High Prevalence of a Monogenic Cause in Han Chinese Diagnosed With Type 1 Diabetes, Partly Driven by Nonsyndromic Recessive *WFS1* Mutations

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Diabetes 2020;69:121–126 | https://doi.org/10.2337/db19-0510

It is estimated that ∼1% of European ancestry patients clinically diagnosed with type 1 diabetes (T1D) actually have monogenic forms of the disease. Because of the much lower incidence of true T1D in East Asians, we hypothesized that the percentage would be much higher. To test this, we sequenced the exome of 82 Chinese Han patients clinically diagnosed with T1D but negative for three autoantibodies. Analysis focused on established or proposed monogenic diabetes genes. We found credible mutations in 18 of the 82 autoantibody-negative patients (22%). All mutations had consensus pathogenicity support by five algorithms. As in Europeans, the most common gene was *HNF1A* (MODY3), in 6 of 18 cases. Surprisingly, almost as frequent were diallelic mutations in *WFS1*, known to cause Wolfram syndrome but also described in nonsyndromic cases. Fasting C-peptide varied widely and was not predictive. Given the 27.4% autoantibody negativity in Chinese and 22% mutation rate, we estimate that ∼6% of Chinese with a clinical T1D diagnosis have monogenic diabetes. Our findings support universal sequencing of autoantibody-negative cases as standard of care in East Asian patients with a clinical T1D diagnosis. Nonsyndromic diabetes with *WSF1* mutations is not rare in Chinese. Its response to alternative treatments should be investigated.

Genetic risk for diabetes is, in most cases, a complex trait. However, monogenic forms of diabetes do occur (1). These are often misdiagnosed as either type 1 (T1D) or type 2 diabetes—an error with therapeutic consequences, as in many of these cases patients can be treated with sulfonylureas or glucagon-like peptide 1 agonists, obviating insulin injections and improving metabolic control (2–4). Patients with pathogenic *GCK* variants can be treated only with lifestyle advice.

Correct diagnosis in patients clinically diagnosed with T1D (T1Dclin) is challenging. Because of the extremely high specificity of T1D autoantibodies, screening for autoantibody negativity is a meaningful first step. This narrows the search to ∼20% of T1Dclin patients, most of whom, however, still probably have autoimmune T1D (5). Family history is currently the most important clue, based on autosomal dominant inheritance (1). However, an "agnostic" testing of autoantibody-negative case subjects in the SEARH for Diabetes in Youth cohort found that 50% with documented monogenic diabetes had no family history (6). A similar testing in the Norwegian Childhood Diabetes Registry showed convincing evidence of monogenic diabetes in ∼4% of autoantibody-negative childhood-onset cases (T1Dclin in the vast majority) (7). Preserved endogenous insulin secretion has been proposed as a screening criterion (8), but it may not be reliable in T1Dclin cases. Given the substantial benefit to the individual patient, and with recent methodological advances in molecular diagnostics, a case can be made for universal testing of all autoantibody-negative T1Dclin patients. To

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Received 21 May 2019 and accepted 20 October 2019

This article contains Supplementary Data online at http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db19-0510/-/DC1.

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test this, we undertook sequencing in Chinese autoantibody-negative T1Dclin case subjects. T1D is much less common in East Asians (EA) (Chinese, Koreans, and Japanese) compared with Europeans (9). With a lower denominator, we hypothesized that the positive yield would be higher.

RESEARCH DESIGN AND METHODS

Participants

In the process of recruiting case subjects for the discovery stage of a T1D genome-wide association study (GWAS), the first in EA (10), we tested for autoantibodies in most of the 1,121 subjects (newly diagnosed, with BMI < 24 kg/m^2 and with at least one episode of ketosis; 586 male and 535 female). Informed consent was obtained from the patients or parents/guardians in a protocol approved by the ethics committee of The First Affiliated Hospital of Nanjing Medical University, in conformity with the Declaration of Helsinki.

Selection of Genes

We selected a broad list of monogenic diabetes genes from the literature (8) (Supplementary Table 1). To cover possible broad phenotypic heterogeneity, we included genes for neonatal and syndromic diabetes, e.g., *WFS1*, whose mutations might cause diabetes without other manifestations of Wolfram syndrome (WS) (11), and mtDNA 2967–3367.

Pancreatic Islet–Specific Autoantibody Testing

T1Dclin case subjects were tested for autoantibodies against GAD (GADA), islet antigen 2 (IA-2A), and ZnT8 (ZnT8A) by radioimmunoassay (12). Case subjects negative for all three were excluded from the GWAS and recruited for our project.

Whole-Exome Sequencing

Out of the 195 autoantibody-negative subjects available, 82 DNA samples that passed the quality control of the sequencing company were sequenced: (no significant degradation; quantity $\geq$500 ng). Capture was carried out with the Agilent SureSelect Human All Exon V6 library followed by sequencing on the Illumina HiSeq at a 100$\times$ depth by the Shanghai Yuanshen Company. Variants in known monogenic diabetes genes, called by either SAMtools or GATK, were filtered to retain only protein-altering variants (nonsynonymous, frameshift, in-frame insertions/deletions, canonical splicing) and exclude variants with a minor allele frequency (MAF) $\geq$0.0001 for missense, or $>$0.001 for truncating, in any population in three public databases (1000 Genomes, Exome Aggregation Consortium [ExAc], and Exome Variant Server). For recessive *WFS1*, the MAF threshold was 0.005. All results reported here were confirmed by Sanger sequencing. Variants were evaluated by five pathogenicity-prediction algorithms (Table 1) and classified by the revised ACMG/AMP (American College of Medical Genetics and Genomics/Association for Molecular Pathology) guidelines (13). For comparison, exome data from 866 unselected Han Chinese subjects, similarly sequenced for reasons other than diabetes, were also annotated.

To detect copy-number variants, we searched for extended genomic regions with loss of heterozygosity (LOH) in exome variants. Coverage (read counts) of exons in LOH regions was then compared between the patient with LOH and each other subject.

Identification of Mitochondrial Mutations

The 113 autoantibody-negative patients whose DNA sample was unsuitable for whole-exome sequencing (WES) were checked for mitochondrial variants. Briefly, total DNA was used as a template to amplify a target sequence of mtDNA (2966–3346) containing known Chinese mutations. PCR used were forward, TCAACAATAGGGTTTACGAC, and reverse, AGGAATGCCATTGCGATTAG, followed by Sanger sequencing.

Statistical Analysis

Given the known limitations of pathogenicity-prediction algorithms, we generated additional support for the variants discovered, and estimates of the false discovery rate, by comparing our case subjects with 866 Han Chinese without diabetes.

First, we compared the prevalence of all variants meeting the filtering criteria between our case exomes and the control exomes by the Fischer exact test for each gene separately.

In addition, we estimated the proportion of our positive findings that might be due to background variant frequency in the population by applying the expected proportion (P_{exp}) of carriers among the 866 control subjects to our 82 case subjects and comparing with the observed proportion (P_{obs}) (Supplementary Table 2).

The case and control exomes were sequenced by very similar workflows and at the same depth. To confirm similar variant yield per individual, we compared yields for synonymous variants. To also confirm identity of genetic background, we compared the two groups on the first two components of principal components analysis of synonymous variants.

Data and Resource Availability

The data sets generated and/or analyzed during the current study are available from the corresponding author upon request. The VCF (Variant Call Format) files generated during analyzed the current study are not publicly available due to Chinese policy that public sharing of genomic data is not allowed.

RESULTS

Of Chinese T1Dclin Patients, 27% Were Antibody Negative

By radioimmunoassay, 53.7%, 40.7%, and 33.8% of the patients were positive, respectively, for GADA, ZnT8A, and IA-2A. Negativity for all three radioimmunoassays was 27.4% (Supplementary Fig. 1).

Table 1—Genetic variants found in monogenic diabetes genes

Patient ID	Gene	Transcript ID	CDS change	AA change	Hom/ het	Age of diagnosis (years)	Family history	HbA_{1c} % (mmol/ mol)	FCP (pmol/L)	SNP 138	maxMAF	ExAC	gnomAD	Pathogenicity
1	*HNF1A*	NM_000545.5	c.1192C>G	p.Q398E	Het	20	No	NA	NA		0	—	—	D, D, N, D, D
2	*HNF1A*	NM_000545.5	c.865delC	p.P289fs	Het	12	Yes	9.1 (76)	NA		0.0007	0.0002	0.00006272	NA, NA, NA, NA, NA
3	*HNF1A*	NM_000545.5	c.686G>A	p.R229Q	Het	16	No	9.8 (84)	734.8		0	—	—	D, D, D, D, D
4	*HNF1A*	NM_000545.5	c.1512C>A	p.S504R	Het	4	No	12.3 (111)	49.56		0.0001	—	0.000008134	D, P, D, D, D
5	*HNF1A*	NM_000545.5	c.956-1G>C	.(splicing)	Het	12	No	7.4 (57)	6.8		0	—	—	NA, NA, NA, D, NA
6	*HNF1A*	NM_000545.5	c. 347C>T	p.A116V	Het	18	No	NA	426.24					D, D, D, D, D
7	*WFS1*	NM_006005.3	c.1096_1097 insAGGACAGCAAG	p.Q366fs	Het	9	No	15.6 (147)	170.16		0	—	—	NA, NA, NA, NA, NA
			c.1376T>G	p.L459R							0	—	—	D, D, D, D, D
8	*WFS1*	NM_006005.3	c.472G>A	p.E158K	Het	18	No	NA	111.7		0.0002	0.00001659	0.0000204	T, D, D, D, D
			c.985T>A	p.F329I						rs188848517	0.002	0.0001	0.0002	D, D, D, D, D
9	*WFS1*	NM_006005.3	c.1892C>T	p.S631F	Hom	5	No	NA	69.93		0	—	—	D, P, D, D, D
10	*WFS1*	NM_006005.3	c.472G>A	p.E158K	Het	22	No	NA	NA		0.0002	0.00001659	0.0000204	T, D, D, D, D
			c.985T>A	p.F329I						rs188848517	0.002	0.0001	0.0002	D, D, D, D, D
11	*ABCC8*	NM_000352.3	c.1834G>A	p.E612K	Het	29	Yes	NA	170.9		0.00003006	0.00001652	0.000008143	T, B, D, D, D
12	*ABCC8*	NM_000352.3	c.1811T>C	p.L604P	Het	14	No	14.2 (132)	NA		0	—	—	T, D, D, D, D
			c.793C>T	p.R265W							0	—	—	D, D, N, D, D
13	*INS*	NM_000207.2	c.94G>A	p.G32S	Het	7	Yes	16 (151)	166.5	rs80356664	0	—	—	D, D, D, D, D
14	*GCK*	NM_000162.3	c.665T>A	p.V222D	Het	3	Yes	6.1 (43)	314		0	—	—	D, D, D, D, D
15	*GCK*	NM_000162.3	c.661G>A	p.E221K	Het	36	No	NA	NA	rs193922317	0	—	—	T, D, D, D, D
16	*NEUROD1*	NM_002500.4	c.316G>A	p.A106T	Het	13	Yes	NA	399.6		0	—	—	D, D, D, D, D
17	*HNF1B*	NM_000458.2	WGD	WGD	Het	25	Yes	8.4 (68)	NA					NA, NA, NA, NA, NA
18	*HNF1B*	NM_000458.2	WGD	WGD	Het	14	No	13.7 (126)	480					NA, NA, NA, NA, NA

Fasting C-peptide (FCP), pmol/L. In the pathogenicity column, the results of evaluation algorithms are indicated in single-letter codes in this order: For SIFT (scale-invariant feature transform), D, deleterious; T, tolerated. For Polyphen-2, D, probably damaging; P, possibly damaging; B, benign. For LRT (likelihood ratio test), D, deleterious; N, neutral. For MutationTaster, D, disease causing; N, polymorphism. For LR, D, deleterious; T, tolerated. Reference list for previous reports of some mutations is provided in Supplementary Table 4. CDS, coding DNA sequence; gnomAD, Genome Aggregation Database; hom, homozygous; het, heterozygous, ID, identification number; maxMAF, maximum MAF; NA, not available; SNP, single nucleotide polymorphism; WGD, whole gene deletion.

Monogenic Diabetes in 22% of Chinese Autoantibody-Negative T1Dclin Patients

We had genomic DNA suitable for WES from 82 of these autoantibody-negative patients. Among these 82 exomes, the yield of synonymous variants per patient per gene was not significantly different from that of the 866 Chinese control subjects (mean ± SEM 0.72 ± 0.26 vs. 0.82 ± 0.32, respectively; $P = 0.81$). Principal components analysis, based on the exome variants, showed complete overlap of the two population samples (Supplementary Fig. 2). Of our 82 case subjects, 18 (22.0%) (95% CI 14.6–32.0) had variants likely to represent disease-causing mutations (Table 1)—a percentage several-fold higher than that reported with European ancestry cohorts defined by similar, though not identical, criteria (7,14). All were predicted to be pathogenic by three or more of the five algorithms. Variants in six patients met ACMG-AMP (13) criteria for very strong (PVS1) and another four for strong (PS3 or PS4) evidence of pathogenicity. All 18 had, at the very least, moderate pathogenicity evidence (PM2). It is important to note that these ratings rely on features other than computational prediction of pathogenicity, and, therefore, they constitute completely independent evidence. Three additional patients, not counted here, narrowly missed our predetermined MAF cutoff (Supplementary Table 3) but also likely have monogenic diabetes.

The most common gene mutated was *HNF1A* (maturity-onset diabetes of the young [MODY3]) with 6 of 18 patients. Two mutations were null, and one was absent from all databases. All were either truncating or rated deleterious/disease causing by four or all five of the five algorithms (Table 1). Some were previously reported with MODY3 (Supplementary Table 4). Among the 866 control subjects, there were only 2 patient with *HNF1A* variants meeting the same predetermined criteria. Thus, $P_{obs} = 7.3\%$ (95% CI 3.9–14.4) of autoantibody-negative T1Dclin Chinese patients have *HNF1A* mutations. P_{exp}, derived from the control subjects, was 0.2% (95% CI 0.08–0.4%) with $P = 6.5 \times 10^{-6}$, false discovery $q = 0.03$.

Somewhat surprisingly, almost as common as MODY3 were diallelic variants of *WFS1*, recessively mutated in WS, in four case subjects not reported to have any other syndromic features and initially recruited for the T1D GWAS. One was homozygous, and in another two cases, the two variants were close enough to be confirmed in *trans* by alignment inspection (Supplementary Fig. 3). All of these variants were rated deleterious by at least four of the five algorithms, and two have previously been reported in cases of fully expressed WS (Supplementary Table 4). Only one of the 866 control subjects had two missense mutations, both predicted benign by all five algorithms. For 4 of 82 vs. 0 of 866, $P_{obs} = 4.9\%$ (95% CI 2.4–11.1) vs. $P_{exp} = 0\%$ (95% CI 0–0.6), $P = 6.5 \times 10^{-6}$, false discovery $q = 0$. Thus, by our best estimate, 5% of autoantibody-negative Chinese T1Dclin case subjects have nonsyndromic diabetes due to WFS1 mutations.

One patient was thoroughly examined and found to be normal by fundoscopic eye exam, audiogram, and urine density (Supplementary Fig. 4), confirming the reported absence of other WS manifestations (optic nerve atrophy, hearing loss, and diabetes insipidus) in that case.

The remaining six patients had mutations in other MODY genes (Table 1), but the numbers were too small for statistics (Supplementary Table 2). Two patients had mutations in *KLF11* (MODY7) and *PAX4* (MODY9), OMIM (Online Mendelian Inheritance in Man) genes whose role in monogenic diabetes remains unconfirmed. Only one *KLF11* mutation met pathogenicity-prediction criteria, versus two control subjects ($P = 0.25$), not providing support for this gene. *NEUROD1* is better established as the cause of MODY6 (15) and supported by our finding of a mutation in one patient (deleterious by all 5 algorithms) vs. 0 of 866 control subjects. Other well-established genes found to be mutated were *HNF1B*, *ABCC8*, and *GCK* (each in two patients) and *INS* (one patient).

Both *HNF1B* mutations were complete gene deletions within the known recurrent microdeletion at 17q22, reported to account for as many as 50% of MODY5 cases (16). The two patients had LOH over at least 1.4 Mb that encompassed *HNF1B* among 28 genes (Fig. 1, top). Over the LOH region in each patient, each of 178 exons had approximately half the read counts of the average of all other patients (Fig. 1, bottom); $P = 7.5 \times 10^{-15}$ and 1×10^{-16} for patients 17 and 18, respectively. Adjacent to the deletion, there were no shared haplotypes, indicating independent occurrence in two different ancestral chromosomes.

Fasting C-peptide, available in 56 of 82 patients, varied widely and was no different between patients with or without a mutation (mean 249.5 vs. 280.5, $P = 0.6699$). (Supplementary Fig. 5*A*).

For the 82 patients (37 females), the median age at diagnosis was 20 years (range 1–61). Patients with mutations were younger: median age at diagnosis 13.5 vs. 23.2 years ($P = 0.0297$) (Supplementary Fig. 5*B*).

In a parallel study, 126 T1Dclin autoantibody-negative patients, including 44 whose DNA sample was unsuitable for WES, were tested for mtDNA mutations by Sanger sequencing. Four had the m.3243A>G mutation and two the m.3316A>G, both previously reported in Chinese patients with diabetes (17,18). Heteroplasmy, estimated from the sequencing peaks, ranged from 6.2 to 50.4% (Supplementary Table 5)—well within the described range (19).

The distribution of genetic causes of 18 confirmed cases of monogenic diabetes and 6 cases of mitochondrial diabetes is shown in Supplementary Fig. 6.

DISCUSSION

With 27.4% of Chinese T1Dclin patients being autoantibody negative, and 22.0% having monogenic diabetes, our best estimate for the overall prevalence of monogenic diabetes in patients diagnosed with T1D is 6%, which is considerably higher than the ~1% reported in comparable childhood cohorts of European descent (6,7). In the U.K.,

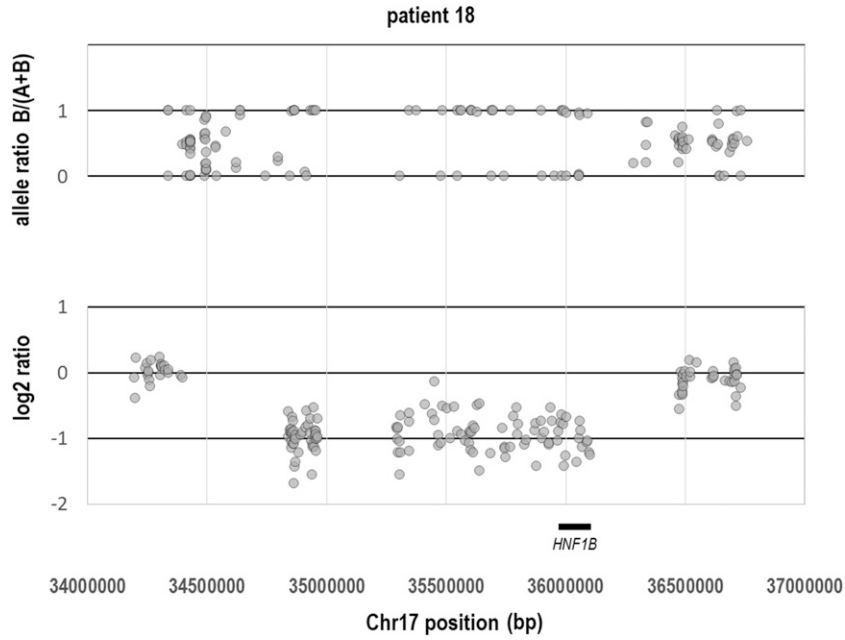

Figure 1—Demonstration of the 17q22 microdeletion that encompasses *HNF1B* in patient 18. Top: LOH. A plot of the proportion of reads for one of the two alleles calculated as B / (A + B), where A and B are the read counts for each allele (by the Illumina convention, the nonreference nucleotide is called A if it is A or T and is otherwise called B). Homozygotes cluster around 0 or 1 and heterozygotes around 0.5. Complete LOH can be seen over 1.4 Mb. Only positions with at least one nonreference allele are shown (all others are homozygous reference). Bottom: Copy number over the LOH region in each patient was estimated by comparing read counts at each exon (normalized as counts per million) with the average of all other patients. With division by that average, intact DNA clusters around 1 and heterozygous deletion around 0.5. To harmonize with the conventional display from microarray data, we plotted the ratio as base 2 log (intact DNA is 0, and heterozygous deletion is −1). Only exons with ≥50 mapped reads are included. A heterozygous deletion is clearly demonstrated over the LOH; $P = 10^{-16}$ by paired *t* test comparing each exon with the average of all other patients. bp, base pair; Chr, chromosome.

3.6% was reported among patients chosen for preserved C-peptide (8)—a very different population from our T1Dclin case subjects. Our results show that C-peptide cannot distinguish monogenic cases presenting with a clinical picture leading to the diagnosis of T1D.

This percentage is even higher if we add the mitochondrial cases. Such high incidence is not surprising, given that the denominator (autoimmune T1D) is much less common in EA. These findings make a strong argument for universal autoantibody testing of all Chinese (and, arguably, Korean and Japanese) T1Dclin patients with sequencing of the autoantibody-negative cases. Studies similar to ours in European ancestry patients may also reveal monogenic diabetes rates substantially higher than currently reported if diallelic WFS1 mutants are included. Despite the low yield and high cost, the benefit to individual patients may well justify the expense, as most of these monogenic diabetes cases are amenable to alternative treatments.

Our other important finding is the high prevalence of nonsyndromic *WFS1* cases, much more common than WS and comparable with that reported in consanguineous families in Lebanon (11), in a nonconsangineous population. Nonsyndromic diabetes has also been reported with homozygosity for a nonsynonymous variant frequently found in Ashkenazi Jewish individuals (20), but it is clearly not confined to that variant. The therapeutic implications of this diagnostic reassignment remain to be seen, but successful use of incretin interventions has been reported (21,22). It should definitely be included in all monogenic diabetes panels.

We expect that these preliminary findings will stimulate much larger studies in various populations to better define the prevalence of monogenic diabetes in agnostic searches. Despite the limitations of our study, including small sample size (counterbalanced by the large effect size and highly significant results) and lack of detailed phenotype data (a convenience sample collected for a different purpose), we propose that our findings will apply to the vast majority of T1Dclin cases and justify serious consideration of agnostic screening of all EA diagnosed with T1D.

Acknowledgments. The authors thank all patients who consented to participate in the study. For valuable technical assistance, the authors thank Min Shen and Yingjie Feng from The First Affiliated Hospital of Nanjing Medical University.

Funding. The study was supported by grants from the National Natural Science Foundation of China (81830023, 81270897, and 81670715) and the Key Research and Development Program of the Science and Technology Commission Foundation of Jiangsu Province (SBE2017750381). Zhejiang MaiDa Gene Tech Co., Ltd., is indebted to the 5313 Leading Talents Project of Zhoushan, China, for generous funding of this project.

Duality of Interest. This study is supported by Zhejiang MaidaGene Technology Co., Ltd. M.L., S.W., X.H., Y.L., Z.T., L.C. and C.P. are employees, and M.L. a shareholder, of Zhejiang MaiDa Gene Tech Co., Ltd., a publicly funded for-profit corporation that will be offering genetic testing services. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. M.L. helped with the study design and interpretation of results and wrote the manuscript. S.W. performed the bioinformatic analysis of the exome sequencing data. K.X. summarized clinical information of T1Dclin patients from 11 hospitals and helped with correcting the manuscript. Y.C., Q.F., Y.G., Yu.S., M.Z., and M.S. are clinicians who recruited the T1Dclin patients. H.C. tested the pancreatic autoantibodies. X.H., Z.T., and L.C. carried out the Sanger sequencing of all WES variants. X.H. designed the PCR primers for each variant. Y.L. participated in the writing and corrections of the manuscript. Z.L. and Yo.S. collected the control sequencing data from 866 WES for the selected genes. T.Y. and C.P. developed the study concept and supervised the study. T.Y. and C.P. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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