmacogenetic approach, is to undertake a gene * drug interaction study to identify variants that are associated directly with altered drug outcomes.

Disclosures

EP has received honoraria from Lilly, MSD and Novo Nordisk.