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Brief Report

Monogenic diabetes in Japan and India: A call for broader screening

Masashi Hasebe [a,b,c,1], Venkatesan Radha [d,1], Anandakumar Amutha [d], Daisuke Tanaka [a,e], Toshinori Imaizumi [a], Daisuke Yabe [a], Satoshi Yoshiji [a,b,2,*], Nobuya Inagaki [a,c,2,*], Viswanathan Mohan [d,f,2,*], on behalf of PAN INDIA Monogenic Study Collaborators Group and Japan Diabetes Society Monogenic Diabetes Committee

[a] Department of Diabetes, Endocrinology and Nutrition, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan
[b] Department of Human Genetics, McGill University, Montréal, Québec H3A 0G1, Canada
[c] Department of Diabetes and Endocrinology, Medical Research Institute KITANO HOSPITAL, PIIF Tazuke-Kofukai, Osaka 530-8480, Japan
[d] Madras Diabetes Research Foundation (ICMR Collaborating Centre of Excellence), Chennai, Tamil Nadu 600 086, India
[e] Department of Diabetes and Endocrinology, Shiga General Hospital, Shiga 524-8585, Japan
[f] Dr. Mohan's Diabetes Specialities Centre (IDF Centre of Excellence in Diabetes Care), Chennai, Tamil Nadu 600 086, India

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ABSTRACT

Nationwide cohorts from Japan and India show monogenic diabetes is present in a considerable proportion of young, non-obese individuals with diabetes. Clinical presentations are heterogeneous; notably, only up to ~ 70% of cases had three-generation family history. These findings call for broader genetic testing in Asia beyond classical clinical screening criteria.

1. Introduction

Monogenic diabetes, of which maturity-onset diabetes of the young (MODY) is the most common form, accounts for approximately 0.4% of all diabetes cases overall, with higher proportions reported in selected young-onset cohorts [1,2]. These estimates derive largely from Europe and the US, where dedicated diagnostic services and registry-based efforts have facilitated systematic ascertainment and follow-up [3–5]. However, comparable nationwide diagnostic infrastructures are limited in many Asian countries, and as a result the prevalence and clinical spectrum of monogenic diabetes remain insufficiently characterized [6].

Timely genetic diagnosis of monogenic diabetes is crucial because genotype-guided management enables individualized care. For instance, *GCK*-MODY generally does not require pharmacologic treatment because hyperglycemia reflects a higher glycemic set point and therefore does not typically respond to glucose-lowering therapy, with a low risk of complications [7]. *HNF1A*- and *HNF4A*-MODY usually respond well to sulfonylureas, often allowing insulin withdrawal [8]. In addition, recent evidence suggests that incretin-based therapies and sodium–glucose cotransporter 2 inhibitors may provide additional glycemic benefits in selected individuals with *HNF1A*- and *HNF4A*-MODY, although robust, systematic evidence remains lacking [9–13]. By contrast, *HNF1B*-MODY is generally characterized by poor sulfonylurea responsiveness, early insulin requirement, and progressive kidney disease [14]. Other subtypes, such as those caused by variants in the K_{ATP} channel genes *ABCC8* or *KCNJ11*, can often be effectively managed with sulfonylureas instead of insulin, particularly in neonatal-onset cases [8]. Nevertheless, despite the clear potential of genotype-guided therapy,

* Corresponding authors at: Madras Diabetes Research Foundation (ICMR Collaborating Centre of Excellence), Dr. Mohan's Diabetes Specialities Centre (IDF Centre of Excellence in Diabetes Care), No 4, Conran Smith Road, Gopalapuram, Chennai 600 086, India (Viswanathan Mohan). Department of Diabetes and Endocrinology, Medical Research Institute KITANO HOSPITAL, PIIF Tazuke-Kofukai, Osaka 530-8480, Japan (Nobuya Inagaki). Department of Human Genetics, McGill University, 740 Avenue Dr. Penfield, Montréal, Québec H3A 0G1, Canada (Satoshi Yoshiji).

E-mail addresses: mhasebe@kuhp.kyoto-u.ac.jp (M. Hasebe), radharv@yahoo.co.in (V. Radha), amuthanandh@gmail.com (A. Amutha), datanaka@kuhp.kyoto-u.ac.jp (D. Tanaka), imaizumits@kuhp.kyoto-u.ac.jp (T. Imaizumi), ydaisuke@kuhp.kyoto-u.ac.jp (D. Yabe), satoshi.yoshiji@mcgill.ca (S. Yoshiji), inagaki@kuhp.kyoto-u.ac.jp (N. Inagaki), drmohans@diabetes.ind.in (V. Mohan).

[1] Masashi Hasebe and Venkatesan Radha contributed equally to this work as co-first authors.
[2] Satoshi Yoshiji, Nobuya Inagaki, and Viswanathan Mohan jointly supervised this work.

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many monogenic diabetes cases are likely missed due to limited access to genetic testing and the absence of standardized screening criteria [15,16]. These barriers are particularly pronounced in Asian populations, partly because many screening criteria and prediction tools have been developed and validated mainly in predominantly European-ancestry cohorts [17]. Furthermore, monogenic diabetes is increasingly recognized as having diverse clinical presentations, which can complicate case identification [18,19].

Recently, our groups independently reported two nationwide cohorts of monogenic diabetes from Asia: the Japan Diabetes Society (JDS) study from Japan and the PAN INDIA study from India, both conducted through specialist networks [20,21]. Both studies focused on young, non-obese individuals with diabetes considered unlikely to have type 1 diabetes and applied targeted sequencing panels of monogenic diabetes genes. However, important differences existed between the cohorts in genetic, sociocultural, and healthcare contexts. We compared the JDS and PAN INDIA studies to identify shared and context-specific features that could inform screening strategies in Asia and beyond. To improve comparability, variant interpretation was standardized using the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) criteria, with available gene-specific specifications from the ClinGen Monogenic Diabetes Variant Curation Expert Panel (VCEP) [22,23]. We harmonized core variables, summarized diagnostic yield and gene distributions, and contrasted age at diabetes diagnosis, body mass index (BMI), glycated hemoglobin (HbA1c), and family history within each country's context. This observational, cross-sectional comparative study provides a harmonized comparison of the two cohorts and considers their clinical implications for screening.

2. Materials and methods

2.1. Study design and cohorts

The JDS cohort enrolled individuals who developed diabetes before the age of 35, had a BMI below 30 kg/m^2, and tested negative for islet autoantibodies. Participants were recruited through referrals from pediatric and adult diabetes specialists across Japan between 2019 and 2024. A family history of diabetes was not required, allowing the inclusion of sporadic or low-penetrance cases [24,25]. The age threshold of 35 years was selected to align with commonly used definitions of young-onset diabetes, as in the development and validation of the MODY probability calculator [26].

The PAN INDIA study is a nationwide network of 65 diabetes clinics across India, coordinated by Dr. Mohan's Diabetes Specialities Centre and the Madras Diabetes Research Foundation in Chennai, where most participants were enrolled. For the present collaborative analysis, we included only individuals who were referred to and evaluated at these centers. These individuals met the eligibility criteria of the PAN INDIA study, which included age at diagnosis of 30 years or younger, BMI $\leq$ 30 kg/m^2, parental history of diabetes, and absence of ketonuria; preserved C-peptide and negative islet autoantibodies were assessed as optional screening measures. Both studies received approval from the relevant institutional review boards, and written informed consent was obtained from all participants or their legal guardians. Clinical and biochemical information was collected in both cohorts as comprehensively as feasible under each study's protocol. Methodological details are provided in the respective primary publications [20,21]. For the present analysis, we restricted analyses to unrelated probands.

2.2. Genetic testing and variant interpretation

In the JDS cohort, targeted sequencing covered exons and flanking intronic regions of 11 genes (*ABCC8, GCK, HNF1A, HNF1B, HNF4A, INS, INSR, KCNJ11, NEUROD1, PDX1*, and *WFS1*). The panel was deliberately restricted to genes with well-established clinical validity and therapeutic relevance in Japan. Genes with limited evidence for a causal role in monogenic diabetes (e.g., *BLK*, *KLF11*, *APPL1*) were not included [8,27], whereas *INSR* was included given reports from Japanese cohorts of young-onset, non-obese diabetes due to heterozygous variants [28,29]. For individuals with deafness, testing for the mitochondrial m.3243A>G variant was performed at the referring institutions, and only those with negative results were enrolled in the JDS cohort. The PAN INDIA study used a broader custom panel comprising 75 genes relevant to monogenic diabetes, including the mitochondrial gene *MT-TL1*.

Given the evolving nature of variant interpretation, we updated variant classifications for this comparative analysis, and some classifications therefore differ from those in the original cohort publications [20,21]. For both cohorts, variants were classified using the ACMG/AMP guidelines [22]. For genes with available gene-specific specifications from the ClinGen Monogenic Diabetes VCEP (*GCK*, *HNF1A*, and *HNF4A*), we interpreted variants using those specifications to guide criteria application and strength assignment [23]. For other genes, we applied the ACMG/AMP guidelines with relevant ClinGen Sequence Variant Interpretation Working Group recommendations, generally favoring lower evidence strengths where appropriate [30]. Copy-number variations (CNVs) and mitochondrial DNA variants were interpreted using the ACMG/ClinGen constitutional CNV technical standards [31] and the ClinGen ACMG/AMP mtDNA specifications [32], respectively. Two independent clinicians reviewed the evidence and reached consensus on the final classification. Variants classified as pathogenic or likely pathogenic (P/LP) were considered disease-causing, whereas variants classified as of uncertain significance (VUS), likely benign, or benign were not. Where available, findings were confirmed with bidirectional Sanger sequencing.

In the JDS cohort, when no P/LP variant was detected by sequencing, multiplex ligation-dependent probe amplification (MLPA) was performed for the same genes (excluding *INSR*) in participants with features suggestive of *HNF1B*-MODY, including renal cysts, urogenital malformations, or pancreatic hypoplasia/aplasia, because whole-gene deletions are a common cause of *HNF1B*-MODY [33]. In the PAN INDIA cohort, MLPA was performed in selected cases with targeted sequencing findings suggestive of CNVs.

2.3. Data collection and cross-cohort comparison

Both cohorts provided data on genetic findings, family history, and clinical characteristics. For each study, we calculated the proportion of probands diagnosed with monogenic diabetes (diagnostic yield) and summarized the distribution of P/LP variants across genes. For autosomal recessive disorders, individuals were classified as having monogenic diabetes only when biallelic P/LP variants (homozygous or compound heterozygous) in the corresponding gene were identified. Among monogenic diabetes cases, we assessed the presence of a family history of diabetes spanning three successive generations, which is part of the classical screening criteria for monogenic diabetes [34]. For clinical comparisons, data were analyzed for probands with P/LP variants in transcription factor genes (*HNF1A*, *HNF1B*, and *HNF4A*), including only those with available data for each variable. Variables included age at diagnosis, BMI, and HbA1c.

Comparisons between the JDS and PAN INDIA cohorts examined the proportion of monogenic diabetes cases, the distribution of affected major genes (*GCK*, *HNF1A*, *HNF4A*, and *HNF1B*), the proportion of those with a three-generation family history among monogenic diabetes cases, and clinical characteristics of probands according to genotype. Given inherent differences between the cohorts, these comparisons were considered exploratory.

2.4. Statistical analysis

Analyses were performed using R version 4.4.1 (R Foundation for

Statistical Computing, Vienna, Austria).

Categorical variables were summarized as counts and percentages. Continuous clinical variables (age at diagnosis, BMI, HbA1c) were summarized as median with interquartile range (IQR). Categorical variables were compared between cohorts using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared within genotype strata using Welch's *t*-test or the Wilcoxon rank-sum test, as appropriate according to their distribution. All tests were two-sided, and *P* values < 0.05 were considered statistically significant.

3. Results

3.1. Genetic findings across cohorts

Monogenic diabetes was confirmed in 23.3% (54/232) of the JDS cohort and 7.3% (49/675) of the PAN INDIA cohort, with a significantly higher diagnostic yield in the JDS cohort ($P < 0.001$; Fig. 1). Among monogenic diabetes cases, the proportion of *GCK*-MODY differed substantially, with 40.7% (22/54) in the JDS cohort compared with 2.0% (1/49) in the PAN INDIA cohort ($P < 0.001$; Fig. 2). *HNF1A*-MODY was common in both cohorts, representing 40.7% (22/54) of monogenic diabetes cases in the JDS cohort and 26.5% (13/49) in the PAN INDIA cohort ($P = 0.13$). There were no statistically significant differences in the proportions of *HNF4A*-MODY (9.3% vs 12.2%, $P = 0.62$) and *HNF1B*-MODY (9.3% vs 20.4%, $P = 0.11$), although both subtypes were numerically more frequent in the PAN INDIA cohort. Lists of all identified P/LP variants, including the applied ACMG/AMP evidence codes and their rationale, are provided in Supplementary **Table S1** for the JDS cohort and **Supplementary Table S2** for the PAN INDIA cohort. A comparative summary of monogenic diabetes proportions and gene-level distributions between the two cohorts is presented in Table 1.

3.2. Three-generation family history

Among probands with monogenic diabetes, 68.5% (37/54) in the JDS cohort and 38.8% (19/49) in the PAN INDIA cohort reported diabetes in three consecutive generations (Fig. 3). Despite the PAN INDIA cohort requiring a parental history for inclusion, the proportion with a three-generation family history was significantly lower than in the JDS cohort ($P = 0.002$).

3.3. Clinical characteristics of probands according to genotype

Across both cohorts, probands with *HNF1A*-MODY, *HNF4A*-MODY, and *HNF1B*-MODY exhibited substantial heterogeneity in age at diagnosis, BMI, and HbA1c. Broad distributions were seen within each genotype group, and considerable overlap was observed across groups (Fig. 4).

Age at diagnosis was similar between cohorts for *HNF1A*-MODY and *HNF4A*-MODY, whereas probands with *HNF1B*-MODY in the PAN INDIA cohort were diagnosed at a younger age than those in the JDS cohort ($P = 0.013$; Fig. 4**A**). BMI did not differ significantly between cohorts for any subtype (all $P \geq 0.05$; Fig. 4**B**). Notably, HbA1c levels were consistently higher in the PAN INDIA cohort than in the JDS cohort across all three subtypes (Fig. 4**C**), although the difference reached statistical significance only for *HNF1B*-MODY ($P = 0.020$). All related results are summarized in **Supplementary Table S3**.

4. Discussion

In this comparative study of two referral-based Asian cohorts of monogenic diabetes, monogenic diabetes was confirmed in 23.3% of the Japanese cohort and 7.3% of the Indian cohort. The yield in the Japanese cohort was comparable to that reported in referral-based European studies, where suspected MODY cohorts have generally shown diagnostic yields of approximately 16% to 23% [17]. By contrast, the yield in the Indian cohort was lower than that range. These findings indicate that systematic genetic testing can identify monogenic diabetes in a clinically meaningful proportion of young, non-obese individuals with diabetes in Asian populations. Notably, only about two-thirds of genetically confirmed cases in Japan and one-third in India reported diabetes across three generations, highlighting the limited reliability of this criterion for

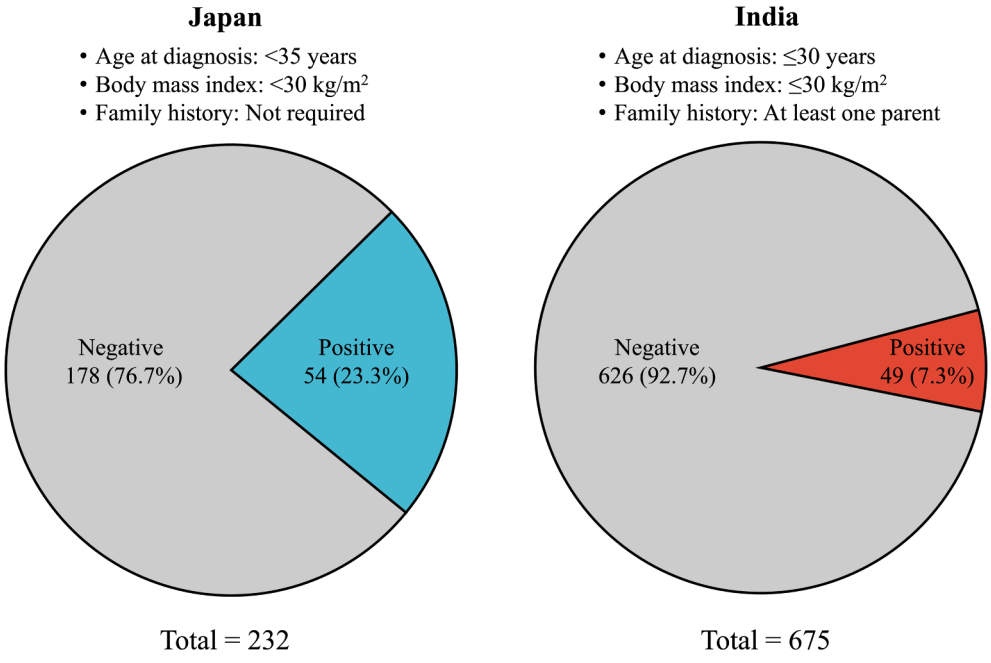

Fig. 1. Proportion of probands with monogenic diabetes in referral-based cohorts from Japan and India. Bulleted items above each panel indicate the inclusion criteria for each cohort.

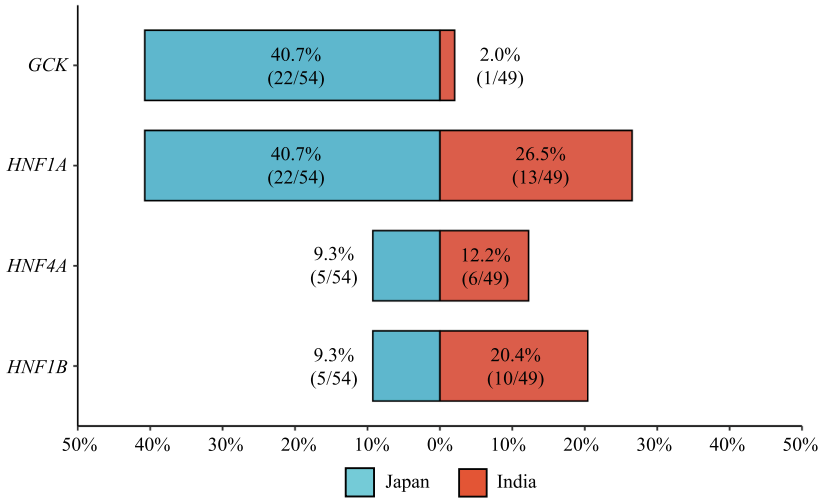

Fig. 2. Distribution of affected genes among probands with monogenic diabetes in referral-based cohorts from Japan and India. Percentages and counts represent the proportion (*n/N*) of probands with variants in each major gene (*GCK*, *HNF1A*, *HNF4A*, and *HNF1B*) among all probands with monogenic diabetes in each cohort (Japan, $N = 54$; India, $N = 49$).

Table 1
Proportion of genetically confirmed monogenic diabetes and distribution of monogenic diabetes genes in the JDS and PAN INDIA cohorts.

Group	Gene or condition	JDS, *n* (%)*	PAN INDIA, *n* (%)*	*P*
Overall proportion	Monogenic diabetes	54/232 (23.3)	49/675 (7.3)	<0.001
MODY genes	*GCK*	22/54 (40.7)	1/49 (2.0)	<0.001
	HNF1A	22/54 (40.7)	13/49 (26.5)	0.13
	HNF4A	5/54 (9.3)	6/49 (12.2)	0.62
	HNF1B	5/54 (9.3)	10/49 (20.4)	0.11
Other MODY genes	*INS*	0/54 (0.0)	1/49 (2.0)	–
Other monogenic forms of diabetes	*WFS1*-related diabetes	0/54 (0.0)	4/49 (8.2)	–
	MIDD	Not assessed	10/49 (20.4)	–
	H syndrome	Not assessed	4/49 (8.2)	–

* For the overall proportion row, percentages are calculated using all probands tested in each cohort as the denominator. For all other rows, percentages are calculated among probands with genetically confirmed monogenic diabetes.
The table compares the proportion of genetically confirmed monogenic diabetes and the distribution of monogenic diabetes genes in the JDS and PAN INDIA cohorts. Overall proportions were calculated using all tested probands as the denominator, whereas gene-level distributions were calculated among genetically confirmed cases. *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, and *INS* are MODY genes. Other monogenic forms of diabetes in this table include disorders caused by P/LP variants in *WFS1* (*WFS1*-related diabetes), the m.3243A>G mitochondrial variant (MIDD), and *SLC29A3* (H syndrome). *WFS1*-related diabetes and H syndrome denote diabetes associated with biallelic P/LP variants in *WFS1* and *SLC29A3*, respectively. The PAN INDIA cohort consists only of probands who were referred to Dr. Mohan's Diabetes Specialities Centre and the Madras Diabetes Research Foundation in Chennai. *P* values were obtained using the chi square test or Fisher's exact test, as appropriate.
Abbreviations: JDS, Japan Diabetes Society; MIDD, maternally inherited diabetes and deafness; MODY, maturity-onset diabetes of the young; P/LP, pathogenic or likely pathogenic.

screening. Clinical characteristics likewise varied widely within and across genotypes, underscoring the heterogeneous presentation of monogenic diabetes. Together, these findings highlight the importance of offering genetic testing for suspected cases in Asian populations without overreliance on family history or isolated clinical features.

4.1. Comparative findings and clinical interpretation

The lower overall yield in the PAN INDIA cohort, despite using a broader gene panel, may reflect differences in ascertainment rather than panel content. A major factor is the relative paucity of *GCK*-MODY, which may be explained by differences in case detection: in Japan, cases were often identified incidentally through school health checks or screening, whereas in India, recruitment was hospital-based and mainly involved symptomatic individuals. Because *GCK*-MODY—one of the most prevalent subtypes of monogenic diabetes—typically presents with a mild and stable phenotype, such cases are less likely to be detected through hospital-based recruitment [35]. Consistent with this, among monogenic diabetes cases, subtypes with more overt or syndromic presentations, such as *HNF1B*-MODY and *WFS1*-related diabetes, were more frequent in the PAN INDIA cohort. However, a previous UK study also suggested that factors beyond ascertainment may contribute to lower positive testing rates in referred individuals of South Asian origin [36]. Such factors may include the high burden of young-onset type 2 diabetes in South Asian populations, which could reduce the relative contribution of monogenic diabetes in hospital-based cohorts [37,38]. Overall, these observations indicate that the frequency of monogenic diabetes can be influenced by healthcare systems, recruitment, and clinical contexts.

A three-generation family history of diabetes is part of the classical screening criteria for monogenic diabetes [34], yet both cohorts showed that it is an imperfect indicator. Family history was not an inclusion criterion in the JDS cohort, whereas the PAN INDIA cohort required a parental history; nevertheless, three-generation history was reported more often in Japan than in India among genetically confirmed cases (Fig. 3). This difference may reflect variable penetrance, recall or documentation issues, and differences in data collection or healthcare context [25,39,40]. In addition, because both the JDS and PAN INDIA cohorts are referral cohorts enriched for suspected monogenic diabetes, the proportion of patients with a three-generation family history would be expected to be higher than in the general population. Even in this

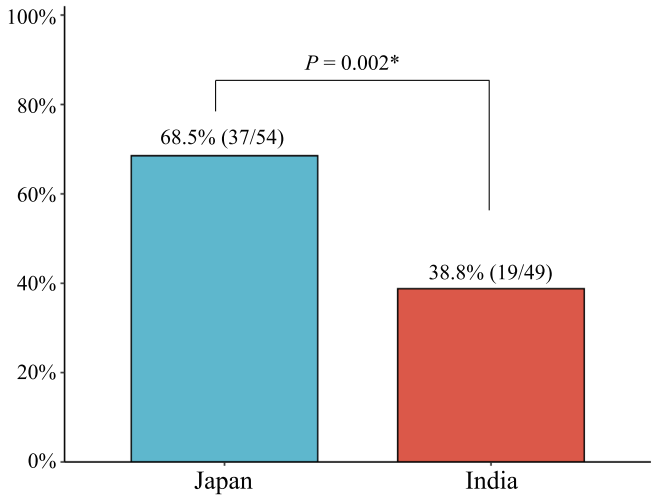

Fig. 3. Proportion of probands with a three-generation family history of diabetes among monogenic diabetes cases in referral-based cohorts from Japan and India. Percentages and counts indicate the proportion of probands with pathogenic or likely pathogenic variants who reported diabetes in three consecutive generations. The difference between cohorts was statistically significant ($P = 0.002$).

setting, however, only 68.5% of monogenic diabetes cases in the JDS cohort and 38.8% in the PAN INDIA cohort had a documented three-generation family history of diabetes. This suggests that in a population-based cohort the proportion would likely be even lower. Taken together, these findings imply that many genetically confirmed cases would have been missed if screening had relied solely on this criterion, and that the absence of a three-generation family history should not deter clinicians from pursuing genetic testing when clinical suspicion is present. This limitation is particularly relevant because a family history is often absent in sporadic cases arising from de novo variants and in autosomal recessive conditions. Nevertheless, family history, which reflects clinically reported diabetes rather than genotyped co-segregation, remains useful to identify relatives for formal segregation testing under ACMG/AMP criteria (PP1, BS4) and is recommended to be collected across three or more generations in clinical practice [22,41]. Its interpretation, however, should take account of generational and practical limitations.

Both cohorts demonstrated substantial heterogeneity in age at diagnosis, BMI, and HbA1c among probands with monogenic diabetes, with wide overlap across genotype groups (Fig. 4). These findings suggest that no single clinical measure can reliably distinguish monogenic from non-monogenic diabetes. Differences in age at diagnosis and BMI between cohorts were generally modest and inconsistent across subtypes. In contrast, HbA1c was consistently higher in the Indian cohort, which may reflect factors beyond ascertainment, including polygenic, environmental, or healthcare-related influences [42,43]. Taken together, these factors may help explain both the inter-cohort differences and the heterogeneity observed within individual subtypes. Recognizing this complexity underscores the importance of broader access to genetic testing, as relying on clinical features alone risks missing affected individuals.

4.2. Toward broader screening and implementation

Building on the Japanese and Indian referral-based cohorts, our findings support broader consideration of genetic testing in Asian populations beyond classical screening criteria for monogenic diabetes. Testing could reasonably be offered to individuals diagnosed before the age of 35 years who do not have obesity (e.g., BMI < 30 kg/m^2), irrespective of family history, which is often an imperfect indicator due to incomplete penetrance and/or limited information. Because BMI thresholds used to define obesity and related risk vary across populations [44], ancestry-specific BMI cut-points may be considered. Ideally, testing should follow confirmation of preserved C-peptide and negative islet autoantibodies. Where laboratory testing is not readily available, practical substitutes such as the absence of ketonuria can help identify candidates for testing. The threshold for testing may also be lowered when characteristic subtype features are present, such as renal cysts suggestive of *HNF1B*-MODY [14].

To enable such broader screening, effective strategies in Asia will require both clinically usable, validated tools to help identify individuals for genetic testing and greater clinical awareness. Experience from the UK shows that the introduction and wider use of the MODY probability calculator facilitated a steady rise in identified cases [3]. However, because its performance remains limited in non-European populations [20,45], region-specific prediction models calibrated for Asian populations will be essential. Such models will need to rely on readily available clinical variables at the point of care and be easy to integrate into routine workflows to guide referrals. Equally important is promoting awareness of monogenic diabetes among healthcare professionals. Educational initiatives that emphasize the heterogeneous and sometimes mild presentations of monogenic diabetes can prevent missed diagnoses. Multidisciplinary approaches, such as the Genetic Diabetes Nurse program in the UK, have been associated with sustained improvements in diagnostic yield [3].

Broader implementation also requires careful consideration of panel design and variant interpretation. For initial testing, prioritizing well-established, actionable genes (e.g., *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *ABCC8*, *KCNJ11*) can improve specificity, with stepwise expansion to larger panels if first-tier testing is negative, since adding very rare candidates may increase complexity without improving yield [29]. Interpreting variants can be particularly difficult in non-classical presentations or for genes with limited evidence of pathogenicity. Large European biobank–based studies have indicated that pathogenicity for several non-major genes remains uncertain, warranting caution in broader screening contexts [27,46]. Because current evidence on gene–disease associations and penetrance largely derives from European-ancestry populations, region-specific analyses using Asian biobank and disease-cohort resources will be important to refine gene lists and screening criteria.

4.3. Variant interpretation and case classification

Compared with the original cohort reports [20,21], fewer variants were classified as P/LP after reclassification using ACMG/AMP criteria, available ClinGen gene-specific specifications, and relevant ClinGen

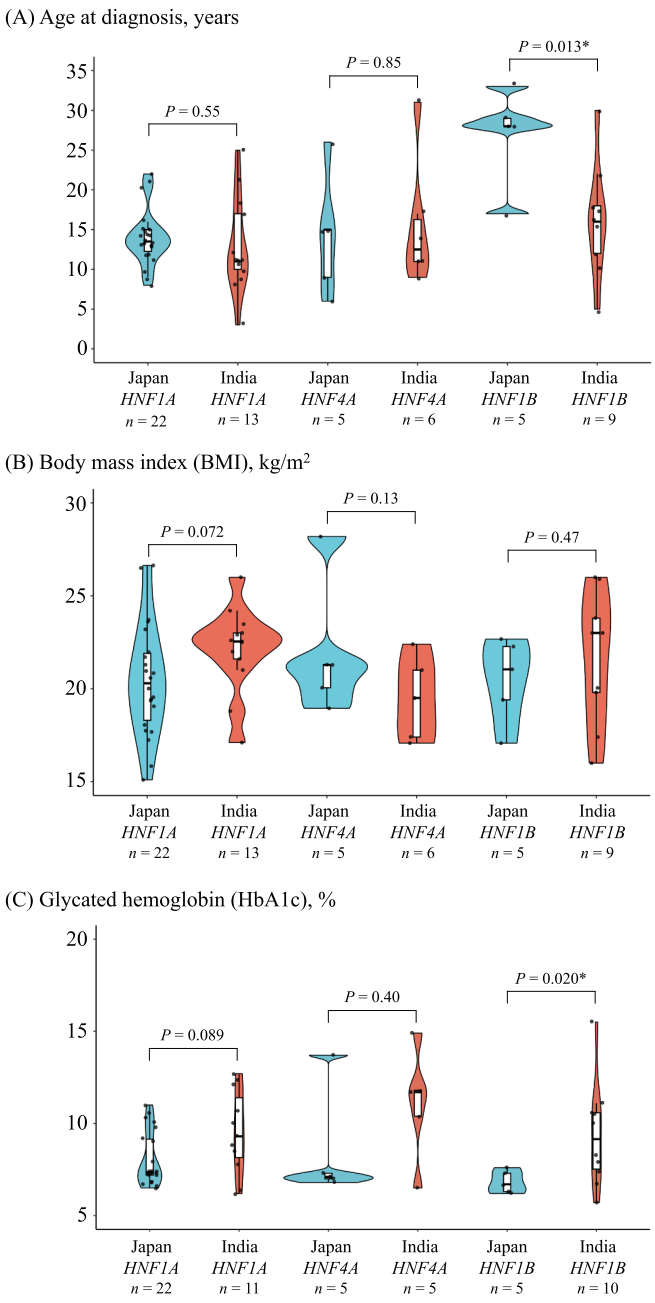

Fig. 4. Clinical and biochemical characteristics of probands stratified by monogenic diabetes subtype in nationwide cohorts from Japan and India. Panels show (A) age at diagnosis (years), (B) body mass index (BMI, kg/m^2), and (C) glycated hemoglobin (HbA1c, %) among probands with *HNF1A*-MODY, *HNF4A*-MODY, and *HNF1B*-MODY. Violin plots depict distributions; boxes represent interquartile ranges (IQR); horizontal lines indicate medians; whiskers extend to 1.5 × IQR. Two-sided *P* values for between-cohort comparisons within each subtype are shown. *n* indicates the number of probands with available data in each cohort-subtype group for the variable shown. *$P < 0.05$.

Sequence Variant Interpretation Working Group recommendations [22,23,30]. Even in *GCK*, *HNF1A*, and *HNF4A*, for which gene-specific specifications are available, most previously unreported non-truncating variants, particularly missense variants, were classified as VUS because supporting segregation, functional, and prior case-level evidence was insufficient. The challenge was greater for genes without monogenic diabetes-specific variant interpretation specifications. In these genes, even predicted loss-of-function variants were often classified as VUS unless loss of function was a well-established disease mechanism, as in *HNF1B* [47]. Therefore, the smaller number of genetically confirmed cases in the present comparative analysis likely reflects both stricter application of current criteria and limited supporting evidence.

Moreover, much of the available evidence has been derived predominantly from populations of European ancestry [48]. This limitation is likely to be particularly important in Asian and other underrepresented populations, for which case and reference data remain sparse. Reliable classification of monogenic diabetes variants will require more ancestry-diverse clinical datasets, family-based studies, functional data, and well-curated case-level evidence.

4.4. Strengths and limitations

A major strength of this study is that it was based on two nationwide cohorts from Japan and India, among the largest systematically characterized monogenic diabetes cohorts in Asia. By integrating genetic, clinical, and biochemical information, this comparison delineated both shared and context-specific features within distinct healthcare settings. These findings reinforce the importance of offering genetic testing beyond classical screening criteria for young, non-obese individuals with diabetes in Asia. Another strength is that variant classification was standardized across both cohorts using ACMG/AMP criteria, available ClinGen gene-specific specifications, and relevant ClinGen SVI recommendations, improving cross-cohort comparability and reducing overcalling.

This study also has limitations. First, the inclusion criteria, sequencing panels, and recruitment settings differed between the two cohorts, and therefore the results of the cross-cohort analyses should be interpreted as exploratory. Second, cases of monogenic diabetes diagnosed after approximately 35 years of age, in individuals with a BMI $\geq$ 30 kg/m^2, positive islet autoantibodies, or variants in genes not covered by the panel, particularly in the JDS cohort, may have been missed, although such cases are considered rare [29,49–51]. Third, for individuals without detected P/LP variants, the underlying genetic basis remains uncertain. Some may have undetected monogenic causes, whereas others may represent a heterogeneous group at the interface between monogenic and type 2 diabetes [19]. Fourth, because we applied variant classification conservatively, many variants remained classified as VUS, although some may still be relevant to diabetes risk.

5. Conclusions

In summary, two referral-based cohorts from Japan and India highlighted both shared and divergent features across distinct settings. A clinically meaningful proportion of young, non-obese individuals had monogenic diabetes in both cohorts, and cross-cohort comparisons revealed that (i) the absence of a three-generation family history should not deter clinicians from considering genetic testing and (ii) clinical features show substantial heterogeneity even within the same subtype. These findings underscore the heterogeneity of monogenic diabetes and the importance of broader genetic testing across Asian populations and beyond, particularly for suspected MODY.

CRediT authorship contribution statement

Masashi Hasebe: Writing – original draft, Project administration, Investigation, Formal analysis. **Venkatesan Radha:** Writing – review & editing, Project administration, Investigation, Conceptualization. **Anandakumar Amutha:** Writing – review & editing, Project administration, Formal analysis. **Daisuke Tanaka:** Writing – review & editing, Project administration, Investigation, Formal analysis. **Toshinori Imaizumi:** Writing – review & editing, Project administration, Investigation. **Daisuke Yabe:** Writing – review & editing, Resources, Project administration. **Satoshi Yoshiji:** Writing – original draft, Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Nobuya Inagaki:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Viswanathan Mohan:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2026.113268.

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