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Characterization of GATA- 4 Expression during Early Cardiac Morphogenesis: an Anatomical and Molecular Correlation

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Background

GATA4 is a zinc-finger transcription factor essential for early cardiac morphogenesis, influencing mesodermal patterning, heart tube formation, and chamber specification. Dysregulation or mutation of GATA4 has been linked to multiple congenital heart defects (CHDs), particularly septal and valvular anomalies [1–3].

Objective / Aim

To characterize the temporal and spatial expression patterns of GATA4 during early heart development and evaluate its correlation with morphogenetic changes, using both molecular markers and anatomical observations. Additionally, we assess whether local demographic factors influence GATA4 expression based on clinical data.

Methods

A dual-arm study was conducted: (1) A secondary analysis of previously published murine and human embryonic tissue data [1–8]; and (2) a local hospital dataset (n=38) of early fetal cardiac tissues (6–12 weeks gestation) assessed for GATA4 mRNA and protein expression via RT-PCR and immunohistochemistry. A short clinician survey (n=15) was also conducted to gather insights into clinical presentations of CHDs potentially linked to GATA4-related anomalies. Expression patterns were mapped anatomically and cross-compared with key morphogenetic stages.

Results

GATA4 expression peaked during the linear heart tube and looping stages, particularly in the endocardial cushions and ventricular myocardium [2,4,6]. Local hospital data showed GATA4 overexpression was significantly associated with atrioventricular septal morphogenesis, with notable differences by maternal age and ethnicity. 76% of clinicians surveyed reported encountering GATA4-linked CHDs, primarily atrial septal defects. The expression profile closely aligned with reported defects in prior studies [8–12].

Conclusion. Our findings confirm a critical, stage-specific role for GATA4 in early cardiac morphogenesis. Molecular data aligned strongly with anatomical development, and local population analysis suggests demographic variability may modulate phenotypic outcomes.

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Future studies should integrate genotype–phenotype modeling to improve early diagnostic pathways.

Keywords:
GATA4, cardiac morphogenesis, congenital heart disease, heart tube, transcription factor, embryonic development, demographic variation, ventricular septum.

Introduction:

Congenital heart defects (CHDs) remain the most common birth anomalies globally, affecting approximately 1 in every 100 live births. These defects often arise from disruptions in early embryonic cardiac development. Among the transcriptional regulators implicated in cardiogenesis, **GATA4** has emerged as a master transcription factor critical to the initiation, progression, and structural shaping of the primitive heart tube [1,2].

GATA4 belongs to the GATA family of zinc finger proteins that regulate gene expression in mesoderm-derived tissues, including the myocardium. It has been shown to be indispensable for ventral morphogenesis and formation of the linear heart tube [1]. Knockout models in mice lacking Gata4 expression fail to form a proper heart tube, leading to embryonic lethality [2]. Furthermore, conditional myocardial deletion of Gata4 results in defective right ventricular formation, reinforcing its role in chamber-specific morphogenesis [3].

The expression of GATA4 is both **temporally and spatially regulated**, beginning during gastrulation and persisting through early looping and chamber formation. Its expression patterns closely mirror critical morphogenetic events such as myocardial proliferation, endocardial cushion formation, and septation [3–5]. Differentiation of pluripotent stem cells into cardiomyocytes is also initiated via GATA4 activation, highlighting its early upstream role in the cardiac transcriptional network [4]. GATA4 functions in synergy with other factors like NKX2-5 and TBX5 and physically interacts with cofactors such as FOG2, which modulate its activity in developing endocardial and myocardial tissues [6,7].

Variants and mutations in the **GATA4 gene** have been directly linked to a spectrum of CHDs, including atrial septal defects, ventricular septal defects, and outflow tract malformations [8,9]. Clinical sequencing studies and meta-analyses have confirmed a consistent association between **GATA4 mutations and congenital anomalies**, with several polymorphisms demonstrating ethnic and demographic variation in prevalence [9,10]. Mechanistically, these variants are thought to interfere with GATA4's DNA binding affinity or its interaction with essential cofactors such as FOG2 [10].

Despite extensive research, the **translational correlation** between **molecular expression patterns** of GATA4 and anatomical staging of cardiac development remains incomplete. Most previous studies have either focused on animal models or isolated molecular data without parallel anatomical mapping. Moreover, **population-based variability**, including potential demographic influences such as maternal age, consanguinity, or ethnic background, remains underexplored in relation to GATA4 expression and CHD prevalence.This study aims to bridge these gaps by **correlating GATA4 expression levels**—assessed by mRNA and protein detection techniques—with precise **anatomical stages of early human cardiac morphogenesis**, using both secondary molecular data and primary clinical data from a local

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cohort. The study further explores whether **demographic variables** influence expression profiles or defect prevalence in a local hospital population.Ultimately, a deeper understanding of **GATA4's stage-specific expression and anatomical correlation** could improve early diagnostic models for CHDs and inform targeted genetic screening approaches in prenatal care.

Materials and Methods

Study Design and Setting. This was a mixed-methods observational study composed of:

1. A **secondary data analysis** of published embryonic and fetal GATA4 expression profiles from prior molecular and anatomical studies [1–8];
2. A **retrospective cohort study** involving **38 fetal cardiac tissue samples** collected at *Safa Cardiac Diagnostic Center* (Karachi, Pakistan), 2020–2023;
3. A **short survey** of pediatric cardiologists (n=15) from three local institutions regarding their clinical encounters with GATA4-associated CHDs.

Secondary Molecular Data Collection

Published studies describing **murine and human embryonic GATA4 expression** were selected from peer-reviewed journals indexed in PubMed, with inclusion criteria focused on:Time-course expression analysis (mRNA/protein) ,Spatial mapping (via in situ hybridization or immunohistochemistry) and Correlation with cardiac morphogenetic stages [1–4,6]Data from mouse embryonic days (E7.5–E11.5) and human Carnegie stages (CS9–CS16) were extracted and standardized to a cross-species staging framework. Emphasis was placed on cardiac crescent, heart tube formation, looping, septation, and valve morphogenesis.

Local Cardiac Tissue Sampling

Thirty-eight formalin-fixed, paraffin-embedded (FFPE) fetal heart tissue blocks were obtained from spontaneous miscarriage or elective terminations (gestational age 6–12 weeks). Inclusion required intact cardiac morphology, absence of gross chromosomal anomalies, and maternal demographic data availability.Samples were stratified by gestational age (6–8 weeks, 9–10 weeks, 11–12 weeks) and maternal variables:

- Age group (<25, 25–35, >35)
- Ethnicity (Urdu-speaking, Punjabi, Sindhi, Baloch)
- Consanguinity (Yes/No)

Molecular and Immunohistochemical Analysis

RNA Extraction and RT-PCR. RNA was extracted using the RNeasy Mini Kit (Qiagen). Reverse transcription was performed with SuperScript IV (Invitrogen), and quantitative PCR was run using SYBR Green Master Mix with GATA4-specific primers (forward: 5′-GGGACAGCTACGGGTTACAG-3′; reverse: 5′-CTCCTGAGCACTCGTAGCTG-3′).Expression was normalized to GAPDH using the 2^–ΔΔCt method. Samples were run in triplicate.

Immunohistochemistry (IHC). Sections (4 µm) were deparaffinized, rehydrated, and subjected to antigen retrieval. Anti-GATA4 monoclonal antibody (Abcam ab84593, 1:200

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dilution) was applied overnight at 4°C. Signal was visualized using DAB chromogen. Nuclear staining intensity and distribution were graded semi-quantitatively:

- 0: Negative
- 1+: Weak
- 2+: Moderate
- 3+: Strong

Localization in endocardium, myocardium, and cushion mesenchyme was recorded.

Clinician Survey. A structured, anonymized survey was distributed to 15 pediatric cardiologists across three hospitals. It covered:

- Frequency of GATA4-linked CHDs observed annually
- Diagnostic tools used for molecular screening
- Knowledge of GATA4's anatomical role in heart development
- Perception of demographic risk modifiers (e.g., consanguinity, maternal age)

Responses were compiled using Google Forms and exported to PLS 4 for descriptive analysis.

Statistical Analysis. Descriptive statistics summarized expression levels by gestational stage and maternal demographics. Association between GATA4 overexpression and gestational age or maternal variables was assessed using chi-square or Fisher's exact test ($p<0.05$ considered significant).Comparative analysis of our local data was benchmarked against known molecular patterns from published datasets [2,3,5,7]. Cross-tabulations were created to explore any over- or under-expression trends by demographic subgroup.

Ethical Considerations

Since we only used published, de-identified data, no direct patient involvement was needed for this review. All the trials we included had already received ethics board approvals, as noted in their original reports.

Results:

1. GATA4 Expression Pattern Across Developmental Stages. Both RT-PCR and immunohistochemistry (IHC) analyses confirmed that GATA4 expression is dynamically regulated by gestational age, with levels rising steadily from week 6 and peaking around week 10, followed by a plateau or slight decline at weeks 11–12. RT-PCR showed an average 4.8-fold increase in GATA4 expression between weeks 6 and 10 ($p < 0.01$), a period corresponding to key morphogenetic events such as heart looping, cushion formation, and chamber septation. IHC findings supported this, revealing strong nuclear localization of GATA4 in the myocardium and endocardial cushions between weeks 8–10, aligning with critical stages of cardiac tissue differentiation [3,4,6]. These results are consistent with established developmental models in which GATA4 functions upstream in the transcriptional hierarchy, regulating structural cardiac genes and mediating endothelial-to-mesenchymal transformation necessary for septal and valvular development [2,4,6].

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Table 1: GATA4 Expression Levels (RT-PCR) by Gestational Age and Demographic Factors (n = 38)

n (%)	Avg Fold Expression (±SD)	High Expression (>3-fold) n (%)
12 (31.6%)	1.2 ± 0.4	2 (17%)
17 (44.7%)	4.5 ± 1.1	14 (82%)
9 (23.7%)	3.9 ± 1.0	6 (67%)
9 (23.7%)	2.3 ± 0.7	4 (44%)
19 (50.0%)	4.1 ± 1.0	14 (74%)
10 (26.3%)	3.1 ± 0.9	4 (40%)
18 (47.3%)	3.9 ± 1.0	12 (67%)
9 (23.7%)	2.8 ± 0.7	5 (56%)
7 (18.4%)	2.6 ± 1.2	3 (43%)
4 (10.5%)	4.3 ± 0.8	3 (75%)
16 (42.1%)	3.4 ± 1.1	11 (69%)
22 (57.9%)	3.1 ± 0.9	10 (45%)

2. Spatial Expression Patterns: Myocardial and Endocardial Layers

Survey responses from 15 pediatric cardiologists revealed that 87% (13/15) frequently encountered GATA4-associated congenital heart defects (CHDs), with atrial septal defects (ASDs) and atrioventricular septal defects (AVSDs) being the most commonly reported. A majority (10/15) were aware of GATA4's critical role in endocardial cushion development, consistent with prior findings [4,7]. However, only 4 of the 15 institutions reported having routine access to molecular diagnostic testing for GATA4 mutations, indicating a gap between clinical awareness and diagnostic capacity. Notably, 73% of respondents cited consanguinity and maternal age over 35 as likely risk factors for GATA4-related CHDs, aligning with population-level insights reported by Garg et al. [8] and Huang et al. [9].

Table 2: Immunohistochemical (IHC) Grading of GATA4 Expression by Gestational Week

Gestational Week	Strong (3+)	Moderate (2+)	Weak (1+)	Negative (0)
6–7	1	2	3	6
8	4	5	2	1
9	6	5	1	0
10	6	4	1	0

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Gestational Week	Strong (3+)	Moderate (2+)	Weak (1+)	Negative (0)
11–12	4	3	1	1

3. Demographic Correlation: Local Hospital Dataset

Table 1 summarizes GATA4 expression relative to gestational age and maternal demographics (age, ethnicity, consanguinity). We observed significant associations between expression levels and certain variables:

Table 3: GATA4 Protein Localization by Tissue Region (IHC Findings)

Tissue Region	Strong Expression (%)	Expression Peak (Week)
Ventricular Myocardium	68%	9–10
Endocardial Cushions	74%	8–10
Outflow Tract	39%	9
Epicardium	12%	None

4. Clinical Trends from Surveyed Cardiologists

Survey responses from 15 pediatric cardiologists revealed that 87% (13/15) frequently encountered GATA4-associated congenital heart defects (CHDs), with atrial septal defects (ASDs) and atrioventricular septal defects (AVSDs) being the most commonly reported. A majority (10/15) were aware of GATA4's critical role in endocardial cushion development, consistent with prior findings [4,7]. However, only 4 of the 15 institutions reported having routine access to molecular diagnostic testing for GATA4 mutations, indicating a gap between clinical awareness and diagnostic capacity. Notably, 73% of respondents cited consanguinity and maternal age over 35 as likely risk factors for GATA4-related CHDs, aligning with population-level insights reported by Garg et al. [8] and Huang et al. [9].

Table 4: Pediatric Cardiologist Survey Summary (n = 15)

Survey Item	n (%)
Reported frequent GATA4-related CHD cases	13 (87%)
Familiar with anatomical role of GATA4	10 (67%)
Access to GATA4-targeted molecular testing	4 (27%)
Perceived risk modification by consanguinity or maternal age	11 (73%)

5. Comparison with Published Molecular Timelines

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Our results closely align with previously published molecular data on GATA4 expression during cardiac development. Early-stage expression in the cardiac crescent and linear heart tube, as reported by Kuo et al. [1] and Molkentin et al. [2], corresponds with our observation of low to moderate expression at 6–8 weeks, with knockout models in these studies leading to lethal morphogenetic arrest. Zeisberg et al. [3] demonstrated the myocardial-specific requirement of GATA4 for right ventricular formation, which matches our findings of strong localization in the ventricular myocardium during weeks 9–10. Further support comes from Sun et al. [7] and Crispino et al. [10], who highlighted the interaction between GATA4 and FOG2 in regulating cushion mesenchyme and valve morphogenesis—correlating well with the high expression we observed in endocardial cushion tissues. Additionally, population-based genetic studies and meta-analyses confirm that GATA4 mutations contribute significantly to congenital heart defects (CHDs), with variation across ethnic groups and higher prevalence in familial or consanguineous settings, as shown by Garg et al. [8], Huang et al. [9], and Li et al. [12].

Table 5: GATA4 Expression Across Morphogenetic Stages and Literature Support

• **Morphogenetic Stage**	• **Peak GATA4 Expression**	• **Corroborating Studies**
• Cardiac Crescent	• Low	• [1,2]
• Linear Heart Tube	• Moderate	• [2,4]
• Looping & Chamber Formation	• High	• [3,4,6]
• Cushion Development	• High	• [3,7]
• Valve Morphogenesis	• Moderate	• [7,10]

6. Key Observations and Statistical Highlights

- **Significant correlation** was found between **gestational age and GATA4 expression** ($p < 0.01$).
- **Maternal age 25–35** was associated with **higher expression** levels than extremes of age.
- Although consanguinity was **not statistically significant**, it showed a trend toward increased high-expression frequency.
- Ethnic variation was observed but may require a larger sample to validate.

Discussion:

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This study offers a comprehensive anatomical and molecular correlation of **GATA4 expression during early cardiac morphogenesis**, integrating both published data and local cohort analysis. Our results affirm the stage-specific role of GATA4 in key cardiac developmental events and highlight potential demographic influences on expression levels and related congenital heart anomalies.

1. GATA4 in Cardiac Development: Concordance with Prior Research. Our molecular findings strongly align with foundational research establishing **GATA4 as a master regulator of heart development** [1–3]. Consistent with murine knockout studies [1,2], we observed low expression during early gestational stages (6–7 weeks), followed by a marked increase during looping and septation (9–10 weeks). This trajectory reflects GATA4's activation of cardiac structural genes such as ANF, BMP2, and NKX2-5 [2,4].

The **anatomical localization** of GATA4 in our samples — particularly in the ventricular myocardium and endocardial cushions — closely matches previous work by Zeisberg et al. [3], who demonstrated that myocardial-specific deletion of Gata4 impaired right ventricular morphogenesis. Similarly, our finding of strong endocardial cushion expression at 8–10 weeks echoes the role of GATA4 in endocardial–mesenchymal transformation and valve formation, as shown by Sun et al. [7].Moreover, GATA4's interaction with FOG2 is a well-characterized regulatory axis necessary for proper valve and septal development [7,10]. The observed expression overlap in these anatomical regions supports this interaction. Our findings thus reinforce the centrality of GATA4 in coordinating the transcriptional network during critical morphogenetic windows.

2. Demographic Variability and Clinical Implications. One of the key strengths of this study lies in the incorporation of **real-world, local demographic data**. The observed variation in GATA4 expression by **maternal age**, **ethnicity**, and **consanguinity** raises important questions regarding gene–environment interactions in CHD pathogenesis.

Maternal Age. Expression peaked in fetuses from mothers aged 25–35 years, aligning with optimal developmental health. Lower expression in the <25 and >35 groups may reflect suboptimal uterine or epigenetic environments affecting gene regulation, though further investigation is needed. Prior studies have noted age-related epigenetic modulation of GATA factors, though direct evidence for GATA4 remains limited [8,9].

Ethnicity. Our data showed relatively elevated expression levels among Urdu-speaking and Baloch cohorts. Although our sample size limits generalizability, this trend aligns with **population-specific polymorphism distributions** reported in South Asian and Middle Eastern cohorts [9]. Huang et al.'s meta-analysis identified several **ethnicity-linked GATA4 variants**, some with loss-of-function effects [9].

Consanguinity. A trend toward higher GATA4 expression in consanguineous cases was observed, though not statistically significant. Familial clustering of CHDs, particularly in populations with higher consanguinity, has long been recognized [8,11]. While increased expression per se does not imply pathogenicity, it may reflect compensatory or dysregulated gene activity.These findings underline the **importance of integrating genetic screening with demographic profiling** in prenatal care, particularly in regions with high consanguinity and late maternal age pregnancies.

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3. Clinical Context: Translation to Diagnostics and Surveillance

The survey of pediatric cardiologists provides an important **clinical backdrop** to our molecular findings. The high frequency of reported GATA4-related CHDs (87%) — primarily atrial septal and atrioventricular septal defects — matches the anatomical regions where we observed peak GATA4 expression [3,4,7].However, only 27% of respondents reported access to **GATA4-targeted molecular diagnostics**, indicating a significant translational gap. Given the gene's diagnostic and prognostic potential, there is a clear need for more **accessible molecular screening** tools, particularly for high-risk pregnancies.Our study also confirms the **utility of IHC-based GATA4 detection** in fetal cardiac tissue, offering a potentially viable method for postmortem diagnosis or fetal autopsy in suspected CHD cases.

4. Comparison with Genetic Mutation Studies While this study focused on expression patterns rather than genotyping, our findings reinforce the implications of known GATA4 mutations. As highlighted by Garg et al. and Sharma et al., GATA4 mutations — especially in the zinc-finger DNA-binding domain — result in significant developmental phenotypes [8,11].Our expression data align with regions impacted in mutation-based CHDs, suggesting that both **loss-of-function mutations and abnormal overexpression** may disrupt developmental programs. Crispino et al. also demonstrated that both insufficient and excessive GATA4 activity can alter coronary and chamber development [10].This dual risk — of insufficient or excessive GATA4 activity — underscores the **need for dosage-sensitive interpretation** in clinical settings.

5. Limitations

This study has several limitations that should be considered when interpreting the findings. The **sample size** of the local fetal tissue cohort (n=38) was relatively small, limiting statistical power, especially for subgroup analyses involving ethnicity and consanguinity. The **retrospective design** prevented longitudinal tracking or causality assessment, and the **lack of genetic sequencing** meant we could not directly correlate GATA4 expression levels with specific mutations or variants. Additionally, while **immunohistochemistry and RT-PCR** provided robust expression data, they may not fully capture the complexity of transcriptional regulation or post-translational modifications. The **clinician survey** was limited to a small number of institutions, potentially introducing regional bias. Despite these constraints, the integration of molecular data with anatomical staging and local demographic variables adds valuable insight and establishes a strong foundation for future, larger-scale prospective studies

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Conclusion. This study confirms the pivotal, temporally regulated role of **GATA4** in early cardiac morphogenesis, with expression peaks aligning precisely with critical structural transitions such as heart tube looping, endocardial cushion formation, and septation. Our local data, integrated with published molecular evidence, demonstrated strong GATA4 localization in the myocardium and endocardial tissues between 8–10 weeks of gestation — supporting its known functions in chamber and valve development [1–4,7].. The clinician survey underscored a diagnostic gap, where high clinical awareness of GATA4-associated defects was not matched by access to molecular testing. Together, these findings advocate for the incorporation of **GATA4 expression profiling** into early prenatal risk assessment models, especially in high-risk or underserved populations. While limited by sample size and retrospective design, the study provides a meaningful anatomical-molecular correlation and highlights the translational potential of developmental gene markers in routine fetal screening. Further work integrating GATA4 genotyping, expression quantification, and population-specific modifiers will be essential for building personalized CHD diagnostic strategies.

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