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Original Research

Cytogenetic Findings and Pregnancy Outcomes in Fetuses With Apparently Isolated Increased Nuchal Translucency or Cystic Hygroma

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Abstract

Background: To evaluate cytogenetic findings and pregnancy outcomes in fetuses with apparently isolated increased nuchal translucency (NT) or cystic hygroma and to characterize molecular testing results, primarily based on whole-exome sequencing (WES) or clinical exome sequencing (CES), in clinically selected cases. **Methods:** This retrospective cohort study included 81 fetuses diagnosed with apparently isolated increased NT or cystic hygroma between January 2016 and October 2024. All cases underwent invasive prenatal testing with conventional karyotyping. Pregnancy outcomes were subsequently analyzed among fetuses with a normal karyotype. Molecular testing, primarily based on WES or CES, was performed solely in clinically selected cases during prenatal or postnatal evaluation when persistent, evolving, or newly recognized postnatal clinical concerns were present. These findings were analyzed descriptively and were not used to estimate the cohort-level diagnostic yield. **Results:** Among the 81 fetuses, 60 (74.1%) presented with apparently isolated increased NT, whereas 21 (25.9%) presented with apparently isolated cystic hygroma. Chromosomal abnormalities were identified in 35 cases (43.2%). Trisomy 21 was the most frequent abnormality (24.7%), followed by trisomy 18 (9.9%) and monosomy X (6.2%). Chromosomal abnormalities were more frequently identified in fetuses with apparently isolated cystic hygroma than in those with apparently isolated increased NT; however, this difference was not statistically significant (52.4% vs. 40.0%; $p = 0.443$). Within the increased NT group, the median NT thickness was significantly greater in fetuses with chromosomal abnormalities than in those with a normal karyotype (4.50 vs. 3.50 mm; $p = 0.005$). Among fetuses with a normal karyotype, live birth occurred in 94.4% of those with apparently isolated increased NT and in 70.0% of those with apparently isolated cystic hygroma. Molecular evaluation, predominantly based on WES or CES, was performed in 11 clinically selected cases. 2 cases yielded potentially relevant but unconfirmed findings, 4 demonstrated non-diagnostic findings of uncertain relevance or possible carrier/incidental significance, 1 fetus with aneuploidy had an additional non-diagnostic molecular finding, and 4 evaluations were negative or otherwise non-diagnostic. None of the molecular findings could be considered a confirmed explanation for the initial increased NT or cystic hygroma phenotype. Among the 41 live-born children with a normal karyotype, clinically relevant postnatal abnormalities or diagnoses were documented in 8 (19.5%). As molecular testing and postnatal follow-up were selective and heterogeneous, the findings were interpreted descriptively, and neither a cohort-level molecular diagnostic yield nor a median duration of postnatal follow-up could be calculated. **Conclusions:** Chromosomal abnormalities were identified in a substantial proportion of fetuses with apparently isolated increased NT or cystic hygroma. Among fetuses with a normal karyotype, live birth rates were high, particularly in the increased NT group. However, these outcomes reflect the apparently isolated phenotype documented at the initial first-trimester assessment and should be interpreted together with the available postnatal clinical findings. Molecular testing, predominantly based on WES or CES, yielded heterogeneous case-level findings, none of which could be established as a confirmed explanation for the initial prenatal phenotype on the basis of the available records. Because molecular testing was selectively performed, these findings should not be interpreted as an estimate of the cohort-level diagnostic yield.

Keywords: nuchal translucency; cystic hygroma; aneuploidy; prenatal diagnosis; karyotype; pregnancy outcome; exome sequencing

1. Introduction

Increased nuchal translucency (NT) and cystic hygroma identified during the first trimester are well-established sonographic markers associated with chromosomal abnormalities and adverse perinatal outcomes [1]. NT is defined as the ultrasound measurement of subcutaneous fluid accumulation at the back of the fetal neck obtained between 11 + 0 and 13 + 6 weeks of gestation, according to standardized first-trimester scanning guidelines [2].

In contrast, cystic hygroma is a septated lymphatic malformation located in the cervical region. It is strongly associated with chromosomal abnormalities and major structural anomalies and has also been linked to an increased risk of adverse pregnancy outcomes [3].

A substantial body of evidence has shown that increased NT is associated with chromosomal and genetic abnormalities, with pooled rates of adverse outcomes exceeding 40%, particularly when NT persists or measures ≥3.5 mm [4]. Similarly, first-trimester septated cystic hy-

groma has been associated with chromosomal abnormalities in nearly 60% of cases and is frequently followed by pregnancy loss. Nevertheless, outcomes are considerably more favorable in euploid fetuses without associated structural anomalies [5].

Importantly, a normal conventional karyotype does not necessarily indicate a favorable prognosis. Even in euploid fetuses, increased NT and cystic hygroma may still be associated with major structural abnormalities and perinatal loss [4,5,6].

Chromosomal microarray analysis (CMA) has been reported to provide an additional diagnostic yield of approximately 4%–7% for pathogenic copy number variants in fetuses with apparently isolated increased NT and a normal karyotype, with higher yields in cases with associated structural anomalies [7]. Next-generation sequencing approaches, particularly exome sequencing, may provide a further incremental diagnostic yield of approximately 4% in fetuses with isolated increased NT after a negative CMA result [8,9]. However, larger cohort studies suggest that the benefit of exome sequencing is substantially lower in truly isolated cases, particularly when no additional structural abnormalities develop later in pregnancy. These findings emphasize the importance of careful case selection when considering advanced molecular testing [10].

Against this background, we aimed to evaluate the cytogenetic findings and pregnancy outcomes of fetuses with apparently isolated increased NT or cystic hygroma managed at a tertiary referral center and to describe molecular testing results, predominantly based on whole-exome sequencing (WES) or clinical exome sequencing (CES), in clinically selected cases.

2. Materials and Methods

2.1 Study Design and Population

This retrospective cohort study was conducted at the Genetic Diseases Diagnosis and Evaluation Center of a tertiary referral university hospital. The study included fetuses diagnosed with apparently isolated increased nuchal translucency (NT) or cystic hygroma between January 2016 and October 2024.

Cases were identified from institutional prenatal diagnosis records. The source population comprised pregnant individuals who were referred to the perinatology unit or evaluated in the institutional outpatient clinic for first-trimester combined screening. Initial first-trimester ultrasonographic assessments were performed in the same perinatology unit by experienced perinatologists, although examinations were not necessarily performed by the same operator. All fetuses with increased NT or cystic hygroma documented between 11 + 0 and 13 + 6 weeks of gestation who underwent invasive prenatal testing and had an available conventional karyotype result were included. No additional exclusion criteria were applied.

Increased NT was defined as an NT measurement of at least 3.0 mm in the absence of any additional major structural abnormality at the initial assessment. For the purposes of this study, the 3.0-mm cutoff was selected to include fetuses with NT measurements of 3.0–3.4 mm, a range that has also been associated with an increased risk of chromosomal abnormalities [1]. Cystic hygroma was defined as a septated, fluid-filled cervical lesion without any additional major structural abnormality documented at the time of initial diagnosis.

Cases were classified as apparently isolated when no additional major structural abnormality was documented at the initial first-trimester ultrasound assessment. This classification therefore reflected the phenotype recorded at cohort entry rather than confirmation that the finding remained isolated throughout pregnancy. Pregnancies terminated following the diagnosis of a chromosomal abnormality generally did not progress to the gestational age at which a detailed second-trimester structural assessment would normally be performed. Among pregnancies that continued, records confirming completion of detailed second-trimester anomaly scanning, fetal echocardiography, and serial prenatal ultrasonographic follow-up were not systematically available in the retrospective dataset. These examinations may have been performed as part of routine clinical care; however, their completion could not be reliably verified or quantified. Accordingly, the term apparently isolated does not imply that the phenotype was confirmed to remain isolated throughout gestation.

2.2 Prenatal Diagnostic Procedures

Invasive prenatal testing was performed by chorionic villus sampling or amniocentesis, depending on the gestational age and clinical circumstances. Conventional cytogenetic analysis was performed in all cases; however, detailed information regarding culture conditions, chromosome-banding methods, and analytical resolution was not systematically retrievable from the retrospective laboratory records.

2.3 Pregnancy Outcomes

Pregnancy outcome data were obtained from the medical records. Outcomes were categorized as spontaneous pregnancy loss before 22 completed weeks of gestation, termination of pregnancy, or live birth. Live birth was defined as complete expulsion or extraction of the fetus showing any evidence of life after birth, irrespective of gestational age. Pregnancy outcomes were analyzed separately among fetuses with a normal karyotype.

2.4 Postnatal Clinical Follow-up

For live-born children with a normal karyotype, available pediatric and genetic records were reviewed for clinically relevant postnatal abnormalities or diagnoses, molecular testing, diagnostic certainty, and duration of follow-up. Diagnostic certainty was categorized according to the avail-

able documentation as chromosomally or molecularly confirmed, clinically documented without molecular confirmation, suspected, or an undiagnosed phenotype. Follow-up duration was recorded only when explicitly documented in the medical records.

2.5 Molecular Genetic Testing

WES or CES was performed selectively according to clinical indications and was not applied systematically across the cohort. In one additional case, an external postnatal molecular finding was documented, although the complete original report and testing method were unavailable. The test designation as WES or CES was reproduced from the original clinical laboratory report and was not reclassified by the authors. Testing was performed either prenatally in fetuses with persistent clinical concerns or postnatally in children with relevant clinical findings identified during follow-up. Accordingly, the molecular testing results were evaluated as descriptive case-level observations and were not used to calculate the cohort-level diagnostic yield.

Selection for molecular testing was based on the presence of persistent or evolving prenatal findings, postnatal phenotypic abnormalities, suspected syndromic features, developmental concerns, or the need for clinician-directed genetic evaluation during follow-up. Because the study was retrospective, the specific clinical indications for testing and the availability of parental segregation, variant phase, parental origin, and longitudinal phenotypic information varied among cases. All locally performed WES and CES analyses were conducted as solo testing. The testing configuration of the externally performed TSC2 analysis could not be retrieved from the available records.

Molecular findings were interpreted in the context of the initial prenatal phenotype, karyotype and CMA results when available, timing of testing, postnatal phenotype, reported inheritance pattern, and available clinical records. Pathogenic or likely pathogenic variants were not automatically considered explanatory for increased NT or cystic hygroma unless the molecular finding and inheritance pattern were compatible with the observed phenotype.

Variant classifications and negative results were reproduced from the original clinical laboratory reports or available external clinical records, and no independent variant reclassification was performed. Zygosity was available for all reported variants; however, parental segregation, variant phase, parental origin, specific American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) evidence criteria, and complete external molecular reports were included only when retrievable and were not inferred when unavailable.

2.6 Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics, cytogenetic findings, pregnancy outcomes, and molecular testing results. Continuous variables were expressed as the mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the data distribution. The distribution of continuous variables was assessed using the Shapiro–Wilk test within each ultrasound group. Categorical variables were reported as counts and percentages.

The association between ultrasound findings and chromosomal abnormality status was evaluated using Fisher's exact test, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Pregnancy outcomes among fetuses with a normal karyotype were compared exploratorily using Fisher's exact test, and relative risks (RRs) with 95% CIs were reported where appropriate. Within the increased NT group, NT thickness was compared between fetuses with chromosomal abnormalities and those with a normal karyotype using the Mann–Whitney U test. In the increased NT subgroup, multivariable logistic regression was performed to evaluate the association between NT thickness and chromosomal abnormalities after adjustment for maternal age.

For comparisons of baseline characteristics between fetuses with apparently isolated increased NT and those with apparently isolated cystic hygroma, maternal age was compared using Welch's independent-samples t-test, whereas gravidity, parity, previous miscarriage, and gestational age at the invasive procedure were compared using the Mann–Whitney U test. Categorical baseline variables were compared using Fisher's exact test; the Fisher–Freeman–Halton exact test was used for the overall comparison of procedure type.

Analyses were performed using available data, and the multivariable logistic regression was restricted to complete cases for the variables included in the model. A two-sided p value < 0.05 was considered statistically significant. No adjustment for multiple comparisons was made because the analyses were exploratory and hypothesis-generating; therefore, p values should be interpreted descriptively. All statistical analyses were performed using Python version 3.13.5 (Python Software Foundation, Beaverton, OR, USA; python.org), SciPy version 1.17.0 (SciPy community; scipy.org), and statsmodels version 0.14.6 (statsmodels developers; statsmodels.org).

3. Results

The final analysis included 81 fetuses with either apparently isolated increased NT or apparently isolated cystic hygroma. Of these, 60 (74.1%) had apparently isolated increased NT, and 21 (25.9%) had apparently isolated cystic hygroma.

Baseline maternal, obstetric, and procedural characteristics are presented in Table 1.

The mean maternal age was 31.8 ± 6.3 years. No statistically significant differences were observed between the two groups in maternal age (p = 0.836), gravidity (p = 0.267), parity (p = 0.622), gestational age at the inva-

Table 1. Baseline characteristics of fetuses with apparently isolated increased nuchal translucency or apparently isolated cystic hygroma (n = 81).

Variable	Total (n = 81)	Apparently isolated increased NT (n = 60)	Apparently isolated cystic hygroma (n = 21)	*p* value
Maternal age, years (mean ± SD)	31.8 ± 6.3	31.8 ± 6.4	31.5 ± 6.0	0.836
Gravidity (median [IQR])	2 [1–3]	2 [1–3]	2 [2–3]	0.267
Parity (median [IQR])	1 [0–2]	1 [0–2]	1 [0–1]	0.622
Previous miscarriage (median [IQR])	0 [0–0]	0 [0–0]	0 [0–1]	0.002
Gestational age at procedure, weeks (median [IQR])	13.3 [12.6–16.0]	14.7 [12.5–16.0]	13.0 [12.6–13.3]	0.085
CVS, n (%)	46 (56.8%)	28 (46.7%)	18 (85.7%)	
Amniocentesis, n (%)	33 (40.7%)	30 (50.0%)	3 (14.3%)	0.005
Combined/other, n (%)	2 (2.5%)	2 (3.3%)	0 (0.0%)	
NT measurement, mm (median [IQR])*	3.6 [3.2–4.7]	3.6 [3.2–4.7]	—	—
Parental consanguinity, n (%)	8 (9.9%)	6 (10.0%)	2 (9.5%)	1.000

* NT thickness was evaluated only in fetuses with apparently isolated increased NT. It was not analyzed in the cystic hygroma group because septated hygromas often extend beyond the range of standard NT measurement. Gestational age at the procedure refers to the timing of the invasive diagnostic procedure rather than the timing of the initial ultrasound diagnosis. All initial NT measurements and cystic hygroma diagnoses were made between 11 + 0 and 13 + 6 weeks of gestation. *p* values represent comparisons between the apparently isolated increased NT and cystic hygroma groups. The *p* value for procedure type represents the overall comparison across CVS, amniocentesis, and combined/other categories. SD, standard deviation; IQR, interquartile range; CVS, chorionic villus sampling; NT, nuchal translucency.

Table 2. Cytogenetic findings and chromosomal abnormality comparison according to ultrasound finding.

Cytogenetic result	Total (n = 81)	Increased NT (n = 60)	Cystic hygroma (n = 21)
Normal karyotype	46 (56.8%)	36 (60.0%)	10 (47.6%)
Any chromosomal abnormality	35 (43.2%)	24 (40.0%)	11 (52.4%)
Trisomy 21	20 (24.7%)	17 (28.3%)	3 (14.3%)
Trisomy 18	8 (9.9%)	4 (6.7%)	4 (19.0%)
Monosomy X (45, X)	5 (6.2%)	1 (1.7%)	4 (19.0%)
Other chromosomal abnormalities*	2 (2.5%)	2 (3.3%)	0 (0.0%)

* Other chromosomal abnormalities included trisomy 13 and tetraploidy. Chromosomal abnormalities were more frequent in fetuses with cystic hygroma than in those with increased NT; however, the difference did not reach statistical significance (52.4% vs. 40.0%; OR, 1.65; 95% CI, 0.61–4.49; $p = 0.443$, Fisher's exact test).

sive procedure ($p = 0.085$), or parental consanguinity ($p = 1.000$). The distribution of previous miscarriage differed significantly between the groups ($p = 0.002$). Procedure type also differed significantly between the groups ($p = 0.005$), with chorionic villus sampling was performed more frequently in the cystic hygroma group, whereas amniocentesis was performed more often in the apparently isolated increased NT group. NT thickness was evaluated only in fetuses with apparently isolated increased NT. Pregnancies terminated following the diagnosis of a chromosomal abnormality generally did not progress to the gestational age required for detailed second-trimester structural assessment. Among pregnancies that continued, records confirming completion of detailed anomaly scanning, fetal echocardiography, and serial prenatal ultrasonographic follow-up were not systematically available. Therefore, subgroup-specific completion rates for these assessments could not be reliably determined.

Cytogenetic findings and the comparison of chromosomal abnormality rates according to ultrasound findings are summarized in Table 2. Overall, 46 fetuses (56.8%) had a normal karyotype, whereas chromosomal abnormalities were identified in 35 cases (43.2%). Trisomy 21 was the most common aneuploidy (20/81, 24.7%), followed by trisomy 18 (8/81, 9.9%) and monosomy X (5/81, 6.2%). Chromosomal abnormalities were more frequent in fetuses with cystic hygroma than in those with apparently isolated increased NT; however, the difference was not statistically significant (52.4% vs. 40.0%; OR, 1.65; 95% CI, 0.61–4.49; $p = 0.443$, Fisher's exact test).

Within the apparently isolated increased NT group, the median NT thickness was significantly greater in fetuses with chromosomal abnormalities than in those with a normal karyotype (4.50 mm [IQR, 3.55–5.30] vs. 3.50 mm [IQR, 3.15–4.00]; $p = 0.005$, Mann–Whitney U test). In an exploratory multivariable logistic regression analysis of the increased NT subgroup, NT thickness remained independently associated with chromosomal abnormalities after adjustment for maternal age (adjusted OR, 2.42 per 1-mm increase; 95% CI, 1.27–4.62; $p = 0.007$).

Table 3. Pregnancy outcomes among fetuses with a normal karyotype.

Outcome	Apparently isolated increased NT (n = 36)	Apparently isolated cystic hygroma (n = 10)
Spontaneous pregnancy loss before 22 completed weeks, n (%)	1 (2.8%)	2 (20.0%)
Termination of pregnancy, n (%)	1 (2.8%)	1 (10.0%)
Live birth, n (%)	34 (94.4%)	7 (70.0%)

Live birth was defined as complete expulsion or extraction of the fetus showing any evidence of life after birth, irrespective of gestational age.

Pregnancy outcomes for fetuses with a normal karyotype are presented in Table 3. Live birth occurred in 94.4% of apparently isolated increased NT cases and 70.0% of apparently isolated cystic hygroma cases. In an exploratory comparison, the live birth rate was lower in the cystic hygroma group than in the increased NT group, although the difference did not reach statistical significance (RR, 0.74; 95% CI, 0.49–1.12; Fisher's exact $p = 0.061$). Pregnancy loss and termination of pregnancy were uncommon in the apparently isolated increased NT group but occurred more frequently in the cystic hygroma group. Because live birth does not necessarily indicate the absence of postnatal morbidity, available postnatal records were also reviewed. Among fetuses with a normal karyotype, most available postnatal evaluations were unremarkable; however, clinically relevant postnatal abnormalities or diagnoses were documented in a subset of children, as described below.

Molecular evaluation, predominantly based on WES or CES, was documented in 11 clinically selected cases, as summarized in Table 4. Testing was performed prenatally in five cases and postnatally in five cases. In one additional case, a postnatal molecular result was obtained from an external clinical record, although the complete original report was unavailable. Ten cases had a normal karyotype, whereas one fetus had trisomy 21.

Two euploid cases had potentially relevant but unconfirmed molecular findings. These included a heterozygous PIEZO1 variant, and a heterozygous TSC2 variant associated with a recorded postnatal diagnosis of tuberous sclerosis. Although the TSC2 finding was clinically relevant to the postnatal phenotype, its relationship to the initial cystic hygroma remained uncertain. Four additional euploid cases had non-diagnostic findings of uncertain relevance, possible carrier status, or incidental significance. These involved DNA2, CFTR, DLL1/SCARB1, and NACC1/CUX2. In the NACC1/CUX2 case, a 15q13.3 microdeletion detected by postnatal chromosomal microarray was considered more clinically relevant to the postnatal epilepsy phenotype. One fetus with trisomy 21 had an additional homozygous GAA variant classified as a variant of uncertain significance, which was considered non-diagnostic. Four evaluations were negative or otherwise non-diagnostic, including one postnatal CES evaluation and three prenatal WES analyses in fetuses with apparently isolated increased NT.

Zygosity was available for all reported variants. All locally performed WES and CES analyses were conducted as solo testing, and variant classifications were reproduced from the original clinical laboratory reports without independent reclassification. However, parental segregation, variant phase, parental origin, and the specific ACMG/AMP evidence criteria were generally not retrievable from the retrospective records. For the externally tested TSC2 case, the testing configuration and complete original molecular report were unavailable. Therefore, classification of a variant as pathogenic or likely pathogenic was not considered equivalent to confirmation of a molecular diagnosis or evidence that the variant explained the initial prenatal phenotype. Based on the available clinical and molecular records, none of the molecular findings could be established as a confirmed explanation for the initial increased NT or cystic hygroma.

Because molecular testing was performed selectively, at different time points, and for heterogeneous clinical indications, these findings were interpreted descriptively and were not used to calculate a cohort-level diagnostic yield.

At least one postnatal clinical record or documented postnatal clinical status was available for all 41 live-born children with a normal karyotype. Clinically relevant postnatal abnormalities or diagnoses were documented in eight children (8/41, 19.5%), as summarized in Table 5. Molecular testing was performed in some, but not all, of these children, and the degree of diagnostic certainty varied among cases. The depth and duration of postnatal follow-up were heterogeneous and were not systematically documented. Follow-up duration was explicitly recorded for only one child, who was evaluated at 8 years of age; therefore, a median postnatal follow-up duration could not be calculated.

4. Discussion

In this retrospective cohort of 81 fetuses with apparently isolated increased NT or cystic hygroma, chromosomal abnormalities were identified in 43.2% of cases. Trisomy 21 was the most common abnormality, followed by trisomy 18 and monosomy X. These findings are consistent with those of large population-based studies demonstrating a strong association between increased NT and chromosomal abnormalities, particularly trisomy 21 and other major aneuploidies [1,3,11].

Table 4. Molecular testing results, predominantly based on WES or CES, in clinically selected fetuses or children with apparently isolated increased nuchal translucency or cystic hygroma (n = 11).

Case	Initial prenatal finding	Karyotype/CMA	Timing/test	Test configuration	Gene/reported disorder	Transcript	Variant	Zygosity	Inheritance/ segregation	Classification	Classification source	Confirmed molecular diagnosis	Relevance to prenatal phenotype	Reported outcome/ phenotype/ follow-up
1	Cystic hygroma	Normal karyotype; normal CMA	Prenatal WES	Solo WES	PIEZO1/dehydrated hereditary stomatocytosis with or without pseudohyperkalemia and/or perinatal edema	/	c.2707C>T; p.Gln903Ter	Heterozygous	AD; parental origin not available	LP	Original clinical laboratory report	No	Potentially relevant but unconfirmed; causality for cystic hygroma was not established.	Pregnancy termination at 25 + 0 weeks
					CFTR/cystic fibrosis	/	c.1397C>G; p.Ser466Ter	Heterozygous	AR; parental origin and phase not available	P			Possible carrier or complex-allele finding; not considered explanatory for cystic hygroma because variant phase was unavailable.	
					CFTR/cystic fibrosis	/	c.3209G>A; p.Arg1070Gln	Heterozygous	AR; parental origin and phase not available	P			Possible carrier or complex-allele finding; not considered explanatory for cystic hygroma because variant phase was unavailable.	
2	Cystic hygroma	Normal karyotype	Prenatal WES	Solo WES	DNA2 / Seckel syndrome 8; Rothmund-Thomson syndrome type 4; mitochondrial DNA deletion syndrome with progressive myopathy	NM_001080449.3	c.662C>G; p.Ala221Gly	Heterozygous	AR/AD reported; segregation not available	VUS/LP	Original clinical laboratory report	No	Finding of uncertain relevance; no confirmed relationship with cystic hygroma was established.	/
3	Increased NT (3.2 mm)	Normal karyotype; postnatal array result not available	Postnatal array + CES	Solo CES	CFTR/CFTR-related disorders	NM_000492.4	c.2657+5G>A; intronic	Heterozygous	AR/AD reported; segregation and second-allele status not available	P	Original clinical laboratory report	No	Possible carrier or incidental finding; a single heterozygous CFTR variant was not considered explanatory for increased NT.	Live-born at 31 + 2 weeks by cesarean delivery, 1930 g; clinodactyly, webbed neck, hypotelorism, joint limitation, pectus carinatum, and coarse facial appearance

Table 4. Continued.

Case	Initial prenatal finding	Karyotype/CMA	Timing/test	Test configuration	Gene/reported disorder	Transcript	Variant	Zygosity	Inheritance/ segregation	Classification	Classification source	Confirmed molecular diagnosis	Relevance to prenatal phenotype	Reported outcome/ phenotype/ follow-up
4	Cystic hygroma	Normal karyotype	Postnatal CES	Solo CES	DLL1/neurodevelopmental disorder with nonspecific brain abnormalities, with or without seizures	NM_005618.4	c.1574dup; p.Ala528SerfsTer7	Heterozygous	AD; segregation not available	LP	Original clinical laboratory report	No	Finding of uncertain relevance; no corresponding clinical phenotype or segregation evidence was available.	Alive and reported as healthy
					SCARB1/high-density lipoprotein cholesterol level quantitative trait locus 6	NM_005505.5	c.727-2A>C	Homozygous	segregation not available	P/LP			Finding of uncertain relevance; no corresponding clinical phenotype was documented.	
5	Increased NT (3.3 mm)	Normal karyotype	Postnatal CES	Solo CES	/	/	No diagnostic variant identified	/	/	Negative / non-diagnostic	Original clinical laboratory report	No; non-diagnostic evaluation	Negative/non-diagnostic evaluation; no diagnostic variant was identified.	Live-born at 38 weeks by cesarean delivery; no definite postnatal diagnosis recorded
6	Increased NT (3.4 mm)	Normal karyotype; postnatal array identified a 15q13.3 microdeletion	Postnatal WES	Solo WES	NACC1/neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination	/	c.914_922del; p.Thr305_Tyr307del	Heterozygous	AD; parental origin not available	LP	Original clinical laboratory report	No for the exome finding; 15q13.3 microdeletion confirmed by postnatal CMA	Non-diagnostic exome finding; the postnatal 15q13.3 microdeletion was considered more clinically relevant.	Live-born at 39 weeks by cesarean delivery; refractory epilepsy; postnatal 15q13.3 microdeletion
					CUX2/developmental and epileptic encephalopathy 67	/	c.1456T>C; p.Ser486Pro	Heterozygous	AD; parental origin not available	VUS			The exome finding was not established as the explanation; the postnatal 15q13.3 microdeletion may be more clinically relevant	
7	Cystic hygroma	Normal karyotype; normal CMA	External postnatal molecular test; complete report unavailable	Not reported	TSC2/tuberous sclerosis	/	/	Heterozygous	AD; parental origin not available	P	External clinical record; complete original laboratory report not retrievable	Postnatal clinical diagnosis recorded; complete molecular report unavailable	Clinically relevant to the postnatal tuberous sclerosis phenotype; its relationship to cystic hygroma remained uncertain.	Live-born at 38 weeks by cesarean delivery; epilepsy and tuberous sclerosis diagnosed postnatally

Table 4. Continued.

Case	Initial prenatal finding	Karyotype/CMA	Timing/test	Test configuration	Gene/reported disorder	Transcript	Variant	Zygosity	Inheritance/ segregation	Classification	Classification source	Confirmed molecular diagnosis	Relevance to prenatal phenotype	Reported outcome/ phenotype/ follow-up
8	Cystic hygroma	Trisomy 21	Postnatal WES	Solo WES	GAA/glycogen storage disease II	/	c.490A>T; p.Ile164Phe	Homozygous	AR; segregation not available	VUS	Original clinical laboratory report	No	Additional non-diagnostic finding in an aneuploid fetus; not considered explanatory, and interpretation was limited by trisomy 21.	/
9	Increased NT	Normal karyotype	Prenatal WES	Solo WES	/	/	No pathogenic or likely pathogenic variant identified	/	/	Negative/ non-diagnostic	Original clinical laboratory report	No; non-diagnostic evaluation	Negative/non-diagnostic evaluation; no pathogenic or likely pathogenic variant was identified.	/
10	Increased NT	Normal karyotype	Prenatal WES	Solo WES	/	/	No pathogenic or likely pathogenic variant identified	/	/	Negative/ non-diagnostic	Original clinical laboratory report	No; non-diagnostic evaluation	Negative/non-diagnostic evaluation; no pathogenic or likely pathogenic variant was identified.	/
11	Increased NT	Normal karyotype	Prenatal WES	Solo WES	/	/	No pathogenic or likely pathogenic variant identified	/	/	Negative/ non-diagnostic	Original clinical laboratory report	No; non-diagnostic evaluation	Negative/non-diagnostic evaluation; no pathogenic or likely pathogenic variant was identified.	/

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CES, clinical exome sequencing; CMA, chromosomal microarray analysis; LP, likely pathogenic; NT, nuchal translucency; P, pathogenic; VUS, variant of uncertain significance; WES, whole-exome sequencing.

Note 1: Variant classifications and negative results were reproduced from the original clinical laboratory reports or available external clinical records. No independent variant reclassification was performed. A pathogenic or likely pathogenic classification was not considered evidence that the variant explained the initial prenatal phenotype. Where the original laboratory report provided a combined classification, such as VUS/LP or P/LP, the classification was reproduced as reported and was not adjudicated by the authors.

Note 2: All locally performed WES and CES analyses were conducted as solo testing. The testing configuration of the externally performed TSC2 analysis could not be retrieved from the available records. Information regarding parental segregation, variant phase, parental origin, transcript, or follow-up duration was included when available; unavailable information was left blank and was not inferred.

Note 3: Molecular findings were categorized according to their relevance to the initial prenatal phenotype as potentially relevant but unconfirmed, uncertain or possible carrier/incidental findings, an additional non-diagnostic finding in an aneuploid fetus, or negative/non-diagnostic evaluations, independently of the reported variant pathogenicity classification. The TSC2 finding was clinically relevant to the recorded postnatal diagnosis of tuberous sclerosis but was not established as an explanation for the initial cystic hygroma.

Note 4: For the TSC2 case, the postnatal diagnosis of tuberous sclerosis was documented in the clinical record; however, the complete external molecular report was unavailable.

Table 5. Clinically relevant postnatal abnormalities or diagnoses among live-born children with a normal karyotype (n = 8).

Case	Initial prenatal finding	Karyotype/CMA	Prenatal procedure/gestational age	Delivery	Clinically relevant postnatal abnormality or diagnosis	Molecular testing/result	Diagnostic certainty	Follow-up duration/last known status
1	Cystic hygroma	Normal karyotype	CVS at 13 weeks	Cesarean delivery at 37 weeks	Congenital diaphragmatic hernia; possible Noonan syndrome	/	Suspected clinical diagnosis; molecular confirmation unavailable	/
2	Cystic hygroma	Normal karyotype; normal CMA	CVS at 12 + 2 weeks	Cesarean delivery at 38 weeks	Epilepsy; tuberous sclerosis	Heterozygous TSC2 variant classified as P in the available record; complete external report unavailable	Clinically documented postnatal diagnosis; complete molecular report unavailable	/
3	Cystic hygroma	Normal karyotype; postnatal array normal	CVS at 13 + 1 weeks	Vaginal delivery at 37 + 2 weeks	Pulmonary stenosis; pectus excavatum	Postnatal chromosomal microarray: normal	Clinically documented abnormalities; no molecular diagnosis established	/
4	Increased NT (3.2 mm)	Normal karyotype; postnatal array result not available	CVS at 13 + 2 weeks	Cesarean delivery at 31 + 2 weeks; birth weight 1930 g	Clinodactyly, webbed neck, hypotelorism, joint limitation, pectus carinatum, and coarse facial appearance	Postnatal array + CES; heterozygous CFTR c.2657+5G>A, classified as P in the available record	Undiagnosed phenotype; no confirmed molecular diagnosis explaining the phenotype	/
5	Increased NT (3.4 mm)	Normal karyotype; postnatal 15q13.3 microdeletion	CVS at 13 + 4 weeks	Cesarean delivery at 39 weeks	Refractory epilepsy; 15q13.3 microdeletion	Postnatal WES: heterozygous NACC1 c.914_922del, p.Thr305_Tyr307del (LP) and heterozygous CUX2 c.1456T>C, p.Ser486Pro (VUS); postnatal array: 15q13.3 microdeletion	Chromosomally confirmed diagnosis by postnatal CMA; exome findings not established as diagnostic	/
6	Increased NT (4.7 mm)	Normal karyotype	CVS at 13 + 6 weeks	Cesarean delivery at 38 weeks	Psychomotor developmental delay	CES was performed; a subsequent WES result was pending in the available record.	Clinically documented phenotype; no final molecular diagnosis available.	8 years
7	Increased NT (3.9 mm)	Normal karyotype	CVS at 12 weeks	Vaginal delivery at 39 weeks	Pyloric stenosis, surgically treated; neurofibromatosis	/	Clinically documented diagnoses; molecular confirmation unavailable	/
8	Increased NT (4.9 mm)	Normal karyotype; postnatal 9q34 deletion	CVS at 12 weeks	Cesarean delivery at 39 weeks	Kleefstra syndrome; microcephaly, undescended testis, pes equinovarus, and neonatal intensive care admission	Postnatal chromosomal microarray: 9q34 deletion	Chromosomally confirmed postnatal diagnosis	/

Note: Only children with a clinically relevant postnatal abnormality or diagnosis were included. A child with an isolated patent foramen ovale and a separate child whose record indicated only that WES was under review, without any documented postnatal abnormality or diagnosis, were excluded.

Prenatal course: Longitudinal prenatal information, including persistence or resolution of the initial finding and the development of additional prenatal abnormalities, was not systematically retrievable from the retrospective records.

Follow-up: The duration of postnatal follow-up was not systematically recorded. Therefore, a median follow-up duration could not be calculated from the available records.

Cross-reference: Table 5 Cases 2, 4, and 5 correspond to Table 4 Cases 7, 3, and 6, respectively.

Abbreviations: CES, clinical exome sequencing; CMA, chromosomal microarray analysis; CVS, chorionic villus sampling; LP, likely pathogenic; NT, nuchal translucency; P, pathogenic; VUS, variant of uncertain significance; WES, whole-exome sequencing.

Within the apparently isolated increased NT group, NT thickness was significantly greater in fetuses with chromosomal abnormalities than in those with a normal karyotype. This finding is consistent with previous large cohort studies demonstrating that the risk of chromosomal abnormalities increases with greater NT thickness [1,11].

Although chromosomal abnormalities were numerically more frequent in fetuses with cystic hygroma than in those with apparently isolated increased NT (52.4% vs. 40.0%), this difference was not statistically significant. This likely reflects the relatively small number of cases in the cystic hygroma subgroup. Nevertheless, the observed numerical trend is consistent with previous reports suggesting that cystic hygroma is associated with a higher risk of chromosomal abnormalities than isolated increased NT [3,12].

Among fetuses with a normal karyotype, live birth rates were high, particularly in the apparently isolated increased NT group. Previous studies have reported generally favorable outcomes in euploid fetuses when no additional major structural abnormalities are identified [5,13]. However, detailed second-trimester anomaly scan, fetal echocardiography, and serial prenatal ultrasound records were not systematically available in the present cohort. Therefore, our findings reflect outcomes according to the apparently isolated phenotype documented at the initial first-trimester assessment rather than confirmation that the phenotype remained isolated throughout pregnancy. Moreover, live birth should not be equated with the absence of postnatal morbidity.

Molecular testing in this cohort, predominantly based on WES or CES, should be interpreted cautiously because it was performed selectively rather than systematically. The tested cases represented a heterogeneous subgroup, including fetuses who underwent prenatal testing because of persistent clinical concerns and children who underwent postnatal testing because of subsequently recognized clinical findings. In one additional child, an external postnatal molecular finding was documented, although the complete original report and testing method were unavailable. Accordingly, the molecular results should be interpreted as descriptive case-level observations rather than as an estimate of diagnostic yield. Importantly, a pathogenic or likely pathogenic variant classification did not necessarily indicate either a confirmed molecular diagnosis or an explanation for the initial increased NT or cystic hygroma. Interpretation required consideration of zygosity, inheritance pattern, test configuration, segregation and phase information, classification source, fetal karyotype, and concordance with the available prenatal and postnatal phenotypes. Previous studies have shown that the incremental diagnostic yield of exome sequencing is limited in truly isolated increased NT, particularly when no additional anomalies develop during follow-up [8,9,10]. Conversely, studies of broader cohorts with fetal structural anomalies suggest that exome sequencing may be more informative when additional phenotypic abnormalities are present [14].

Beyond conventional cytogenetic abnormalities, an important clinical question is which fetuses with increased NT or cystic hygroma are most likely to benefit from advanced genomic evaluation. Our findings support a phenotype-driven approach; however, the molecular observations in this cohort should be interpreted cautiously. Two cases had potentially relevant but unconfirmed findings, whereas four cases had findings of uncertain relevance, possible carrier status, or incidental significance. One fetus with trisomy 21 had an additional non-diagnostic molecular finding, and four evaluations were negative or otherwise non-diagnostic. Importantly, clinical relevance to a postnatal phenotype did not establish that a molecular finding explained the initial increased NT or cystic hygroma. All locally performed WES and CES analyses were conducted as solo testing, and parental segregation, variant phase, and parental origin were generally unavailable. Therefore, none of the molecular findings could be established as a confirmed explanation for the initial prenatal phenotype. Given the small and clinically selected sample, the absence of systematic CMA, incomplete segregation data, non-standardized longitudinal prenatal phenotyping, and heterogeneous postnatal follow-up, these observations do not permit conclusions regarding the diagnostic yield of exome sequencing in apparently isolated increased NT or cystic hygroma. A negative prenatal WES result should not be interpreted as excluding all genetic etiologies. These findings support careful phenotype-driven selection and cautious case-level interpretation of advanced genomic testing.

At least one postnatal clinical record or documented postnatal clinical status was available for all 41 live-born children with a normal karyotype. Clinically relevant postnatal abnormalities or diagnoses were documented in eight children (19.5%), as detailed in Table 5. Molecular evaluation was performed in some, but not all, of these children, and the degree of diagnostic certainty varied among cases. The depth and duration of postnatal follow-up were heterogeneous and were not systematically documented. Follow-up duration was explicitly recorded for only one child; therefore, a median postnatal follow-up duration could not be calculated. These findings underscore that an apparently isolated first-trimester phenotype and a normal conventional karyotype do not completely exclude later clinical manifestations.

The lack of systematic CMA represents an important diagnostic gap in this cohort. Conventional karyotyping is effective for detecting major aneuploidies and large chromosomal abnormalities but may fail to detect clinically relevant submicroscopic copy number variants. Therefore, fetuses classified as having a normal karyotype in this study should not be considered genomically normal. The postnatal identification of a 9q34 deletion consistent with Kleefs-

tra syndrome in one child illustrates this limitation, as such submicroscopic abnormalities would not be expected to be detected by conventional karyotyping alone. This finding supports the role of CMA as an important component of the contemporary evaluation of fetuses with increased NT or cystic hygroma.

Limitations

Several limitations should be acknowledged. First, the retrospective, single-center design limits the generalizability of the findings. The cohort was derived from a tertiary referral center and included only fetuses who underwent invasive prenatal testing; therefore, it may have been enriched for pregnancies with a higher pretest probability of chromosomal abnormality. Consequently, the observed chromosomal abnormality proportions should not be interpreted as population-based prevalence estimates.

Second, prenatal phenotyping was not uniform across the cohort. Initial first-trimester ultrasonographic assessments were performed in the same perinatology unit by experienced perinatologists, but not by a single operator. Operator-level information and technical measurement details were not systematically retrievable; therefore, interobserver variability could not be assessed. Pregnancies terminated following the diagnosis of a chromosomal abnormality frequently ended before detailed second-trimester assessment could be performed. Among pregnancies that continued, records confirming completion of detailed anomaly scanning, fetal echocardiography, and serial prenatal ultrasonographic follow-up were not systematically available in the retrospective dataset. Consequently, completion rates for these assessments could not be reliably reported, and additional structural abnormalities that became detectable later in gestation could not be excluded.

Third, although conventional karyotyping was performed in all included cases, detailed technical information regarding culture conditions, chromosome-banding methods, and analytical resolution was not systematically retrievable from the retrospective laboratory records. This limited our ability to describe and compare the technical sensitivity of the cytogenetic evaluations in greater detail.

Fourth, CMA was not systematically performed in fetuses with a normal karyotype. This represents an important diagnostic limitation because conventional karyotyping may fail to detect clinically relevant submicroscopic copy number variants. Consequently, pathogenic copy number variants may have remained undetected, and fetuses with a normal karyotype should not be considered genomically normal. This limitation is particularly relevant because some postnatal diagnoses, including microdeletion syndromes, may not be detected by conventional karyotyping alone.

Fifth, molecular testing, predominantly based on WES or CES, was performed only in a limited, clinically selected subset of cases rather than systematically across the entire cohort, precluding estimation of a cohort-level diagnostic yield. Some molecular findings were identified through postnatal testing, whereas others were obtained prenatally or through external clinical records. Therefore, the timing, indications, and clinical context of molecular evaluation were heterogeneous. All locally performed WES and CES analyses were conducted as solo testing. Because of the retrospective and multisource nature of data collection, parental segregation, variant phase, parental origin, and specific ACMG/AMP evidence criteria were not systematically retrievable. In addition, the testing configuration and complete original molecular report were unavailable for the externally tested TSC2 case. Consequently, none of the documented molecular findings could be considered a confirmed explanation for the initial increased NT or cystic hygroma phenotype.

Sixth, pregnancy outcome assessment was based primarily on pregnancy loss, termination of pregnancy, and live birth. However, live birth should not be equated with the absence of postnatal morbidity. At least one postnatal clinical record or documented postnatal clinical status was available for all 41 live-born children with a normal karyotype; however, the depth and duration of follow-up were heterogeneous and were not systematically documented. Follow-up duration was explicitly recorded for only one child, and a median postnatal follow-up duration could not be calculated. Consequently, clinically relevant abnormalities that developed later may have been under-recorded.

Finally, the relatively small number of fetuses with cystic hygroma limited statistical power and increased the uncertainty of between-group comparisons. The multivariable analysis was exploratory and adjusted only for maternal age; therefore, residual confounding by unmeasured or incompletely documented factors cannot be excluded.

Despite these limitations, this study provides clinically relevant descriptive information on cytogenetic findings and pregnancy outcomes in fetuses with apparently isolated increased NT or cystic hygroma, together with cautiously interpreted molecular observations from clinically selected cases managed in a tertiary referral setting.

Future prospective studies incorporating standardized first- and second-trimester phenotyping, systematic CMA, phenotype-guided molecular testing including WES or CES, and structured long-term postnatal follow-up are needed to more clearly define the genetic findings and clinical outcomes associated with apparently isolated increased NT or cystic hygroma.

5. Conclusions

Chromosomal abnormalities were identified in a substantial proportion of fetuses with apparently isolated increased NT or cystic hygroma. Among fetuses with a normal karyotype, live birth rates were high, particularly in the increased NT group; however, these outcomes reflect the apparently isolated phenotype documented at the ini-

tial first-trimester assessment and should be interpreted together with the available postnatal clinical information, including clinically relevant abnormalities or diagnoses documented in eight of 41 live-born children (19.5%). The absence of systematic CMA highlights an important diagnostic gap in conventional karyotyping, particularly with respect to detecting submicroscopic copy number variants. Molecular testing, predominantly based on WES or CES, yielded heterogeneous case-level findings in clinically selected cases, including potentially relevant but unconfirmed findings, findings of uncertain or possible carrier/incidental significance, an additional non-diagnostic finding in one fetus with aneuploidy, and negative or otherwise non-diagnostic evaluations. Based on the available records, none of these findings could be established as a confirmed molecular explanation for the initial increased NT or cystic hygroma phenotype, and the selectively obtained results should not be interpreted as an estimate of the cohort-level diagnostic yield. Overall, these findings support careful prenatal phenotyping, serial ultrasound follow-up, the appropriate use of CMA, and a phenotype-driven approach to advanced molecular testing.

Abbreviations

AD, Autosomal dominant; AR, Autosomal recessive; ACMG/AMP, American College of Medical Genetics and Genomics/Association for Molecular Pathology; CES, Clinical exome sequencing; CI, Confidence interval; CMA, Chromosomal microarray analysis; CVS, Chorionic villus sampling; IQR, Interquartile range; LP, Likely pathogenic; NT, Nuchal translucency; OR, Odds ratio; P, Pathogenic; RR, Relative risk; SD, Standard deviation; VUS, Variant of uncertain significance; WES, Whole-exome sequencing.

Availability of Data and Materials

The data underlying this study consist of sensitive human genomic and phenotype-linked clinical information derived from retrospective patient records and clinical genetic reports. Patient-level data are not publicly available because of privacy, confidentiality, institutional policy, and ethics committee restrictions. De-identified aggregate or limited analytic data may be available from the corresponding author upon reasonable request, subject to institutional and ethical approval.

Author Contributions

Oİ, CD, and İM contributed to the conception and design of the study. Oİ, CD, Eİ, ÖFÖ, and CDa. collected and curated the data. Oİ, CD, and ÖFÖ analyzed the data. Oİ, CD, ÖFÖ, AEM, and İM contributed to the interpretation of the data. Oİ and CD drafted the manuscript. Eİ, ÖFÖ, CDa, AEM, and İM critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript, participated sufficiently in the work, and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Medical Scientific Research Ethics Committee of Akdeniz University Faculty of Medicine, Akdeniz University, Antalya, Turkey (Approval No. TBAEK 257/2024). The study was conducted in accordance with the Declaration of Helsinki. Because of the retrospective design and the use of anonymized clinical data, the requirement for informed consent to participate was waived by the same ethics committee.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, ChatGPT-5.5 was used solely for language translation, grammar checking, and editorial polishing. No generative AI tool was used to generate scientific content, analyze data, create results, or draw conclusions. The authors reviewed and edited all AI-assisted output and take full responsibility for the content of the manuscript.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG54356.

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