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Original Article

Genetics Section

Molecular Genetic Spectrum and Clinical Correlates of Congenital Hyperinsulinism in India: A Multi-centric Cross-sectional Study

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ABSTRACT

Introduction: Congenital Hyperinsulinism (CHI) is a rare genetic disorder of pancreatic β-cells characterised by persistent hypoglycaemia resulting from inappropriate insulin secretion. Such recurrent hypoglycaemic episodes are often associated with irreversible neurological injury and long-term developmental impairment, underscoring the importance of timely diagnosis and initiation of targeted therapy to improve neurodevelopmental outcomes and quality of life. In India, the true burden of CHI remains uncertain due to limited awareness, diagnostic delays, fragmented care pathways and restricted access specialised centers compounded by the absence of a national surveillance system. Consequently, many infants undergo prolonged empirical medical therapy or delayed surgical intervention, leading to preventable complications and adverse outcomes.

Aim: The present study was undertaken to evaluate the molecular genetic spectrum and clinical correlates of CHI, determine the frequency and distribution of pathogenic variants, assess genotype-phenotype associations, and interpret their implications for management.

Materials and Methods: The current multi-centric cross-sectional study was conducted from July 2022 to December 2025 at Pramukhswami Medical College and Shri Krishna Hospital, Karamsad, Gujarat, India. Eighteen (n =18) children with biochemically confirmed CHI were recruited through coordinated CHI India Association-linked clinics and outreach programs across India. Clinical, biochemical, and treatment details were recorded. Genetic testing was performed using Next-Generation Sequencing (NGS) panels at accredited laboratories including the Madras Diabetes Research Foundation. Variants were classified according to American College of Medical Genetics and Genomics (ACMG) criteria. Clinical and genetic data were summarised using descriptive statistics, and genotype-phenotype associations were assessed using the Kruskal-Wallis test.

Results: Pathogenic or likely pathogenic variants were detected in all 18 children (100%). Mutations involved ABCC8 (n=11), KCNJ11 (n=3), HNF4α (n=2), GLUD1 (n=1), and PMM2 (n=1). Eight (44%) were diazoxide-responsive, seven (39%) unresponsive, and three (17%) partially responsive. Five children (27.8%) underwent surgery; focal lesions were confirmed in those with paternally inherited ABCC8/KCNJ11 mutations. Median birth-weight SDS differed significantly across genotypes (Kruskal-Wallis H=13.04, p=0.023). Neurodevelopmental delay was present in 27.77% of patients.

Conclusion: Genetic testing provides high diagnostic yield in Indian children, with ABCC8 and KCNJ11 mutations predominating. Paternal K_{ATP} mutations predict focal disease and potential surgical cure. Early molecular diagnosis and optimised therapy are crucial for improved outcomes.

Keywords: Congenital Hyperinsulinism, Diazoxide responsiveness, Genetic testing, Hypoglycaemia, Pancreatic β-cells

INTRODUCTION

The CHI is the leading cause of persistent hypoglycaemia in neonates and infants, resulting from inappropriate insulin secretion despite low plasma glucose levels [1,2]. Its estimated global incidence is 1 in 40,000-50,000 live births, with a higher rate in populations with consanguinity or founder mutations [3]. Early diagnosis is crucial, as prolonged or recurrent hypoglycaemia can cause irreversible neurological injury and long-term developmental impairment in nearly one-third to one-half of untreated infants accounting for significant neurocognitive morbidity [4-7]. Timely diagnosis and targeted therapy therefore play a decisive role in determining neurodevelopmental outcomes, quality of life, and may also have medico-legal implications given the preventable risk of hypoglycaemia-related brain injury.

Advances in molecular genetics have transformed CHI diagnosis and management. Mutations in the Adenosine Triphosphate (ATP)-sensitive potassium (K_{ATP}) channel genes, ABCC8 and KCNJ11, account for nearly half of all cases worldwide [8,9]. Additional genes including GLUD1, GCK, HADH, HNF4α, HNF1α, HK1, and UCP2 contribute to a spectrum of phenotypes ranging from mild, diazoxide-responsive forms to severe, medically unresponsive disease [10]. Genetic testing not only aids diagnosis but also predicts diazoxide responsiveness, distinguishes focal from diffuse disease, and guides surgical decision-making [11,12].

In India, the true burden of CHI remains uncertain due to limited awareness, diagnostic delays, fragmented care pathways, and restricted access to molecular testing and specialised centers in the absence of a national surveillance system. Consequently, many children experience delayed definitive and prolonged empirical therapy. Barriers include high testing costs, scarcity of dedicated CHI centers, and limited coordination between pediatric endocrinologists, geneticists, and molecular laboratories [13,14]. These findings underscore the urgent need for indigenous models that integrate genetic testing into multidisciplinary CHI care frameworks. The primary objective of the present study was to evaluate the molecular genetic spectrum and clinical correlates of CHI in an Indian cohort through coordinated clinic-laboratory collaboration within the CHI India Association (CHIA) referral network and the secondary objectives were to determine the frequency and distribution of pathogenic variants, assess genotype-phenotype associations, and interpret their implications for management in the Indian context.

MATERIALS AND METHODS

The present cross-sectional observational study included children with CHI identified through CHIA-affiliated outreach clinics in Gujarat, Maharashtra, Karnataka and Tamil Nadu, India, from July 2022 to December 2025. Patient management was undertaken at respective centres following recommended protocols, while genetic testing was performed at accredited laboratories. Clinical and genetic data were collated and analysed at Pramukhswami Medical College and Shri Krishna Hospital, Bhaikaka University, Karamsad, Gujarat, India. These CHIA-affiliated clinics primarily function as referral points for suspected CHI, which naturally results in a smaller but well-characterised cohort of confirmed cases. The central coordinating site at Pramukhswami Medical College and Shri Krishna Hospital served as the primary referral hub, while molecular testing was performed at the Department of Molecular Genetics, Madras Diabetes Research Foundation, Chennai, Tamil Nadu, and other accredited genetic laboratories in India. Ethical approval was obtained from the Institutional Ethics Committee (IEC/BU/137/Faculty/12/93/2022; dated 2 June 2022). Written informed consent was obtained from parents or legal guardians for participation and genetic testing.

Inclusion and Exclusion criteria: Children presenting with persistent hypoglycaemia (≥2 weeks) were screened. CHI was diagnosed based on standard biochemical criteria: plasma glucose <50 mg/dL with detectable insulin (>2 μIU/mL) and suppressed β-hydroxybutyrate (BOHB) (<1.8mmol/L) and Free Fatty Acid (FFA) levels (<0.5 mmol/L) during hypoglycaemia. Only patients with both biochemical confirmation and genetic evaluation were included. Patients with transient perinatal stress hyperinsulinism or secondary causes such as hypopituitarism, adrenal insufficiency, or sepsis were excluded.

Study Procedure

Detailed clinical assessments were performed during admission and follow-up visits. Demographic data, perinatal history, birth-weight, gestation age, family history of hypoglycaemia or consanguinity, and clinical features (including seizures, feeding difficulties and neuro-developmental status) were recorded. Anthropometric parameters were converted to Standard Deviation Scores (SDS) using WHO growth charts. All patients underwent critical-sample collection during spontaneous or induced hypoglycaemia before intravenous glucose administration. Parameters included plasma glucose, insulin, BOHB, FFA, cortisol, growth hormone, lactate, and ammonia. Suppressed ketones and FFA, along with inappropriately detectable insulin during hypoglycaemia, supported the diagnosis of CHI, while cortisol, growth hormone, lactate, and ammonia were reviewed to exclude alternative endocrine or metabolic aetiologies. The Glucose-Infusion Rate (GIR) was calculated as mg/kg/min. The reference ranges applied for key biochemical parameters are detailed in [Table/Fig-1].

Genetic testing and variant analysis: NGS-based multigene panels including ABCC8, KCNJ11, GLUD1, GCK, HADH, HNF4α, HNF1α, HK1, UCP2, and *INSR* were performed using Illumina platforms (>99% coverage at 20× depth). Variants were confirmed by Sanger sequencing classified per ACMG/Association for Molecular Pathology (AMP) 2015 guidelines [15]. Public databases ClinVar, Genome Aggregation Database (gnomAD) and segregation analysis were used for interpretation. Parental testing was undertaken where feasible.

Parameters	Cohort characteristics		Reference range	Interpretation
	Median	Range		
Plasma glucose (mg/dL)	38	21-49	≥70 mg/dL	Hypoglycaemic range
Insulin (μIU/mL)	8.6	3.2-25.4	<2 μIU/mL	Detectable despite hypoglycemia
β-hydroxybutyrate (BOHB) (mmol/L)	0.12	0.02-0.20	>1.8 mmol/L	Suppressed
Free Fatty Acids (FFA) (mmol/L)	0.15	0.08-0.28	>1.5 mmol/L	Suppressed
Glucose infusion rate (mg/kg/min)	12.5	6-18	4–6 mg/kg/min (infants)	Elevated
Cortisol (μg/dL)	19.2	12.4-29.1	>18 μg/dL	Appropriate
Growth hormone (ng/mL)	12.1	5.6-21.8	>7 ng/mL	Appropriate

[Table/Fig-1]: Baseline biochemical parameters at diagnosis.

Imaging and surgical evaluation: ^{18}F-DOPA PET/CT (-Fluorine-18-labeled 3,4-dihydroxy-L-phenylalanine Positron Emission Tomography/Computed Tomography) or Magnetic Resonance Imaging (MRI) was performed selectively, primarily in patients with clinical and genetic features suggestive of focal CHI (e.g., a paternally inherited K_{ATP} mutations), in line with published recommendations [16], while imaging was not routinely pursued in cases with mutations known to be associated with diffuse disease. Patients with predicted focal forms underwent partial pancreatectomy, while diffuse forms underwent near-total resection when indicated. Histopathology was reviewed centrally.

Therapeutic management: All patients received intravenous glucose for stabilization followed by diazoxide therapy (5-20 mg/kg/day) as first-line treatment. Response was defined as maintenance of euglycaemia ≥72 hours without Intravenous (IV) glucose support. Partial or non-responders received daily octreotide (5-35 μg/kg/day) or four weekly Octreotide Long-Acting Release (LAR)/ Lanreotide depot; unresponsive patients with genetically confirmed focal disease underwent surgery. Long-term growth and neurodevelopmental outcomes were monitored at follow-up visits and via CHIA tele-consultations.

Primary outcome: The primary outcome was the molecular diagnostic yield (proportion of patients with pathogenic or likely pathogenic variants).

Secondary outcomes: Secondary outcomes included: (i) genotype-phenotype correlations (birth-weight SDS, diazoxide responsiveness, and need for surgery); and (ii) neurodevelopmental outcomes during follow-up.

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for Social Sciences (SPSS) version 26. Continuous variables were expressed as median {range/Interquartile Range (IQR)} and categorical variables as percentages. Kruskal-Wallis test was used for group comparisons of continuous variables, while Chi-square or Fisher's-exact tests were applied for categorical variables. The $p<0.05$ was considered statistically significant.

RESULTS

Cohort Characteristics

A total of 18 children with biochemically and genetically confirmed CHI were included. These represented consecutively referred, CHI-confirmed cases from CHIA-linked clinics during the study period. There were 10 males and eight females, with a median age at presentation of five days (range: 0-214 days). Most children (13/18, 72.22) presented in the neonatal period (<28 days), while three children (3/18, 16.67%) had onset beyond one month of age. One child presented at 214 days of age, representing a late presentation outside the neonatal period within the cohort.The median birth weight was 3.2 kg (range: 2.1-4.5 kg), corresponding to a birth-weight SDS of -0.10 (range -1.26 to +2.45). Four infants (22.22%) were macrosomic. Seizures at onset occurred in 10 (55.55%), and family history of neonatal hypoglycaemia was noted in 2/18 (11.11%). Based on imaging findings, focal CHI was confirmed in 3/18 (16.67%) and diffuse disease in 1/18 (5.56%) children; the remaining cases were managed medically or without definitive histopathological classification. No mortality occurred during follow-up. [Table/Fig-2] presents baseline demographic and clinical characteristics. All patients fulfilled biochemical criteria for CHI, with detectable insulin during hypoglycaemia, suppressed ketones and fatty acids, and elevated GIR.

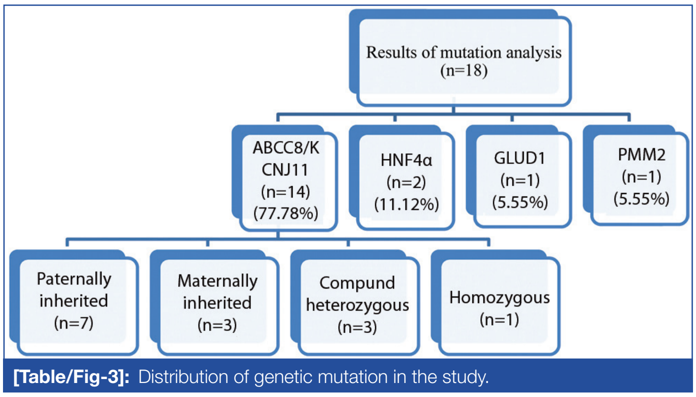
Genetic Mutation Group	Birth-weight SDS		Age at presentation (in days)		Diazoxide responsiveness (n)
	Median	Range	Median	Range	
Compound heterozygous /homozygous ABCC8/ KCNJ11 (n=4)	–0.72	-1.26 to 0.17	6	0 to 30	Responsive: 1
					Partial: 1
					Unresponsive: 2
Paternally inherited ABCC8/ KCNJ11 (n=7)	0.78	-0.02 to 2.45	3	0 to 128	Responsive: 2
					Partial: 1
					Unresponsive: 4
Maternally inherited ABCC8/ KCNJ11 (n=3)	–0.53	-1.23 to 0.28	1	0 to 7	Responsive: 2
					Partial: 0
					Unresponsive: 1
HNF4α (n=2)	0.64	0.31 to 0.97	61.5	49 to 74	Responsive: 2
					Partial: 0
					Unresponsive: 0
GLUD1 (n=1)	–1.01	---	214	---	Responsive: 1
					Partial: 0
					Unresponsive: 0
PMM2 (n=1)	–1.15	---	0	---	Responsive: 0
					Partial: 1
					Unresponsive: 0

[Table/Fig-2]: Birth-weight SDS, age at presentation, and diazoxide responsiveness across genetic mutation groups in the study cohort (n=18).

Genetic Findings

Pathogenic or likely pathogenic variants were identified in all 18 patients (100% diagnostic yield). The majority involved ABCC8 (n=11) and KCNJ11 (n=3), representing the K_{ATP} channel genes known to cause CHI. Variants were also detected in HNF4α (n=2; 11.11%), GLUD1 (n=1; 5.55%), and PMM2 (n=1; 5.55%). Thus, ABCC8 and KCNJ11 together accounted for over three-quarters of the cohort. Based on parental testing, mutations were paternally inherited in 9/18 children (50.00%), maternally inherited in 4/18 (22.22%), and biallelic in 5/18 (27.78%).Among the KATP channel genes, variants included biallelic mutations (n=4), paternal monoallelic mutations (n=7) and maternal variants (n=3). One child in the cohort was identified with compound heterozygous PMM2-associated hyperinsulinism, a rare syndromic and mechanistically distinct causes of CHI. Of the five biallelic cases in the cohort (27.78%), four involved ABCC8 (K_{ATP} channel genes) and one involved PMM2-associated CHI. All identified variants were classified as pathogenic according to ACMG 2015 criteria [15]. No novel mutations were identified in the cohort. The gene-wise distribution of mutations is shown in [Table/Fig-3] and variant-level details appear in [Table/Fig-4].

Inheritance Pattern



[Table/Fig-3]: Distribution of genetic mutation in the study.

Paternally inherited ABCC8/KCNJ11 variants frequently, though not uniformly, correlated with focal CHI. Among the seven children with paternal monoallelic variants, three had focal lesions confirmed on 18F-DOPA PET or histopathology, while the remaining cases either had no localising findings or did not undergo definitive imaging. In contrast, all children with biallelic ABCC8 variants (compound heterozygous or homozygous) exhibited a severe, early-onset, predominantly diazoxide-unresponsive phenotype; one child who underwent surgery showed diffuse disease on histology, whereas the others did not have histological confirmation. Both HNF4α cases showed heterozygous variants inherited from diabetic parents [Table/Fig-5,6], consistent with a Maturity-Onset Diabetes of the Young (MODY)-like pattern and diazoxide responsiveness. The GLUD1 case was paternally inherited with hyperammonemia, while the PMM2 case carried compound heterozygous variants consistent with syndromic CHI and showed no focal lesions on evaluation.

Phenotype-genotype Correlations

No significant differences were observed across genotype groups for age at first hypoglycaemia, insulin concentration, or GIR requirement ($p>0.05$). There was no statistically significant association between genotype category and diazoxide responsiveness (χ^2=11.26, df=10, p=0.338). Birth-weight SDS varied significantly across genotype groups (Kruskal-Wallis H=13.04, p=0.023) being higher in K_{ATP}-related and HNF4α variants than others. However, adjusted Dunn's post-hoc pairwise comparisons were not statistically significant between individual genotype groups. Clinically, biallelic K_{ATP} mutations were associated with early onset (<7days) and predominantly diazoxide-unresponsive disease requiring higher GIR (median 13 mg/kg/min) whereas paternally inherited K_{ATP} were variably responsive (median 8 mg/kg/min), and where evaluated, correlated with focal disease. HNF4α-related CHI presented beyond the neonatal period and was diazoxide-responsive, consistent with its typically mild phenotype. The GLUD1 case showed fasting-induced hypoglycaemia with mild hyperammonemia and responded to diazoxide. The PMM2 case exhibited hypotonia and dysmorphism, aligning with syndromic CHI. Detailed statistical comparisons are presented in [Table/Fig-7].

Therapeutic Response

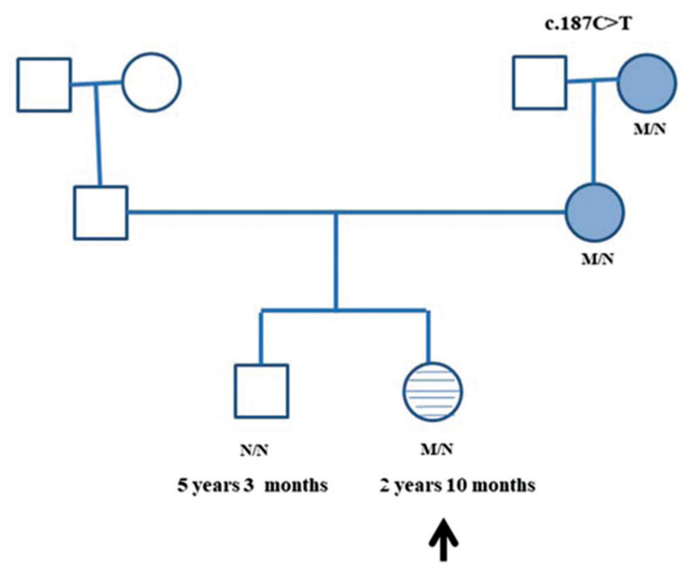
All patients received diazoxide (5-20 mg/kg/day) as first-line therapy.

- Eight children (44.44%) were fully responsive, defined as maintenance of normoglycaemia during normal feeding and age-appropriate fasting;
- Seven patients (38.88%) were unresponsive;
- Three (16.66%) demonstrated a partial response, defined as improvement in glycaemic stability on diazoxide but with persistent hypoglycaemia requiring addition of octreotide or lanreotide to achieve euglycaemia [Table/Fig-2].

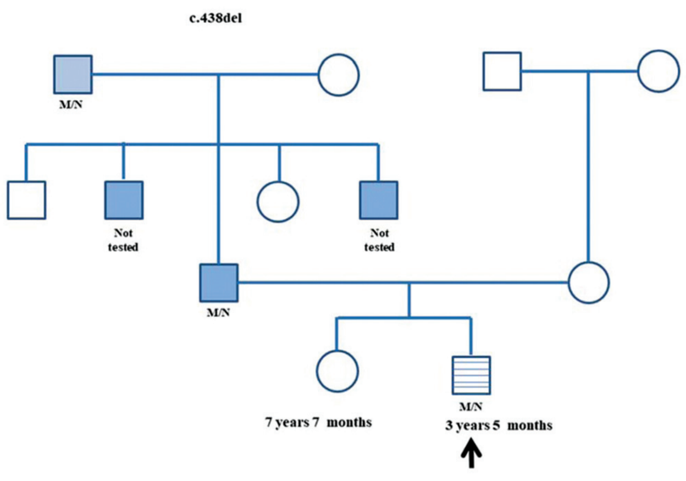
All HNF4α and GLUD1 variants were diazoxide-responsive, whereas most biallelic ABCC8/KCNJ11 variants were unresponsive; responsiveness among paternally inherited monoallelic variants varied, partly reflecting focal disease. Of the 10 children who were unresponsive or only partially responsive to diazoxide, second-line

Case No.	Gene	Inheritance	cDNA (Mother, Father)	Protein (Mother, Father)	Exon / Location	Consequence	Diazoxide response	Histology/ 18F-DOPA	Current treatment/ Management	Developmental outcome
1.	ABCC8	Compound het.	c.2113C>T / c.16T>G	p.Arg705Ter / p.Cys6Gly	Exon 15	Nonsense / Missense	Responsive	N/A	Continuing diazoxide	Normal
2.		Compound het.	c.106C>T / c.331G>A	p.His36Tyr / p.Gly111Arg	Exon 1 / Exon 3	Missense / Missense	Unresponsive	N/A	Lanreotide (LAN)/ Octreotide	Speech & language delay
3.		Compound het.	c.1576C>T / c.1879delC	p.R526C / p.H627fs	Exon 10 / Exon 13	Missense / Frameshift	Partial	N/A	Diazoxide + Octreotide	Gross motor delay
4.		Homozygous / compound?	c.2113C>T / —	p.Arg705Ter	Exon 15	Nonsense	Unresponsive	Diffuse	Near-total pancreatectomy	Normal
5.		Paternal	c.4594A>G	p.Thr1532Ala	Exon 38	Missense	Unresponsive	N/A	Octreotide	Normal
6.		Paternal	c.2014-21G>A	IVS14-21 (intron)	Intron 14	Aberrant splicing	Unresponsive	N/A	Lanreotide	Normal
7.		Paternal	c.2800C>T	p.Arg934Ter	Exon 23	Nonsense	Unresponsive	N/A	Lanreotide/ Octreotide	Normal
8.		Paternal	c.2204G>A	p.Gly735Glu	Exon 16	Missense	Unresponsive	Focal	Partial pancreatectomy	Normal
9.		Paternal	c.2524C>T	p.Arg842Ter	Exon 21	Nonsense	Responsive	Focal	Partial pancreatectomy	Speech & language delay
10.		Maternal	c.4021C>T	p.Gln1341Ter	Exon 33	Nonsense	Responsive	N/A	Diazoxide	Normal
11.		Maternal	c.2473G>A	p.Glu825Lys	Exon 20	Missense	Responsive	N/A	Diazoxide	Normal
12.	KCNJ11	Paternal	c.627G>A	p.Met209Ile	Exon 1	Missense	Responsive	Focal	Partial pancreatectomy	Normal
13.		Paternal	c.902G>A	p.Arg301His	Exon 1	Missense	Partial	N/A	Diazoxide + Octreotide	Gross motor delay
14.		Maternal	c.881C>T	p.Thr294Met	Exon 1	Missense	Unresponsive (post-surgery context)	N/A	Sub-total pancreatectomy → Diazoxide + Octreotide	Normal
15.	HNF4α	Maternal	c.187C>T	p.Arg63Trp	Exon 2	Missense	Responsive	—	Diazoxide	Normal
16.		Paternal	c.438del	p.Val147fs	Exon 5	Frameshift	Responsive	—	Diazoxide	Normal
17.	GLUD1	Paternal	c.833C>T	p.Arg274Cys	Exon 6	Missense	Responsive	—	Diazoxide	Normal
18.	PMM2	Compound het.	c.422G>A	p.Asp148Asn	Exon 5	Missense	Partial	—	Diazoxide + Nifedipine	Normal

[Table/Fig-4]: Detected variants and key genetic as well as clinical data.
The table includes genetic and clinical details of all 18 genetically confirmed CHI cases included in the study. Each row represents a unique patient.



[Table/Fig-5]: Family pedigree of Case No.: 15 with mutation in HNF4α.



[Table/Fig-6]: Family pedigree of Case No.: 16 with mutation in HNF4α.

therapies including octreotide and/or lanreotide were administered, with some patients receiving combination regimens; one child with PMM2-associated CHI additionally received nifedipine. Surgical intervention was performed in five children, including three partial pancreatectomies for focal lesions (all achieving postoperative normoglycemia) and one near-total pancreatectomy for diffuse disease (requiring low-dose diazoxide postoperatively); one additional child also underwent surgery as detailed in [Table/Fig-4]. Surgery was undertaken based on genetic and imaging findings and was not restricted to diazoxide-unresponsive cases. Definitive focal-diffuse classification was not possible for all patients because several diazoxide-unresponsive or partially responsive cases did not undergo ^{18}F-DOPA PET/CT imaging and were managed medically; therefore, only those with available imaging or surgical histology could be assigned focal or diffuse status. No major postoperative complications occurred.

Growth and Neurodevelopmental Outcomes

Birth-weight SDS and genotype were significantly associated (p=0.023). Biallelic K_{ATP} mutations correlated with higher birth weights, reflecting intrauterine hyperinsulinism. Neurological

Section A: Overall group comparisons				
Analysis	**Test Used**	**Statistic**	**p-value**	**Interpretation**
Differences in Birth-weight SDS across genetic mutation groups	Kruskal-Wallis test	H=13.04	0.023	Significant difference in birth-weight SDS across groups.
Differences in age at presentation across genetic mutation groups	Kruskal-Wallis test	H=7.63	0.178	No significant difference in age at presentation.
Association between genetic mutation group and diazoxide responsiveness	Pearson's Chi-square test	χ^2=11.26; df=10	0.338	No statistically significant association between genotype category and diazoxide response.
Section B: Post-hoc pairwise comparisons for birth-weight SDS (Dunn's test)*				
Compound heterozygous / homozygous ABCC8/KCNJ11vs Paternally inherited ABCC8/KCNJ11			0.142	No individual pair-wise comparison remained significant after correction
Compound heterozygous / homozygous ABCC8/KCNJ11vs Maternally inherited ABCC8/KCNJ11			0.772	
Compound heterozygous / homozygous ABCC8/KCNJ11vsHNF4α			0.772	
Compound heterozygous / homozygous ABCC8/KCNJ11vsGLUD1			1.000	
Compound heterozygous / homozygous ABCC8/KCNJ11vsPMM2			1.000	
Paternally inherited vs maternally inherited ABCC8/KCNJ11			0.373	

[Table/Fig-7]: Statistical analysis of genotype–phenotype and treatment associations.
*Dunn's post-hoc pairwise comparisons were adjusted for multiple testing. A p-value <0.05 was considered statistically significant.
All pairwise comparisons were performed; however, only selected comparisons are shown as none remained significant after adjustment

developmental, involving speech and/or gross motor domains, was documented in five children (27.77%), predominantly among those with early-onset recurrent hypoglycaemia and seizures. There was no significant difference in developmental outcome between diazoxide-responsive and unresponsive groups (p=0.48). No mortality was recorded during the current study.

DISCUSSION

Principal Findings

The Present study represents one of the few prospectively characterised, genetically confirmed cohorts of CHI from India. The key findings were: (i) a 100% mutation detection rate among 18 biochemically confirmed CHI cases; (ii) a predominance of ABCC8 and KCNJ11 mutations (77.77%), representing the K_{ATP} channel genes; (iii) clear genotype-phenotype correlations, including paternally inherited K_{ATP} variants associated with focal disease and biallelic variants with diffuse, severe, diazoxide-unresponsive CHI; and (iv) neurodevelopmental delay in 27.77% of affected children. The high genetic yield in this study compared with Indian cohort [4] reflects prospective recruitment, centralised testing, and exclusion of transient or secondary forms. These results reinforce the importance of integrating molecular diagnostics into CHI care within coordinated multidisciplinary frameworks such as CHIA [13].

Genotype-phenotype Correlations

The observed correlations were consistent with international experience [3,7]. K_{ATP}-channel, mutations predominated, similar to findings from large international cohorts [3,8]. Biallelic variants exhibited early-onset, severe disease requiring high GIR and were largely diazoxide-unresponsive, typical of diffuse CHI, whereas paternally inherited monoallelic variants were more frequently associated with focal disease and surgical cure. Non-K_{ATP} variants displayed distinct phenotypes. [17] HNF4α variants presented beyond the neonatal period and were diazoxide-responsive [9,10,18]. The GLUD1 case demonstrated fasting-induced hypoglycaemia with hyperammonemia, typical of hyperinsulinism/hyperammonemia (HI/HA) syndrome with diazoxide responsiveness [19]. The PMM2-associated case represented a rare syndromic form with partial responsiveness and no focal localisation, highlighting expanding genetic heterogeneity. The identification of a PMM2-CHI case in our cohort represents an exceptional presentation and highlights the need for expanding genetic and phenotypic spectrum of CHI [20]. The significant difference in birth-weight SDS (p=0.023) across genotypes supports intrauterine hyperinsulinism as a marker of disease severity. Similar associations between higher birth-weight and severe CHI phenotypes, particularly in recessive K_{ATP} mutations, have been described in previous cohorts and summarised in recent reviews.

Comparative analysis

The genetic detection rate in this cohort (100%) exceeded prior Indian series (68.2%) [4] and international averages 45-85%) [3,7,21]. This likely reflects comprehensive sequencing panels, phenotype-driven inclusion, and careful variant reclassification using segregation data and ACMG criteria [4,15]. The predominance of K_{ATP} mutations parallels global observations [3,8] while the proportion of diazoxide-unresponsive disease (n=7, 38.88%) is comparable to international cohorts (40-45%) [7,21] reinforcing the consistency of treatment responsiveness patterns across populations. Detection of HNF4α, GLUD1, PMM2 variants underscore the evolving literature describing expanding genetic heterogeneity and the value of broad molecular testing beyond targeted panels [8,10]. Notably, the relatively high frequency of paternal inheritance in our cohort may reflect regional demographic factors, including consanguinity and founder effects, which are recognised to shape CHI genotype distributions in Indian populations [3,13]. Collectively, these findings highlight the need for integrated molecular workflows, population-specific variant databases, and national CHI registries to support accurate diagnosis and resource planning in India [22]. The comparative findings across cohorts, including mutation detection rates, diazoxide responsiveness, and outcome profiles, are summarized in [Table/Fig-8] [3,4,21].

Clinical Implications

Early molecular diagnosis is both diagnostic and therapeutically decisive. Genetic results guide diazoxide trial, predict focal versus diffuse disease, and inform surgical referral. Given limited nationwide access to ^{18}F-DOPA PET in India, genetic findings, particularly inheritance patterns in K_{ATP}-channel mutations serve as the primary determinant for distinguishing focal from diffuse disease, which aligns with international practice when PET imaging is unavailable [16]. The CHIA-MDRF collaborative model demonstrates that centralised molecular workflows can deliver accurate, timely and clinically actionable results in resource-constrained settings [13]. Beyond acute management, genetic confirmation also enables recurrence risk assessment, carrier testing in recessive disease, and long-term surveillance in conditions such as HNF4α associated CHI necessitating ongoing surveillance for diabetes and dyslipidemia [9]. From a health systems perspective, a step-wise approach--biochemical confirmation followed by targeted or panel-based genetic testing may be more cost-efficient than reliance on universal advanced imaging. Coordinated clinic-laboratory pathways can reduce diagnostic delays, avoid prolonged empirical therapies, and minimise unnecessary surgical interventions. Scaling such coordinated models within national rare disease frameworks may improve equitable access to precision CHI care.

Parameter	Our study (2025)	Kapoor RR et al., (2013) [3]	Snider KE et al., (2013) [23]	Sharma R et al., (2022) [4]
Period of study	2022-2025	~2000–2010	1997–2010	2011–2020
Type of study	Prospective	Ambispective	Retrospective	Ambispective
Sample size	18	300	417	42
Identified mutations	18	136	328	28
Mutation types	ABCC8, KCNJ11, HNF4*A*, GLUD1, PMM2	ABCC8, KCNJ11, GLUD1, HADH, HNF4*A*	ABCC8, KCNJ11, GLUD1, GCK, HADH, HNF4*A*, UCP2, HNF1α	ABCC8, GLUD1, HADH, *KDM6A*
Mutation detection rate (%)	100% (targeted testing)	45.3%	79%	68.2%
Diazoxide responsiveness	44% responsive	61% responsive	28% responsive	55% responsive
	39% unresponsive	35% unresponsive	72% unresponsive	45% unresponsive
	17% partial	4% partial	---	---
Median birthweight SDS	-0.10 (-1.26 to +2.45)	+1.67 (subgroup)	Not reported	Birthweight in kg (2.86 responders, 3.61 non-responders)
Large for gestational Age (%)	Not directly reported	Not reported	Higher in unresponsive	73.6% in non-responders
Median age at presentation	Day 5 (range Day 0–214)	Day 1 (severe)	Not reported	Day 3 (range Day 1–6 years)
Octreotide Use	For diazoxide-unresponsive patients	Yes (some)	Yes (for unresponsive)	19 patients
Sirolimus use	Used (rarely)	Not reported	Not reported	6 patients
Mortality (%)	0% reported	Not reported	Not reported	2 deaths
Neurodevelopmental outcomes	5 patients (28%) with delay (speech/gross motor)	Not reported	Not reported	Good in most patients
Focal vs diffuse CHI (Histopathology)	Focal confirmed in partial pancreatectomy patients	Focal 16/23	53% focal (Snider)	Mixed; PET used
Novel mutation rate	0 novel mutations detected	36 novel ABCC8 mutations	70% novel K_{ATP}	Not reported
Genetic prediction for focal disease	Paternal ABCC8/KCNJ11 mutation predicted focal CHI	Confirmed paternal mutation association	Genetic prediction sensitivity 97%	PET and genetics combined
Feeding methods	Not reported	Not reported	Not reported	Not reported
GERD prevalence	Not reported	Not reported	Not reported	Not reported
Surgical outcomes	27.78% underwent surgery; focal lesions cured by partial pancreatectomy	Not reported	Not reported	1 partial pancreatectomy

[Table/Fig-8]: Comparison of present study with other CHI cohorts [3,4,21].
GERD: Gastroesophageal Reflux Disease

Neurodevelopmental Outcomes

Neurodevelopmental delay occurred in five children (27.77%), comparable to previously reported reports [5-7]. Delays were more frequent in early-onset, diazoxide-unresponsive cases with recurrent seizures, underscoring the central role of hypoglycaemia severity and duration in neurological injury [5,6,8]. Importantly, neurocognitive injury in CHI is primarily driven by hypoglycaemia rather than the genotype; therefore, molecular confirmation may indirectly reduce morbidity by expediting targeted therapy Incorporating Continuous Glucose Monitoring (CGM) and structured neurodevelopmental follow-up into CHI care is recommended [16].

Notably, the duration of follow-up was heterogeneous due to variable referral timing and ongoing longitudinal care. Moreover, neurodevelopmental assessment was based on serial clinical evaluations rather than standardised psychometric instruments; therefore, reporting a median or range of follow-up duration would not have provided methodologically robust comparative insight. Outcomes were interpreted pragmatically based on clinician-documented delays in speech, gross-motor, or global development. Although this approach limits precise quantification of long-term neurocognitive burden, the observed burden aligns with real-world CHI cohorts [5-7].

Expansion of indigenous CHI testing through multi-center collaborations and integration within the National Rare Disease Policy could facilitate early diagnosis and subsidised testing. Development of an Indian CHI mutation database and integration of molecular with metabolic data may support predictive modeling for therapy and neurodevelopmental outcomes [13].

Limitation(s)

Limitations include the small sample size, reflecting the rarity of CHI and the genetically confirmed design, which may limit statistical power and generalisability. Referral bias from CHIA-linked tertiary centers is possible. Parental segregation testing could not be completed in all families, and functional validation of variants was not available. Limited availability of ^{18}F-DOPA PET imagingprevented radiological confirmation of focal versus diffuse disease in all patients.Neurodevelopmental outcomes were assessed clinically without standardised tools, and follow-up duration varied, limiting long-term outcome interpretation. Nevertheless, the strong phenotype-genotype concordance supports reliability of findings.

CONCLUSION(S)

The present study demonstrates the feasibility and clinical value of integrated molecular testing for CHIin Indian pediatric endocrine practice. The predominance of ABCC8 and KCNJ11 variants mirrors global data, and the high diagnostic yield reflects the effectiveness of coordinated clinical-molecular workflows. Clear genotype-phenotype correlations, particularly regarding diazoxide responsiveness and surgical decision-making underscore the importance of early genetic diagnosis. Expanding collaborative, cost-effective testing networks could enhance diagnostic accuracy, optimise management, and improve long-term outcomes for children with CHI in resource constrained settings.

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