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Molecular Genetic Evaluation of Hyperinsulinemia in Children: A Cross-Sectional Study

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Abstract: ***Background**: Congenital hyperinsulinism (CHI) is the most prevalent cause of persistent hypoglycemia in neonates and infants. It is characterized by uncontrolled insulin secretion from pancreatic β-cells. Early diagnosis is essential to prevent irreversible brain damage. **Aim of the Study**: To identify the molecular genetic variants responsible for congenital hyperinsulinism in children and to assess their correlation with clinical presentation and response to treatment. **Patients and Methods**: In a cross-sectional study, 16 children (aged 1 day to 8 years) with biochemically proven hyperinsulinemic hypoglycemia participated. Whole exome sequencing was performed on genomic DNA isolated from peripheral blood at an accredited next-generation sequencing laboratory. Variant interpretation was in accordance with current guidelines for pathogenicity. **Results**: Genetic variants that were pathogenic/likely pathogenic and related to CHI were found in 10 (62.5%) out of 16 patients. The genes that were most prevalent regarding the presence of variants were ATP Binding Cassette Subfamily C Member 8 (ABCC8) (43.8%), Glutamate Dehydrogenase 1 (GLUD1), Hydroxyacyl-CoA Dehydrogenase (HADH), and Hepatocyte Nuclear Factor 1 Alpha (HNF1A) (6.3% each). There was a significant association between early-onset CHI, particularly during the neonatal/infantile period, and the presence of pathogenic variants, particularly those involving the ABCC8 gene. The presence of genetic variants was significantly higher among patients who responded to antidiabetic therapy. **Conclusion**: CHI shows significant molecular diversity, but ABCC8 mutations are the most prevalent cause. Exome sequencing can be used in the diagnosis of CHI, helping in therapeutic choices and in characterizing CHI, even if some CHI patients present unresolved genetic issues.*

Keywords: Congenital hyperinsulinism; Whole-exome sequencing; ABCC8; GLUD1; HADH; HNF1A; Hypoglycemia

1. Introduction

Congenital Hyperinsulinism (CHI) is a rare disorder characterized by uncontrolled and inappropriate secretion of insulin from pancreatic β-cells. This disease can also cause hypoglycemia among neonates and children [1–3]. Congenital Hyperinsulinism is also considered to be the common cause of chronic hypoglycemia among infants and children. It can cause irreparable harm to the central nervous system if left untreated [2–4].

The estimated incidence of CHI is approximately 1:40,000 live births, although this can vary widely across populations that practice consanguineous marriage, reflecting the autosomal recessive inheritance pattern [4,5]. The condition also varies widely in the extent of its manifestations, ranging from transient, easily managed hypoglycemia and diazoxide resistance to surgically correctable manifestations [6]. The observed heterogeneity is largely attributable to molecular genetic differences, particularly affecting the mechanisms of insulin secretion [6,7].

At the molecular level, the underlying causes of CHI are mostly attributed to pathogenic single-nucleotide variants (SNVs) within genes responsible for the depolarization of pancreatic β-cell membranes, mitochondrial metabolism, and amino-acid-stimulated insulin secretion [5,8]. The main genes found to contribute to the condition include ATP Binding Cassette Subfamily C Member 8 (ABCC8), also known as the sulphonylurea receptor 1 protein, and Potassium Inwardly Rectifying Channel Subfamily J Member 11; a gene encoding the Kir6.2 subunit of the ATP-sensitive potassium (K(ATP)) channel protein [7–9]. Dysfunction of the K(ATP) channel protein impairs plasma membrane depolarization, thereby reducing insulin secretion irrespective of blood glucose concentration [7,8].

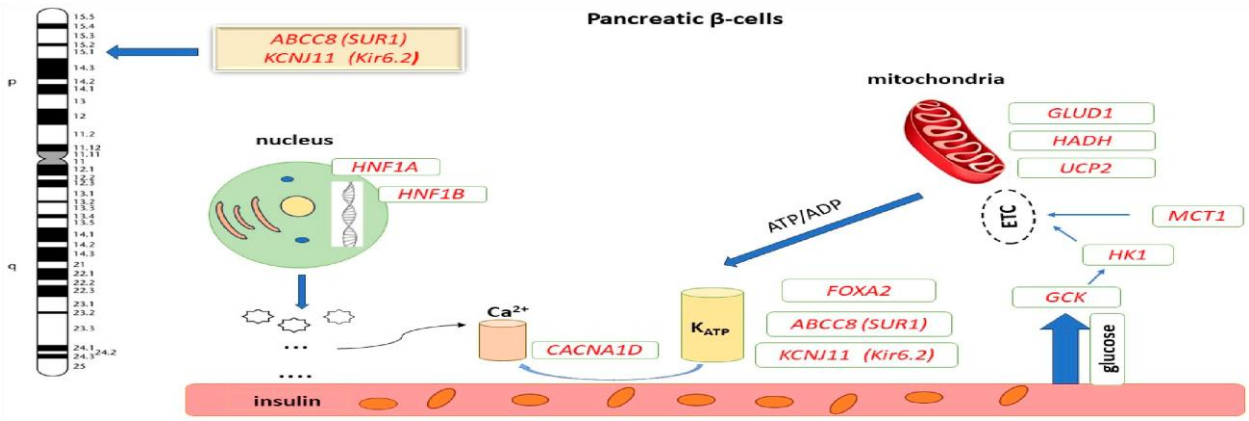

Figure 1: Molecular and genetic mechanisms involved in congenital hyperinsulinism (CHI), including K(ATP) channel dysfunction and mitochondrial metabolic pathways. Adapted from Galcheva et al., 2019 [Front Endocrinol].

In addition to the above-listed abnormalities in K(ATP) channels, other genes identified as influencing CHI through distinct biochemical mechanisms include gain-of-function mutations in the Glutamate Dehydrogenase 1 gene (GLUD1), which lead to increased insulin secretion in the presence of amino acids in hyperinsulinism-hyperammonemia syndrome [10]. HADH (Hydroxyacyl-CoA Dehydrogenase) and other transcription factors, such as Hepatocyte Nuclear Factor 1 Alpha (HNF1A) and Hepatocyte Nuclear Factor 4 Alpha (HNF4A), have been associated with low fatty acid metabolism and insulin secretion in hyperinsulinism in neonates who later develop diabetes [11-13].

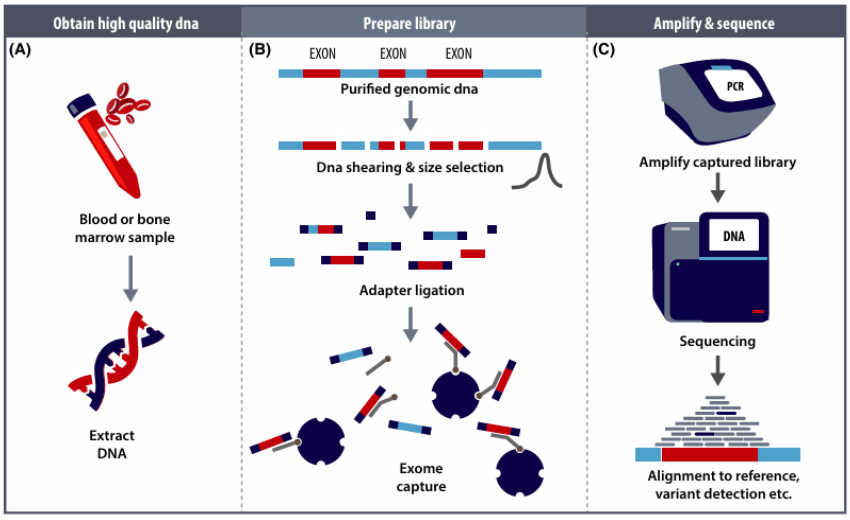

Figure 2: Workflow of whole-exome sequencing (WES) used for molecular diagnosis of congenital hyperinsulinism, including DNA extraction, sequencing, variant calling, and pathogenicity interpretation.

Moreover, despite progress in molecular genetics, a remarkable number of patients with CHI diagnosed using clinical criteria show no detectable pathogenic variants within known gene regions [14,15]. Indeed, a recent large-cohort study reported a confirmed molecular diagnosis in only 45–65% of CHI patients, underscoring the complexity of this condition and the potential involvement of unknown loci, deep intronic variants, and/or mosaic mutations [11,14,15].

The emergence of next-generation sequencing platforms, particularly whole-exome sequencing (WES), has also increased diagnostic rates in CHI, enabling concurrent testing of multiple candidate genes [16-18]. Molecular diagnosis, besides being essential for ascertaining disease pathogenesis, also facilitates predictions regarding treatment responses, surgery, and long-term prognosis [16, 19-21]. Rapid detection of genetic mutations is particularly important for neonatal CHI, as missed diagnoses can lead to adverse neurodevelopmental outcomes [18, 21].

Due to the scarcity of information on the molecular spectrum in congenital hyperinsulinism in this regional area and the importance of genotype and phenotype correlations in clinical management, this research study aims to identify the genetic mutations related to CHI in a pediatric population through whole exome sequencing and establish a relationship between these findings and clinical outcomes. [22-25]

Congenital hyperinsulinism remains poorly characterized in many Middle Eastern populations, and published molecular data from Iraq are extremely limited. Most available genetic studies originate from Europe, North America, and a few neighboring countries, leaving a significant epidemiological gap in Iraqi pediatric populations. Although the present cohort is small, it provides preliminary molecular data on congenital hyperinsulinism in Iraqi children and contributes to the limited regional literature on genotype distribution and treatment response.

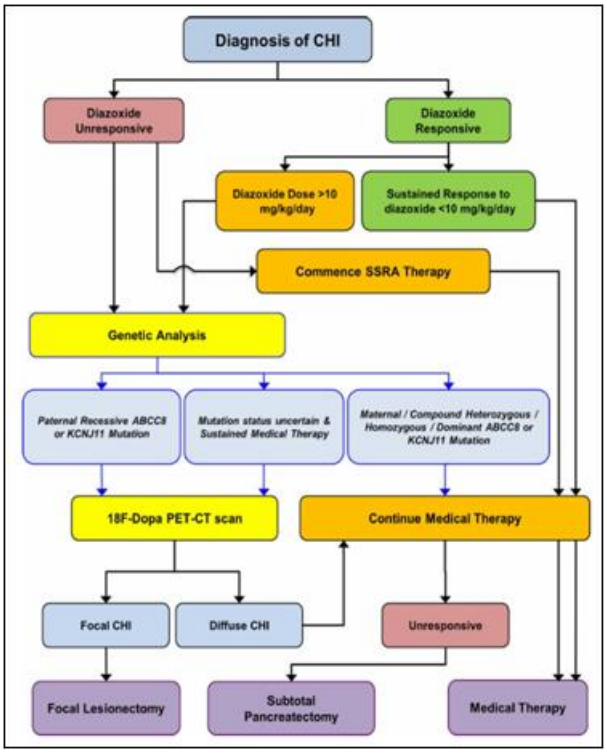

Figure 3: Diagnostic and therapeutic algorithm for congenital hyperinsulinism based on clinical presentation, biochemical criteria, and genetic findings.

2. Materials and Methods

Study Design

This cross-sectional observational study was carried out to evaluate the molecular genetic basis for congenital hyperinsulinism (CHI) in pediatric subjects who developed persistent hypoglycemia.

Study Population

In the study period, 16 children were assessed for hypoglycemic syndrome of various causes. Based on thorough clinical and biochemical analysis, 16 children were found to have congenital hyperinsulinism, and the study was conducted on them.

Patients with hypoglycemia due to other causes, such as endocrine deficiencies (like cortisol and growth hormone deficiency), metabolic disturbances, systemic diseases, and transient neonatal hypoglycemia, were excluded from the CHI.

Diagnostic Criteria for Congenital Hyperinsulinism

The diagnosis of congenital hyperinsulinism was made following international clinical guidelines that include recommendations made by the Pediatric Endocrine Society. CHI was diagnosed after the patient had been documented with hypoglycemia with plasma glucose levels of less than 50 mg/dL, together with inappropriate insulin secretion levels as evidenced by one or more of the following:

- Detectable or inappropriate elevation of serum insulin concentration during hypoglycemia,
- Decreased plasma ketone bodies and free fatty acids,
- A glycemic response of ≥30 mg/dL following administration of glucagon during hypoglycemia
- Necessity for enhanced glucose infusion rates to maintain normoglycemia
- The diagnosis of CHI relied solely on clinical and biochemical findings and did not involve genetic testing.

Clinical Data Collection

The information was obtained retrospectively from the subjects' medical records. The variables were age at presentation, gender, gestational age, birth weight, family history of hypoglycemia, consanguinity, presenting symptoms, biochemical profiles, and treatment response.

Molecular Genetic Analysis

Molecular genetic studies were conducted after clinical improvement. Genomic DNA was isolated from peripheral blood leukocytes using conventional DNA extraction procedures. Molecular analyses were not performed during hypoglycemic attacks because genetic studies do not require specimen collection during hypoglycemia.

Whole-exome sequencing was performed using a targeted clinical exome panel covering known congenital hyperinsulinism–associated genes, including **ABCC8, GLUD1, HADH, and HNF1A**. Sequencing achieved a mean coverage depth >100×, with >98% of target regions covered at ≥20×.

Library preparation, sequencing, and bioinformatic analysis were conducted at a **certified molecular genetics laboratory in Erbil, Iraq**. Variant interpretation followed **ACMG guidelines**, with pathogenicity assessed using ClinVar, population databases, and published literature.

Raw sequencing reads were processed using a standard bioinformatic pipeline including quality control, alignment to the human
reference genome (GRCh38), variant calling, and annotation. Variants were filtered based on read depth, variant quality score, and population allele frequency. Variants with a minor allele frequency greater than 1% in population databases (gnomAD, 1000 Genomes) were excluded unless previously reported as disease-causing. Candidate variants were prioritized based on gene relevance to congenital hyperinsulinism and predicted functional impact.

In silico prediction tools including **SIFT, PolyPhen-2, and MutationTaster** were used to evaluate potential pathogenicity. Variant classification followed the **American College of Medical Genetics and Genomics (ACMG) guidelines**, and variants were categorized as **pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, or benign**. Only pathogenic or likely pathogenic variants were included in the final analysis. Variants classified as VUS were recorded but not considered diagnostic.

Ethical Approval

The study was approved by the Local Institutional Ethics Committee of the Faculty of Medicine, University of Karbala (Approval No.: [265], Date: [1-2-2025]).

Statistical Analysis

Data were entered into a computerized database, cleaned, and analyzed using SPSS version 28. Descriptive statistics were used to summarize categorical variables as frequencies and percentages. The Chi-square test was applied to assess associations between genetic variants and clinical characteristics. A p-value ≤ 0.05 was considered statistically significant, and $p < 0.01$ was considered highly important.

3. Results

Table 1 summarizes the demographic and clinical features of the 16 pediatric patients diagnosed with congenital hyperinsulinism. Most were born at full term (81.3%) and had normal birth weight (75%), with an equal distribution between males and females. Half of the cases (50%) presented during infancy, followed by 37.5% in the neonatal period. Consanguinity was reported in 50% of patients. Clinically, the majority (87.5%) presented with hypoglycemic seizures, while 12.5% were asymptomatic and diagnosed incidentally.

Table 1: Demographic & Clinical Characteristics of Pediatric Patients with Congenital Hyperinsulinism

Variables	Groups	N	%
Maturity	Full term	13	81.3
	Pre term	3	18.8
Sex	Male	8	50
	Female	8	50
Birth weight	LBW	2	12.5
	NBW	12	75.0
	HBW	2	12.5

As shown in Table 2, 50% of patients responded to diazoxide, 31.2% were treated with octreotide, and 18.8% underwent pancreatectomy. Genetic mutations were identified in 62.5% of cases, most commonly in the ABCC8 gene (43.8%), while GLUD1, HADH, and HNF1A mutations were each found in 6.3%. No mutation was detected in 37.5% of patients.

Table 2: Line of Management and Genetic Variant for Pediatric Patients with Congenital Hyperinsulinism

Variables	Groups	Number	Percentage
Line of management	Diazoxide response	8	50.0
	Octreotide	5	31.2
	Pancreatectomy	3	18.8
	Total	16	100%
Genetic variant	ABCC8	7	43.8
	GLUD1	1	6.3
	HADH	1	6.3
	HNF1A	1	6.3
	No identified gene	6	37.5
	Total	16	100

Association Between Clinical Features and Genetic Mutations

Table 3 highlights significant associations between clinical factors and genetic mutations. Early-onset cases, particularly in infancy and the neonatal period, were more likely to harbor mutations, predominantly in **ABCC8** and **GLUD1**. Genetic mutations were also more frequent in full-term births and in patients who responded well to medical treatment. No significant associations were observed with sex or birth weight. Early disease onset and medical treatment response showed statistically significant associations with the presence of pathogenic variants; however, these findings should be interpreted cautiously due to the limited sample size.

No significant association was found between genetic mutations and either a positive family history of hyperinsulinism or the presenting symptoms (symptomatic vs. asymptomatic).

Table 3: Association of Maturity, Response to medical, and Birth weight with the genetic heterogeneity among congenital hyperinsulinism

Variable	Groups	Genes					P-value
		ABCC8	GLUD1	HADH	HNF1A	No	
Age Presenting	Neonatal	3	1	1	0	1	0.001[S]
	Infant	3	0	0	0	5	
	Toddler	1	0	0	0	0	
	Pre-school	0	0	0	0	0	
	School	0	0	0	1	0	
Sex	Male	5	1	1	1	1	0.065[NS]
	Female	2	0	0	0	5	
Maturity	Full term	7	1	0	0	5	0.001[S]
	Pre term	0	0	1	1	1	
Response to medical	Response	6	1	0	1	5	0.004[S]
	No response	1	0	1	0	1	
Birth weight	LBW	1	0	0	1	0	0.723[NS]
	NBW	4	1	1	0	6	
	HBW	2	0	0	0	0	
Family history	Negative	5	1	0	1	6	0.054[NS]
	Positive	2	0	1	0	0	
Presenting Complains	Asymptomatic Hypoglycemia (accidental)	1	0	0	0	1	0.123 [NS]
	Hypoglycemic fit	6	1	1	1	5	
Chi-Square Results are presented as N (%), p<0.05 considered significantly different, [S]= Significant, [NS]= non-significant							

4. Discussion

Compared with the Iranian cohort reported by Razzaghy-Azar et al. (2022), which included 44 patients, the present study provides novel data from an underrepresented Iraqi population. Despite the smaller sample, the mutation detection rate (62.5%) was comparable, supporting the relevance of ABCC8 as the predominant gene across Middle Eastern populations. This study contributes region-specific genetic insight where published data are scarce. (26), Turkey (63%) (27), and the United States (47%) (20). Nonetheless, 37.5% of patients did not have a confirmed genetic diagnosis, consistent with Clemente G., who found that in almost half of cases, a diagnostic gap existed (14). Ritika Kapoor reported that in her study, only 45.3% of patients received a genetic diagnosis (13), and Zenker noted that up to 50% may be associated with unknown loci (23).

This limitation may be due to assay sensitivity, such as the inability to detect mosaic mutations that are absent from the blood or detectable only in pancreatic cells (15). Our data also support the genetic heterogeneity of CHI, as shown in Tables 2 and 3.

Diazoxide was therapeutically effective in 50% of cases in our series. These findings corresponded with those of Munib A., who reported responsiveness in 57.9% of those presenting in the first year of life and in 50% thereafter (28), as well as with those of Zeynep Şıklar, who reported responsiveness in 71% of Turkish Patients (27). Octreotide was found to be a useful second-line agent in our nonresponsive diazoxide group, thereby validating its effectiveness in nonresponsive CHI (17). Pancreatectomy was necessary in our non-responsive CHI, validating its role in CHI that does not respond to treatment (18).

Genetically, in addition to ABCC8, mutations in GLUD1, HADH, and HNF1A were identified (6.3% in each, indicating the complexity of CHI's genetic background). This is

consistent with previous studies that highlighted the broad spectrum of genetic alterations (12).

Clinically, early onset, especially during the neonatal and infant stages, showed a significant association with mutations in ABCC8 and GLUD1, suggesting that mutations may have a more specific association with early events (12) (29). Being a full-term infant was also associated with a higher frequency of identifiable mutations, consistent with findings reported by Maria-Sofia Kalogeropoulou (29).

Additionally, patients who responded satisfactorily to medical treatment were more likely to have recognizable mutations. This concurs with a study by Maria and Patricia, which showed that ABCC8-related CHI tended to react effectively to conserved therapy (30). By contrast, Huseyin Demirbilek reported that 94% of diazoxide-nonresponsive patients carried an ABCC8 mutation, thereby reinforcing the notion of phenotypic variability (31).

There were no significant associations between genetic mutations and positive family history or presentation type (asymptomatic versus symptomatic). The lack of association with family history could be explained by a high rate of de novo mutations. Likewise, symptomatic conditions like hypoglycemic seizures occurred frequently regardless of any genotype. Munib A. explained that seizures were predominantly observed in the subject group (73.7% in the first year and 100% thereafter), rather than due to specific genes, because delayed presentation was the primary factor (28).

Our findings further emphasize the importance of early identification and systematic evaluation of neonatal disorders, consistent with previous regional pediatric studies that have demonstrated improved outcomes with early screening and intervention. (32)

5. Limitations

This study faced several limitations. Key components of the critical sample panel, such as free fatty acids and β-hydroxybutyrate, were unavailable at the study center, thereby limiting a full biochemical assessment. Some essential investigations were also inconsistently accessible within the hospital. Genetic testing was performed in a specialized laboratory located in Erbil (northern Iraq), which was geographically distant from the study site, contributing to logistical challenges and delays. The high cost of genetic analysis, fully covered by the researcher, further limited broader family testing. As a result, parental genetic studies, essential for accurate diagnosis and genetic counseling, could not be performed. Additionally, the turnaround time for genetic results (4–6 weeks) can delay treatment decisions in certain cases.

The small sample size (n = 16) represents a significant limitation and restricts the generalizability of genotype–phenotype correlations. Statistical associations should therefore be interpreted as exploratory rather than confirmatory, and larger multicenter studies are required to validate these findings.

The overutilization of non-targeted laboratory investigations, previously documented in local hospitals, further underscores the need for cost-effective diagnostic pathways, particularly for rare endocrine disorders that require specialized testing. (33)

6. Conclusion

Pathogenic or likely pathogenic variants were identified in **62.5% of children with congenital hyperinsulinism**, with **ABCC8 mutations representing the most frequently detected genetic alteration**. Early disease onset and responsiveness to medical therapy were significantly associated with the presence of detectable mutations. However, these findings should be interpreted cautiously due to the **small sample size and exploratory nature of the analysis**. Whole-exome sequencing can improve the molecular diagnosis of congenital hyperinsulinism and may assist in guiding individualized therapeutic decisions. Nevertheless, the presence of genetically unresolved cases highlights the need for **broader genomic investigations and larger multicenter studies** to better define the molecular spectrum of congenital hyperinsulinism in regional populations.

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Conflict of Interest:
The authors declare no conflict of interest.

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