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Morpho-Functional and Mutational Spectrum of Congenital Hypothyroidismin a Newborn Screening Cohort from Delhi

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Abstract

Congenital hypothyroidism (CH) is a leading preventable cause of intellectual disability, with a notably high incidence in India. However, data integrating its morphologic and genetic etiology in Indian cohorts remain scarce. Aim of this study was to characterize its etiology via thyroid imaging to assess TSH levels across morphological sub-types and genetic analysis in a subset of the CH cases with dyshormonogenesis. In this multicentric prospective study,approximately 200,000 newborns (≥34 weeks) recruited from across20hospitals in Delhi state underwent TSH screening via heel prick. CH was confirmed by venous testing and managed with levothyroxine and etiological evaluation included thyroid ultrasonography and technetium scintigraphy. Dyshormonogenesis was the most common etiology (62%), followed by thyroid dysgenesis. Athyreosis showed the highest TSH levels and dyshormo-nogenesis had significantly lower values ($p<0.001$). Male neonates exhibited greater skeletal maturation delay. Whole exome sequencing revealed monogenic (n=17) and digenic (n=7) inheritance in 24/41 samples (58.53%) of the dyshor-monogenesis cases, with known and novel variants in reported genes and TG was the most frequently mutated gene. Integrating genetic, phenotypic, and functional data may enhance our understanding of CH and guide precision care.

Keywords: congenital hypothyroidism; thyroid dyshormonogenesis; newborn screening; monogenic inheritance; digenic inheritance; India

1. Introduction

Congenital hypothyroidism (CH) remains one of the leading preventable causes of intellectual disability worldwide. The incidence of CH in India has been recently delineated as high, with rates ranging from 1 in 727 to 1 in 1528 across multiple centers, including an Indian Council of Medical Research (ICMR)-supported multicentric study [1]. These data underscore CH as a major public health concern. Etiologically, CH encompasses a spectrum of disorders traditionally classified into four broad categories: thyroid dysgenesis (TD), thyroid dyshormonogenesis, central hypothyroidism, and transient hypothyroidism [2].

In iodine-sufficient regions, TD is the predominant etiology, accounting for approximately 80–85% of CH cases [3,4]. Although the majority of TD cases are sporadic, monogenic causes have been identified in about 2–5% [5,6]. Key genes implicated in TD include TSHR, NKX2-1, PAX8, FOXE1, and GLIS3, with additional associations noted for NKX2-5, CDCA8, JAG1, and NTN1 [7,8]. Dyshormonogenesis arises from pathogenic variants in genes responsible for the synthesis,

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iodination, storage, and secretion of thyroid hormones. Commonly involved genes include TG, TPO, DUOX2, DUOXA2, SLC5A5, SLC26A4, and IYD [7]. Central hypothyroidism may be due to mutations in TSHB, TRHR, TBL1X, and IGSF1[9,10] . Because most newborn screening programs utilize TSH-based algorithms, central hypothyroidism is frequently underdiagnosed in routine screenings. Studies have shown that individuals of Asian descent harbor a higher mutational load for CH-related genes, potentially explaining the increased prevalence seen in migrant populations in Western countries[11,12] as evidenced by increasing incidence reported from geographical area with south east Asian migration in the recent past. Of note, transient congenital hypothyroidism (CH) is a reversible thyroid hormone deficiency, often linked to iodine imbalance, maternal antithyroid drugs, or transplacental TSH receptor-blocking antibodies, with resolution typically within weeks to months.

In this study, we present robust phenotyping robust phenotyping data of the screen positive and con-firmed cases of CH from a large-scale, prospective birth cohort of 203,400~200,000 screened across 20 hospitals in Delhi state (2014–2016). We also analyzed the genetic architecture of a subset of dyshormono genesis cases among the affected neonates and highlight the mutation spectrum including spectrum including oligogenic inheritance observed in this category of CH.

2. Materials and Methods

This prospective multicentric study was conducted across 20 hospitals representing five administrative zones of Delhi (Central, West, East, North, and South), encompassing both public and private healthcare facilities. Institutional Ethics Committee approvals were obtained from all participating centers. Written informed consent was secured from parents or legal guardians after structured counselling and provision of a detailed patient information document indicating the hospital of birth. Participant confidentiality was strictly maintained during data handling and analyses.

A total of ~200000 newborns (≥34 weeks gestation) were screened between November 2014 and November 2016. Heel prick samples were collected by trained nursing personnel, preferably

after 24 hours of life, and blotted on Whatman 903 filter paper. Dried specimens were transported under controlled conditions to the central genetics laboratory at Lok Nayak Hospital attached to Maulana Azad Medical college, a tertiary care centre with a dedicated newborn screening laboratory. Neonates with thyroid-stimulating hormone (TSH) concentrations >20 mIU/L (serum-equivalent units) on newborn screening were recalled for confirmatory venous testing, including serum TSH, free thyroxine (fT4), and free triiodothyronine (fT3). TSH concentrations in dried blood spots were measured using the Genomic Screening Processor (GSP) neonatal TSH assay (PerkinElmer, USA), a time-resolved, solid-phase, two-site fluoroimmunometric assay employing monoclonal antibodies targeting two distinct epitopes on the TSH molecule. The analytical sensitivity of the assay was <2 mIU/L (blood).

All confirmed CH cases underwent skeletal evaluation using anteroposterior knee radiographs to assess the distal femoral epiphysis for estimation of bone age. Bone age was classified as normal (bilateral ossifi-cation nuclei >3 mm) or delayed (small or absent ossification cores), based on established gestation-al-age-specific norms. Thyroid ultrasonography was performed within the first month of life, preferably at the time of diagnostic confirmation. A single experienced radiologist (over 20 years of expertise) conducted imaging using 7–12 MHz linear transducers (ATL Ultramark 9, HDI 5000, IU-22; Philips, Bothell, WA), with the neonate in a supine position and the neck extended. If the thyroid was not visualized in its orthotopic location, ectopic tissue was sought along the migratory tract from the base of the tongue to the anterior neck. Gland size, echotexture, vascularity, and structural anomalies (e.g., cysts or nodules) were documented.

Thyroid scintigraphy was performed using technetium-99m pertechnetate prior to or within five days of initiating therapy. After intravenous administration of 37 MBq (1 mCi) of tracer, imaging was conducted 15 minutes post-injection using a low-energy, pinhole collimator (Vertex V60; ADAC Laboratories, NY) with 120-second frames. Scintigraphy interpretation, performed by a single nuclear

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medicine specialist, classified thyroid uptake as: (a) absent, (b) ectopic, or (c) reduced, normal, or increased in orthotopic location. Reference uptake range for the tracer was 1.7–4.0%, as defined by the collaborating institution namely Institute of nuclear medicine at DRDO, New Delhi. Sub-classification of dyshormonogenesis using perchlorate discharge testing or other functional assays could not be performed due to logistical constraints.

Genetic Analyses

Methodology:

Written informed consent for participation in genetic studies was obtained separately from parents or legal guardians following structured pre-test genetic counseling. A cohort of 47 neonates diagnosed with thyroid dyshormonogenesis was selected for whole exome sequencing (WES) to identify potential disease-causing genetic variants, using a commercial facility(Medgenome, Bengaluru). The WES data analysis pipeline adhered to our previously established protocol. Raw sequencing data underwent quality control using FastQC and were trimmed with Trim-momatic. Processed reads were aligned to the human reference genome (GRCh38) using BWA-MEM. Variant calling was performed with GATK HaplotypeCaller, and variants were annotated using the Variant Effect Predictor (VEP). The analysis targeted ultra-rare, protein-altering variants, including nonsense, frameshift, canonical splice-site, and missense mutations, with a minor allele frequency (MAF) less than 0.001 in public databases such as gnomAD, dbSNP and ClinVar. Variant interpretation followed the American College of Medical Genetics and Genomics (ACMG) guidelines. A curated list of genes associated with thyroid dyshormonogenesis and congenital hypothyroidism was compiled from the Online Mendelian Inheritance in Man (OMIM) and Human Phenotype Ontology (HPO) databases. Variants classified as pathogenic, likely pathogenic, or of uncertain significance (VUS), as well as novel variants without prior annotation, were prioritized for further analysis in these candidate genes.

3. Results

Among 203,400newborns screened, 200 had capillary TSH concentrations >20 mIU/L. Of these, 82/200 (41%) were found to have isolated hyperthyrotropinemia and were subsequently diagnosed with transient congenital hypothyroidism (TCH) on follow-up. Notably, 23% of the transient CH group had undergone early sampling at 22–24 hours of life due to anticipated early discharge.

Of the remaining 118 neonates with confirmed permanent CH, 97 could be recalled and evaluated at the study center. Among the 21 not evaluated, 12 could not be traced despite field visits and administrative efforts, and 07 had expired within the first two postnatal weeks. Causes of death included congenital heart disease (n=2), respiratory distress syndrome in a preterm twin (n=1), and neonatal sepsis(n=4). Two neonates were followed at other centers, and data were not retrievable. (See Figure 1: Study flowchart).

All 97 neonates with confirmed CH underwent ultrasonography and knee X-ray for thyroid morphology and skeletal maturation, respectively. Technetium-99m thyroid scintigraphy was performed in 47 infants. Limitations in performing scintigraphy included loss to follow-up, unavailability of the isotope during a two-month window, and initiation of therapy beyond 7 days of life and early institution of therapy precluding imaging in neonates with a TSH of more than 80.

Based on imaging, 37 neonates (38%) were diagnosed with thyroid dysgenesis (TD), while 60(62%)had normal gland location and were categorized as suspected dyshormonogenesis. Among the TD group, 20 (21%) had agenesis, 9 had ectopic glands, 6 had hypoplasia, and 2 had hemiagenesis.

Comparison of mean capillary TSH values among the different morphological groups is presented in Table 1. Figures 2 and 3 shows that mean and log-transformed TSH levels were highest in the athyreosis group and lowest in those with dyshormonogenesis ($p<0.001$). No statistically significant difference was noted between hypoplasia and dyshormonogenesis groups ($p=0.16$).

Sexual dimorphism in skeletal maturation was observed, with male neonates exhibiting a higher frequency of delayed epiphyseal ossification. Figure 3 illustrates the association between capillary TSH levels and skeletal maturation by sex.

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Genetic analyses:

Genetic analyses were conducted on a subset of 47 neonates with congenital hypothyroidism (CH). Of these, 6 samples failed quality control (QC), leaving 41samples for variant analysis. Among these, 24 (58.53%) neonates carried rare variants in genes associated with dyshormonognesis while 17had no variants in reported genes curated from HPO and OMIM as detailed in the methodology above. A total of 31 rare variants across 14 genes (*TG, TSHR, DUOX2, DUOXA2, PAX8, SLC26A7, LHX4, KMT2D, ADAMTSL1, PLAA, TRAPPC9, TONSL, TXNRD2,* and *TBC1D24*) were identified in 24 subjects. 17 neonates harbored variants in a single CH-associated gene (monogenic), whereas 7 had variants in two such genes (digenic). Of these, 12 were novel with global MAF 0.0 in reported genes. Mutations were most frequently identified in *TG* (6 variants), *DUOX2* (3 variants), and *DUOXA2* (2 variants) among those linked to dyshormonogenesis. Additionally, variants were identified in *TSHR* (3 variants) and *KMT2D* (4 variants). Of note, all except one variant in *DUOXA2* were heterozygous (Table 2). The majority of variants were missense (28/31), with 2 stop-gained and 1 in-frame deletion. 18 variants (58.06%) were classified as variants of uncertain significance (VUS), while 7 were deemed pathogenic or likely pathogenic according to ACMG criteria, and the remaining 6 variants lacked any ACMG annotation at present (Table 2 and supple Table 1). Beyond these 31 variants, others observed with high Combined Annotation Dependent Depletion (CADD) scores but annotated as benign or likely benign in ClinVar and/or ACMG guidelines, are not shown.

4. Discussion

Clinical:

Congenital hypothyroidism (CH) continues to be a significant public health concern in India, with consistently high prevalence across regions. A recent meta-analysis reported CH prevalence as 1 in 1031 among term neonates in non-endemic regions, rising to 1 in 13 in endemic regions, 1 in 20 in offspring of mothers with thyroid disorders, and 1 in 71 in preterm neonates [13] . The multicentric ICMR Task Force study similarly reported CH prevalence rates of 1 in 1130 and 1 in 1141 in neonates from Delhi [1].

Given the high national burden of CH, it is essential to not only ensure early identification and treatment but also to investigate the underlying etiology and population-specific molecular mechanisms. Traditionally, etiologic classification of CH has relied on imaging-based phenotyping. A recent meta-analysis reported that 86% of screen-positive neonates are confirmed to have CH, with 14% classified as transient. Among confirmed cases, thyroid dysgenesis accounts for 56.6%, dyshormonogenesis for 38.7%, and 4.4% remain undefined [13].

In our study cohort, 62% of confirmed CH cases had a structurally normal thyroid, suggestive of dyshormonogenesis. This rising proportion of dyshormonogenesis—as opposed to thyroid dysgenesis—has been increasingly observed in recent Indian and international studies, including the ICMR study which reported a dyshormonogenesis rate of 47% [1,13]. This shift may reflect multiple factors like higher incidence endogamy, shifting of semiskilled and unskilled labor to a metropolitan city like Delhi and emerging genetic insights and enhanced molecular diagnostic capabilities.

Genetic:

Historically, TD has been considered a predominantly sporadic condition, with only 2–5% attributed to monogenic causes, whereas dyshormonogenesis is known to follow an autosomal recessive inheritance due to mutations in different genes affecting thyroid hormone biosynthesis. However, data from next-generation sequencing, particularly whole exome sequencing have challenged this dichotomy. Studies have now identified pathogenic variants in both TD- and dyshormonogenesis-associated genes in neonates with CH, irrespective of imaging phenotype, suggesting that CH pathogenesis is more complex than previously believed and influenced by genetic, epigenetic, and environmental factors[14,15]. Furthermore, we also observed a digenic inheritance in dyshormonogenesis in a proportion of samples that we analysed (Table 2).

The genetic landscape of congenital hypothyroidism (CH) is characterized by significant heterogeneity, encompassing genes directly involved in thyroid development and hormone

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synthesis, as well as those contributing through syndromic or indirect mechanisms. This study identified 31 rare variants across 14 genes (TG, TSHR, DUOX2, DUOXA2, PAX8, SLC26A7, LHX4, KMT2D, ADAMTSL1, PLAA, TRAPPC9, TONSL, TXNRD2, and TBC1D24) in 24 neonates with CH, providing insights into both established and potentially novel genetic contributors (Table 2). Mutations in TG was most common among the subjects, including a novel variant (8:132887432;G>A;ACMG:Likely Pathogenic) . It encodes a glycoprotein critical for thyroid hormone synthesis, and mutations impair hormone production, leading to dyshormonogenesis [16] . Similarly, of the three variants one was novel (14:81088021;A>G; ACMG: prediction not available) in TSHR (thyroid-stimulating hormone receptor) which mediates TSH signaling, and loss-of-function mutations result in reduced thyroid hormone production, a known cause of non-syndromic CH [17].DUOX2 (dual oxidase 2) and DUOXA2 (dual oxidase maturation factor 2) are essential for generating hydrogen peroxide, a key component in thyroid hormone synthesis [18] , and mutations in these genes are established causes of TDS. Both the variants identified in DUOXA2 were novel (15:45116229_G>A, 15:45114733_C>A; ACMG: prediction not available) with only one in homozygous condition. Other genes such as PAX8 (paired box 8), a transcription factor, is crucial for thyroid gland development and SLC26A7 (solute carrier family 26 member 7), a pendrin-like protein, facilitates iodide transport, and mutations can cause CH, often with goiter. Two novel heterozygous variants (2_113246871;G>A; ACMG: Likely Pathogenic, 2:113241683;G>T; ACMG: Likely Pathogenic) were in PAX8. Other genes identified in this study contribute to CH through indirect or syndromic mechanisms. LHX4 (LIM homeobox 4), which also had a novel variant (1:180266438;A>T; ACMG:VUS) is a transcription factor involved in pituitary development, is associated with combined pituitary hormone deficiency (CPHD), which can include central hypothyroidism due to impaired TSH production. This suggests that some CH cases in this cohort may involve central rather than primary hypothyroidism, highlighting the importance of evaluating the hypothalamic-pituitary-thyroid axis. KMT2D (lysine methyltransferase 2D) is primarily linked to Kabuki syndrome, a multisystem disorder that can include transient or persistent congenital hypothyroidism among other endocrine abnormalities. The presence of KMT2D variants including one novel (12:49039547;G>A; ACMG: prediction not available) in this study suggests that some neonates may have syndromic CH, necessitating comprehensive phenotypic assessment. Similarly, ADAMTSL1 (ADAMTS-like 1) is associated with a complex phenotype including developmental glaucoma, craniofacial anomalies, and CH due to thyroid dysgenesis. Role of this gene in CH appears to be part of a broader syndromic presentation, emphasizing the need to consider multisystem disorders in genetic evaluations of CH. The identification of variants in well-established CH genes (TG, TSHR, DUOX2, DUOXA2, PAX8, SLC26A7) reinforces the utility of targeted genetic testing for these loci in CH patients. The presence of syndromic genes like KMT2D and ADAMTSL1 reiterates comprehensive phenotypic evaluations. The high proportion of variants of uncertain significance (VUS, 58.06%) in this study highlights the challenge of interpreting novel variants, particularly for genes with unclear roles (PLAA, TRAPPC9, TONSL, TXNRD2) (Table 2) warranting functional studies. Moreover, the genetic heterogeneity observed, including digenic cases, suggests that CH may result from complex interactions, encouraging further investigation into digenic/oligogenic mechanisms. We observed variants in known genes in only ~60% of our study subjects which confirm the contribution of these genes and also identified potential syndromic contributors (KMT2D). Conversely, observation of a notable number of heterozygous variants in known genes, presence of genes with VUS (Table 2)or even those identified benign albeit with high CADD scores (not shown) emphasizes the need for a revisit of genetic data in the light of the di/oligogenic nature and genes of minor effect (and possible recruitment of familial cases), for a conclusive interpretation and diagnostic precision in CH. Finally, integrating genetic, phenotypic, and functional data will enhance our understanding of CH and inform personalized management strategies. Long et al. [19]reported that neonates with oligogenic CH profiles required higher thyroxine doses compared to those with monogenic CH, supporting the potential utility of molecular profiling in optimizing long-term therapy and achieving precision care in CH.For instance, the clinical expression of mutations in genes such as DUOX2/DUOXA2 varies

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widely between individuals and over time, with some patients requiring no treatment, and some having transient CH. In contrast, DUOX gene mutations can be associated with worsening of thyroid fucntions in the first weeks of life [20]. However, justification for screening and detecting biochemically less severe eventually transient CH cases require assessment of neurodevelopmental sequelae, but this has been proved difficult [21] . Long-term outcome studies of the effect of LT4 treatment on prevention of neurodevelopmental delay in these patients will also be required. This stresses the need for underpinning the molecular spectrum involved [21].

An important ancillary finding in our cohort was the effect of sexual dimorphism on skeletal maturation. Similar findings, with male neonates more likely to present with delayed epiphyseal ossification were previously reported [22]. Since delayed skeletal maturation has traditionally been used as a proxy for disease severity, recognition of sex-specific differences is crucial to avoid overestimation of severity in male neonates. Additionally, sex-based neurodevelopmental vulnerabilities must be considered, given higher reported rates of learning disabilities among boys, which may otherwise be erroneously attributed to more severe CH [22]. Beyond the genes already established for congenital hypothyroidism, our analysis has identified several genes that, while not directly implicated in this condition, demonstrate connections to thyroid-related pathways or associated disorders. A rare IGSF1 variant illustrates its role as the leading genetic cause of congenital central hypothyroidism. IGSF1, a pituitary transmembrane glycoprotein, regulates thyroid hormone homeostasis by sustaining TRH receptor (TRHR) expression through inhibition of TGF-β1–Smad signaling. Loss-of-function mutations impair glycosylation and surface trafficking, reducing TRHR levels and causing hypothyroidism. The disorder is X-linked, predominantly affecting males, with occasional manifestation in female carriers. We did not classify the IGSF1 variant as causative. Being X-linked recessive, definitive interpretation requires parental genotyping to confirm segregation. Without this, the variant may represent a benign familial change rather than a true pathogenic allele. Misinterpretation is common, especially with inherited missense variants of low predictive value. Moreover, studies show that assuming X-linkage without segregation analysis risks error, as genetic heterogeneity and phenocopies are frequent.However, comprehensive validation of these candidate genes through detailed functional analysis and parental screening remains beyond the current scope of this research. Such investigations would require dedicated studies to confirm their pathogenic roles in congenital hypothyroidism and establish definitive genotype-phenotype correlations, representing important avenues for future research in this field.

CH fulfills the classic Wilson and Jungner criteria for population screening in the Indian context [23]. A recent cost-effectiveness analysis demonstrated that newborn screening for CH in India yields a high benefit-cost ratio (1.8–6.0), even when assuming a modest 40% reduction in disability-adjusted life years (DALYs) [24]. This further justifies nationwide implementation of universal newborn screening programs for CH. This study lacked segregation analysis in families, TSH and thyroxine dose comparisons across genotypic groups highlighting the need for further mechanistic and population-level studies.

5. Conclusions

This study combines population screening with molecular analysis, confirming the value of existing protocols while extending etiological understanding via advanced sequencing. Results promise improved diagnosis, genetic counseling, and individualized therapies for congenital hypothyroidism. Future work should dissect unresolved cases through multilocus analyses of rare and common variant interactions to refine genotype–phenotype mapping, prognostication, and targeted interventions.

Appendix A

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