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Genetics-based stratification of diabetes to improve clinical care: a monogenic viewpoint

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Abstract

The ability to define subgroups within a broad disease category, in order to predict disease progression and optimize treatment, is intellectually a very appealing approach. This strategy has proven to be possible in monogenic diabetes; there are clearly defined subtypes for both maturity-onset diabetes of the young (MODY) and neonatal diabetes. Classification of patients into these subtypes has demonstrable clinical utility; the reason for this success is that the subtypes can be robustly defined, and have different etiologies, and there is no overlap between subtypes. Stratification of type 2 diabetes (T2D), given the clinical heterogeneity and increasing prevalence of the disease, would be extremely useful. Unfortunately, classification of T2D is not as straightforward, and attempts have resulted in overlapping, non-etiologic clusters with limited clinical utility. Although these T2D clusters can identify differences in disease progression, simple continuous clinical features, such as age at diagnosis and baseline renal function, are better predictors of this variability. Investigations into using clinical features to predict optimal second-line treatment choices for T2D are underway, and initial results are favorable. Thus, currently, while genetic subgrouping shows clinical utility for monogenic diabetes, it appears that using continuous clinical features to individualize treatment is the best approach for T2D.

Key words: diabetes, genetics, monogenic, stratification

Introduction

One approach to precision medicine is, within a broad clinical category, correctly defining and diagnosing specific subtypes of a disease to improve clinical care. Intellectually this is a very attractive approach, and has proven to be possible in monogenic diabetes; for both maturity-onset diabetes of the young (MODY) and neonatal diabetes, there are clearly defined subtypes with different clinical courses and treatment requirements.[1-3] Defining and understanding these genetic subtypes has led to improved clinical care, which is obviously the ultimate goal. This paper briefly reviews the reasons subtyping has been successful in monogenic diabetes, and discusses the evidence for the best approach to stratification for patients with type 2 diabetes (T2D).

Maturity-onset diabetes of the young (MODY)

MODY was first recognized in the 1970s when the disease was diagnosed using clinical criteria.[4,5] MODY is an early-onset diabetes characterized by autosomal dominant inheritance, not being insulin dependent, and β cell dysfunction; it is usually misdiagnosed as type 1 diabetes (T1D) or T2D.[6,7] The disease is clinically heterogeneous and, prior to the genetic classification, this led researchers to question whether it was a single condition with differing severities or multiple conditions. Genetic studies have shown that there are several subtypes of MODY, with different genetic etiologies. These findings have clinical implications beyond genetic 'stamp collecting', with the subtypes having different clinical features and treatment outcomes.[7]

The four most common subtypes of MODY are caused by mutations in the *glucokinase* (*GCK*) gene, and in *hepatocyte nuclear factor (HNF)1A*, *HNF4A*, and *HNF1B* genes.[5] Patients with mutations in *GCK* are often asymptomatic, with stable, mild fasting hyperglycemia from birth, and are usually diagnosed during routine examinations. These patients generally do not require treatment; in a study in 799 patients with *GCK* mutations (of whom 21% were receiving pharmacologic treatment), median glycated hemoglobin (HbA_{1c}) was very similar in treated and untreated patients (6.5% vs. 6.4%).[9] Furthermore, in a subgroup of patients who discontinued treatment, there was no change in HbA_{1c}. There is also a very low risk of these patients developing diabetes complications, as shown in a study comparing 99 people with *GCK* mutations (median HbA_{1c} 6.9%), 91 family members without diabetes or *GCK* mutations (controls, HbA_{1c} 5.8%), and 83 patients with young-onset T2D (YT2D, HbA_{1c} 7.8%).[10] The mean duration of hyperglycemia was 48 years in the *GCK* group and 17 years in the YT2D group. Despite this long duration of hyperglycemia, clinically significant microvascular disease was present in only 1% of individuals with *GCK* mutations, compared with 2% of controls, and 36% of those with YT2D. Although the prevalence of retinopathy (any level) was higher in the *GCK* group than controls (30% vs 14%), it was exclusively background retinopathy and no patient had maculopathy, or required laser surgery for retinopathy. In contrast, 52% in the YT2D group had retinopathy, 20% had maculopathy, and 28% required laser surgery. None of the *GCK* group had proteinuria and only one patient had persistent microalbuminuria. The prevalence of macrovascular disease was also lower in the *GCK* group (4%) and control group (11%) than the YT2D group (30%, $P < 0.001$ vs. GCK).

Patients with *HNF1A* and *HNF4A* mutations show a progressive increase in hyperglycemia over time and frequently develop complications.[5,7,11] These subtypes require treatment and are both characterized by sensitivity to sulfonylureas. In a crossover trial in patients with T2D or diabetes caused by *HNF1A* mutations, both groups had a similar response to metformin, but the response to gliclazide was almost 4-fold higher in the *HNF1A* group than the T2D group (reduction in mean fasting plasma glucose 4.7 vs. 0.9 mmol/L, $P = 0.0007$).[12] In contrast, patients with *HNF1B* mutations, who also have progressive, severe hyperglycemia, do not respond satisfactorily to sulfonylureas and generally require early insulin treatment.[5,7,11] These patients almost always have renal development disorders, and this subtype is also known as renal cysts and diabetes syndrome (RCAD).

Although genetic classification of MODY subtypes has been possible for some time, it is finally becoming mainstream, as physicians recognize it is important for clinical care, not just for science. A United Kingdom community study of patients diagnosed with diabetes before the age of 30 years found that 3.6% had monogenic diabetes, and that screening of these patients was simple, inexpensive, and effective.[13] Genetic stratification of MODY is successful because the subtypes are robustly defined, each with a different genetic etiology, and there is no overlap between them; that is, the same patient cannot have two types of MODY. Furthermore, the classification has clinical utility, allowing us to predict the clinical course of the disease, and the response to treatment.

Neonatal diabetes

Prior to 2004, neonatal diabetes was defined by the age of diagnosis, with subtypes characterized by clinical course: if the patient improved and stopped insulin, it was transient diabetes; if they did not, it was permanent diabetes; and if they had no pancreas, it was pancreatic aplasia! All subtypes were treated with insulin, some with limited success. This was changed by work published by Gloyn et al. in 2004, which identified that the most common cause of neonatal diabetes is a mutation in the *KCNJ11* gene (encoding the Kir6.2 subunit of the β cell ATP-sensitive potassium [K_{ATP}] channel).[14] In β cells, glucose metabolism leads to increased ATP levels, and ATP binds to the Kir6.2 subunit of K_{ATP} channels, closing the channel and initiating insulin secretion. Mutations in *KCNJ11* prevent this closure, meaning insulin is not produced, and patients present with severe hyperglycemia or ketoacidosis. In addition to potassium-channel subunits, β cell K_{ATP} channels contain regulatory sulfonylurea-receptor subunits. This means it is possible to treat patients with sulfonylureas, causing ATP-independent K_{ATP} channel closure and insulin secretion.

The finding that they could be successfully treated with sulfonylureas was life-changing for many patients. In a study of 49 patients with diabetes caused by *KCNJ11* mutations who initiated high-dose sulfonylurea treatment, 90% were able to discontinue insulin treatment, and, more importantly, all patients had improved glucose control.[15] After treatment for 12 weeks, mean HbA1c was reduced from 8.1% to 6.4% (P <0.001), with no change in the frequency of hypoglycemia, and no reports of severe hypoglycemia. In a case study of an infant who was switched from insulin pump therapy to oral glibenclamide, continuous glucose monitoring showed a marked reduction in variability as well as lowering of glucose levels once glibenclamide was initiated.[16] In contrast to what is often observed in T2D, this response to sulfonylurea treatment is maintained long term, as shown in a 10-year international cohort study in 81 patients with permanent *KCNJ11* neonatal diabetes who switched from insulin to sulfonylurea treatment.[17] Before switching treatment, median HbA_{1c} was 8.1%, and after a median of 10.4 years of follow-up it was 6.4%. In a total of 809 patient-years of follow-up, no patient had hypoglycemia resulting in loss of consciousness, seizure, or hospitalization for intravenous glucose/glucagon treatment. Thus, these results show a true improvement in control.

Since the findings of Gloyn et al. were published, there have been >30 genetic subgroups of neonatal diabetes identified, with two main mechanisms of disease: either abnormal function of pancreatic β cells or abnormal development of the β-cells.[7,18] From a practical point of view, these different genetic etiologies define not only the Hyphenate β-cell phenotype and what treatment is required, including whether exocrine replacement treatment is needed, but also the extra-pancreatic phenotype.[19] With the increase in genetic testing, we now often see patients with neonatal diabetes who are diagnosed with a genetic subtype before the onset of the other syndromic features of that subtype. This means we can predict the development of these features and the clinical course of the disease, as well as the best available treatment. This is true precision medicine.

In most of Europe, we are now picking up every new case of neonatal diabetes. One of the reasons for this success is that there is a simple cutoff to decide which patients to test (being diagnosed with diabetes before six months). As with MODY, the subtypes are robustly defined with different genetic etiologies and no overlap between subtypes, and this classification has clinical utility in that it allows prediction of the clinical course and treatment response.

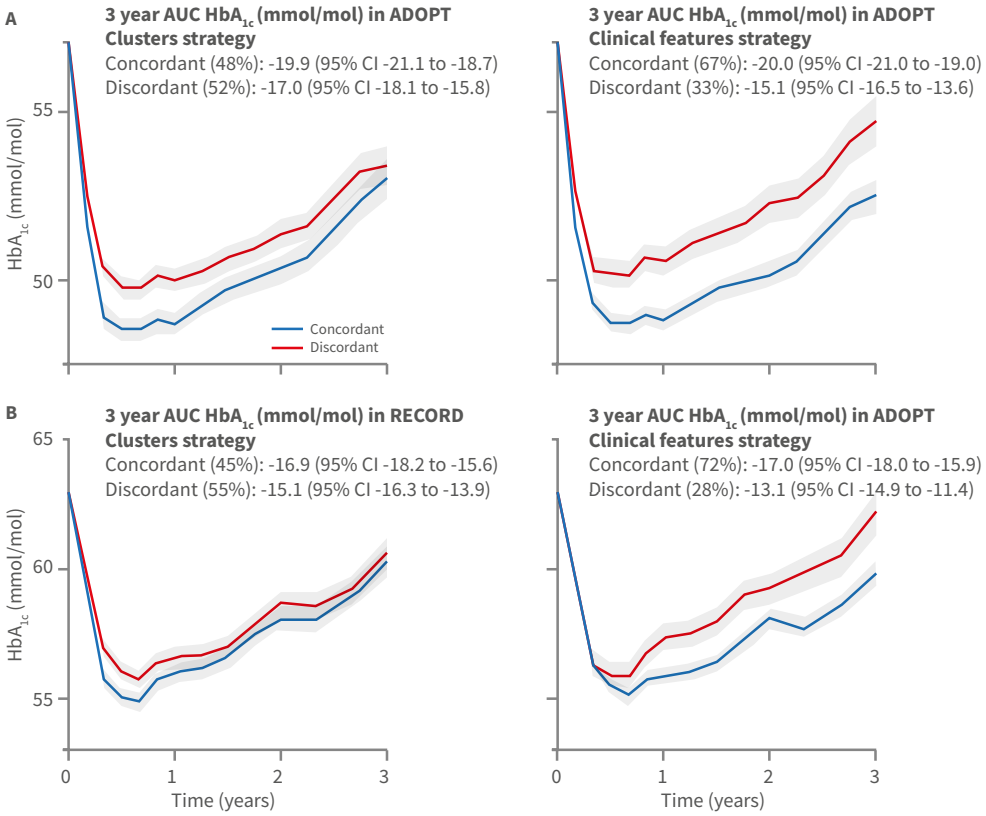
Type 2 diabetes

The observed success of genetic classification for MODY and neonatal diabetes leads to the question, is it possible to use the same strategy for T2D? T2D is a particularly heterogeneous disease with an increasing number of available treatment options, but a limited understanding of how to choose the best option for an individual patient.[20, 21] Given the large heterogeneity, it is likely that there are subgroups of patients who respond better to one treatment than others, and the idea of identifying defined subtypes in order to predict disease course, individualize treatment, and possibly prevent complications, is appealing. A paper published by Ahiqvist et al., in which patients with diabetes were classified into different, replicable clusters with different disease progression and complication risks,[21] had a big impact on how we think about T2D. Although this paper was an important step forward, it was not without limitations, including the difficultly in applying cluster criteria to individuals, and not being designed to assess the treatment response of each cluster. In order to have clinical utility, any subgroup or cluster classification must be able to improve the prediction of an individual's clinical course and treatment response, and this improvement should be over and above what is achievable with separate clinical features that are currently available.[22] Whether clinical or polygenic data are used for classification, the data are continuous rather than discrete, which means subtypes cannot be robustly defined, there will be an overlap between subtypes, and subtypes will not have clear differences in etiology.

John Dennis compared the clinical utility (both outcome prediction and treatment response) of either (i) stratifying patients into the subgroups defined by cluster analysis or (ii) using clinical features in models for each individual.[22] This study used individual patient data from two large randomized trials, ADOPT (A Diabetes Outcome Progression Trial)[23] and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycemia in Diabetes),[24] which assessed the clinical outcomes of patients with T2D in response to treatment with metformin, a sulfonylurea, or a thiazolidinedione.[22] Using these data, it was possible to reproduce the clusters identified by Ahlqvist et al., and there were clear between-cluster differences in disease progression. However, age at diagnosis alone was an equally reliable predictor of glycemic progression; patients diagnosed in their 40s progressed approximately twice as quickly as those diagnosed in their 70s. The cluster groups were also able to predict progression to chronic kidney disease (CKD), but once the results were adjusted for baseline estimated glomerular filtration rate (eGFR), the between-cluster differences in time to CKD were no longer evident. Furthermore, baseline eGFR for an individual was better at predicting reduced renal function than the cluster subgroups.

There were between-cluster differences in glycemic response to the assigned treatments, with one subgroup performing better with a thiazolidinedione, and another with a sulfonylurea; however, models using readily available clinical variables (sex, age, baseline HbA_{1c}, and body mass index [BMI]) were better than the clusters at explaining this variability in response. The question of whether clusters outperformed a model using clinical characteristics was assessed using the clinical trial data with a model and cluster treatment based on one trial data set, and both being tested in a second. In the test data set, the patients were retrospectively assigned an optimal treatment group, either using the clinical data model or as part of their cluster. For each strategy, the patients were divided into two subgroups, those who had been randomized to receive their optimal treatment (concordant), and those who had received a different treatment (discordant).[22] There was a larger difference in treatment response between the concordant and discordant subgroups for the individual clinical features strategy than the clusters strategy, suggesting that the former strategy is more useful for treatment selection (**Figure 1**). There is still the possibility that subgrouping may, in the future, be help guide treatment selection, but any new strategies

Figure 1: *Change in HbA_{1c} over 3 years with concordant and discordant subgroups using the subtypes strategy and the individualized prediction strategy. A) ADOPT development cohort (n=3785), clusters strategy (left panel) and clinical features strategy (right panel); B) RECORD validation cohort (n=4057), clusters strategy (left panel) and clinical features strategy (right panel). Reproduced from,[22] Dennis et al (2019), with permission, under a Creative Commons Attribution 4.0 International License.*
ADOPT, A Diabetes Outcome Progression Trial; AUC, area under the curve; CI, confidence interval; HbA_{1c}, glycated hemoglobin; RECORD, (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycemia in Diabetes)



must be tested for superiority over existing practice. Furthermore, as T2D is such a prevalent disease with reasonably economical treatment options, stratification strategies are more likely to be adopted in clinical practice if they are based on inexpensive, readily-available biomarkers.[25]

The three-way crossover TRIMASTER trial, in T2D patients with suboptimal glycemic control on metformin (with or without a sulfonylurea), was designed to use clinical features to develop a prediction model for optimized treatment with three common second-line treatments.[20] Initial results, reported at the 2021 European Association for the Study of Diabetes (EASD) meeting, showed that simple, readily available strata such as BMI and eGFR were predictive of which treatment a patient should receive.[26]

Conclusion

Correctly defined disease subtypes can improve clinical care, as demonstrated in MODY and neonatal diabetes. Both diseases have robustly defined subtypes with different etiologies and no overlap between subtypes; this classification allows accurate prediction of the clinical course and treatment response. Classification of T2D is not as straightforward, and attempts have resulted in overlapping, non-etiological clusters with limited clinical utility. Thus, currently, it appears that discrete models of disease progression and treatment outcomes using continuous data are most suitable for patients with T2D.

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References

1. Stride A, Hattersley AT. Different genes, different diabetes: lessons from maturity-onset diabetes of the young. *Ann Med.* 2002;34(3):207-216.
2. De Franco E, Flanagan SE, Houghton JA, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet.* 2015;386(9997):957-963.
3. Hattersley AT, Patel KA. Precision diabetes: learning from monogenic diabetes. *Diabetologia.* 2017;60(5):769-777.
4. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. *Diabetes Care.* 2011;34(8):1878-1884.
5. Jang KM. Maturity-onset diabetes of the young: update and perspectives on diagnosis and treatment. *Yeungnam Univ J Med.* 2020;37(1):13-21.
6. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. *Nat Clin Pract Endocrinol Metab.* 2008;4(4):200-213.
7. Hattersley AT, Greeley SAW, Polak M, et al. ISPAD clinical practice consensus guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes.* 2018;19 Suppl 27:47-63.
8. Ateş EA, Üstay Ö, Polat H, et al. Genetic and clinical characterization of patients with Maturity-Onset of Diabetes of the Young (MODY): Identification of novel variations. *Balkan Med J.* 2021;38(5):272-277.
9. Stride A, Shields B, Gill-Carey O, et al. Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations does not alter glycaemia. *Diabetologia.* 2014;57(1):54-56.
10. Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, Hattersley AT. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. *JAMA.* 2014;311(3):279-286.
11. Delvecchio M, Pastore C, Giordano P. Treatment options for MODY patients: A systematic review of literature. *Diabetes Ther.* 2020;11(8):1667-1685.
12. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet.* 2003;362(9392):1275-1281.
13. Shields BM, Shepherd M, Hudson M, et al. Population-Based Assessment of a Biomarker-Based Screening Pathway to Aid Diagnosis of Monogenic Diabetes in Young-Onset Patients. *Diabetes Care.* 2017;40(8):1017-1025.
14. Gloyn AL, Pearson ER, Antcliff JF, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med.* 2004;350(18):1838-1849.

15. Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med.* 2006;355(5):467-477.
16. Zung A, Glaser B, Nimri R, Zadik Z. Glibenclamide treatment in permanent neonatal diabetes mellitus due to an activating mutation in Kir6.2. *J Clin Endocrinol Metab.* 2004;89(11):5504-5507.
17. Bowman P, Sulen Å, Barbetti F, et al. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. *Lancet Diabetes Endocrinol.* 2018;6(8):637-646.
18. Beltrand J, Busiah K, Vaivre-Douret L, et al. Neonatal diabetes mellitus. *Front Pediatr.* 2020;8:540718.
19. De Franco E, Flanagan SE, Houghton JA, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet.* 2015;386(9997).
20. Angwin C, Jenkinson C, Jones A, et al. TriMaster: randomised double-blind crossover study of a DPP4 inhibitor, SGLT2 inhibitor and thiazolidinedione as second-line or third-line therapy in patients with type 2 diabetes who have suboptimal glycaemic control on metformin treatment with or without a sulfonylurea-a MASTERMIND study protocol. *BMJ Open.* 2020;10(12):e042784.
21. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol.* 2018;6(5):361-369.
22. Dennis JM, Shields BM, Henley WE, Jones AG, Hattersley AT. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol.* 2019;7(6):442-451.
23. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355(23):2427-2443.
24. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet.* 2009;373(9681):2125-2135.
25. Dennis JM. Precision medicine in type 2 diabetes: Using individualized prediction models to optimize selection of treatment. *Diabetes.* 2020;69(10):2075-2085.
26. Bernard C. TriMaster supports precision medicine strategy for type 2 diabetes treatment intensification. Published 2021. Accessed December 7, 2021.