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Hypoplastic nasal bone: a potential marker for facial dysmorphism associated with pathogenic copy number variants on microarray

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What is already known about this topic?	What does this study add?
□ A hypoplastic nasal bone is a strong marker for trisomy 21. □ The value of microarray to detect atypical chromosomal abnormalities in pregnancies with a hypoplastic nasal bone at mid-trimester is uncertain.	□ A clinically relevant CNV accounted for 10% of pathogenic karyotypes in fetuses with isolated and non-isolated hypoplastic nasal bone. □ Counselling should include the risk of atypical chromosomal abnormalities and the benefit of microarray in this setting.

Abstract

Objectives

To compare the frequency of abnormal genetic diagnoses spanning a period before and after the availability of chromosomal microarray analysis (CMA). We hypothesised that microarray would provide additional clinically relevant information in cases of isolated hypoplastic nasal bone.

Method

Fetuses with ultrasound detected hypoplastic nasal bone (absent or <2.5th percentile in length) between 16-37 weeks' gestation over a ten-year period were analysed retrospectively.

Results

A total of 118 cases of hypoplastic nasal bone met the inclusion criteria. A pathogenic or potentially pathogenic karyotype was detected more frequently in the era where CMA was available (31/60, 52% vs 19/58, 33%). Of these, 25 cases (42%) had common aneuploidies and 6 cases (10%) had clinically relevant copy number variants (CNVs). A clinically relevant CNV was detected in 2 fetuses that presented with isolated hypoplastic nasal bone on initial ultrasound.

Conclusion

In addition to its known association with trisomy 21 a hypoplastic nasal bone may be an objective marker of facial dysmorphism associated with clinically relevant CNVs. Our results support consideration of invasive testing with microarray for pregnancies in which a hypoplastic nasal bone has been diagnosed on ultrasound irrespective of a low risk screening result for common chromosomal abnormalities.

Introduction

The nasal bones develop as two separate structures from the sixth week of gestation from neural crest cells (1). An absent or hypoplastic nasal bone has been extensively investigated as a sonographic marker for trisomy 21 and is associated with 60% of fetuses with trisomy 21 compared with only 1.4% of euploid fetuses in the second trimester (1). An absent nasal bone is also associated with other common aneuploidies such as trisomy 18, trisomy 13 and Turner syndrome (2). Rare conditions such as Cri du chat (5p-) syndrome, Wolf-Hirshhorn syndrome (4p-) and Fryns Syndrome have also been reported (3-5). These conditions are known to have phenotypically unique facial characteristics but can be difficult to detect by ultrasound subjectively and the nasal bone may offer the means of an objective sonographic marker.

Since cell-free DNA (cfDNA) screening became available, increased detection and earlier diagnosis of trisomy 21 in the first trimester has been reported without necessarily relying on ultrasound (6). The role of ultrasound markers, including nuchal translucency and additional markers in the first trimester, have become less clear in this scenario and their utility questioned. In the second trimester, the impact of a lower pre-test prevalence of trisomy 21 at the time of the anatomy ultrasound has led professional societies to issue statements urging practitioners to abandon the 'genetic sonogram' and recommend against invasive testing solely for the indication of an isolated soft marker (7, 8). Almost simultaneous to the arrival of

cfDNA, prenatal diagnosis capability has expanded with the availability of chromosomal microarray analysis (CMA). Compared to traditional G-band karyotyping, CMA offers higher resolution and with single nucleotide polymorphism CMA, can detect consanguinity and uniparental disomy. Numerous studies have shown that CMA provides additional information in 6-7% of pregnancies with abnormal ultrasound findings and as such is now the recommended first-tier genetic test (9, 10). Studies reporting on abnormal ultrasound findings have included referrals for structural abnormalities, and to a lesser extent, referrals for soft markers and non-structural abnormalities (11, 12).

Importantly, studies evaluating the value of fetal hypoplastic nasal bone have been undertaken mostly prior to CMA being widely utilised in the prenatal setting and this evidence has informed the professional societies' statements (7, 8). Therefore, it remains unclear if the combined prevalence of the common and atypical chromosomal abnormalities detected by CMA justifies invasive testing in cases where a hypoplastic nasal bone is found in isolation on ultrasound following a low risk result on cfDNA screening.

Given the uncertainty surrounding the significance of an isolated hypoplastic nasal bone in pregnancies at low risk of trisomy 21, we aimed to examine the frequency and detection rate of genetic abnormalities associated with a hypoplastic nasal bone during a ten-year period that coincided with a transition from prenatal G-band

karyotype to CMA. Table 1 summarises the context in which the study was conducted. Towards the end of the G-band karyotype era, prenatal CMA was available but only through participation in a local clinical study protocol (13). In the early years of the CMA era, the test of choice was influenced by the clinical findings.

<Table 1>

In this tertiary referral population, we compared the frequency of abnormal genetic diagnoses spanning these two clinical practice eras and hypothesized that 1) invasive testing with CMA would provide additional information in cases of isolated hypoplastic nasal bone and 2) that this finding, particularly in the second trimester, should not be considered solely as a soft marker and invasive testing should be considered irrespective of a low risk result for the common chromosomal anomalies on cfDNA.

Methods

All sonographic examinations performed at The Royal Women's Hospital, a tertiary referral maternity hospital in Melbourne, Australia, that identified a hypoplastic nasal bone in a fetus at 16-37 weeks' gestation between January 2006 and December 2015 were reviewed. A nasal bone was defined as hypoplastic when it was either absent or measured less than the 2.5th percentile. The nasal bone is assessed in the mid-sagittal plane of the fetal profile and measured at the level of the synostosis using the method and reference range as previously described by Sonek et al (14). Examples of ultrasound images comparing normal and abnormal nasal bones in the first and second trimester are shown in Figure 1.

<Figure 1>

Singleton and dichorionic twin pregnancies with a hypoplastic nasal bone that had genetic testing (G-band or CMA) or newborn examination data were included. Chromosomal microarray on fetal material and parental samples where indicated, were performed using whole-genome single nucleotide polymorphism arrays (Affymetrix CytoScan 750K or Illumina HumanCytoSNP-12) with a resolution of approximately 0.20Mb. All genetic testing was performed by the Victorian Clinical Genetics Service, which provides more than 95% of genetic testing for the state of Victoria, Australia.

Cases were excluded if genetic or newborn examination information were not available. Cases were classified as isolated and non-isolated hypoplastic nasal bone according to the initial ultrasound performed in our unit. Subgroup analysis was performed according to two clinical practice eras: pre-CMA (January 2006-December 2011) or CMA era (January 2012 – December 2015). Ultrasound findings, limited demographic and pregnancy data were collected from the ultrasound picture archiving and communication system, electronic clinical reports and medical records. Study data was recorded and managed using REDCap, a secure web-based application designed to support data capture for research studies (15). Mann-Whitney test for non-parametric data was used to compare medians and the Wilson method was used to calculate confidence intervals.

As a retrospective, anonymised audit, this study met the criteria for quality assurance activities outlined by the National Health and Medical Research Council (16) and confirmatory correspondence was received from the hospital's Human Research and Ethics Committee.

Results

During the ten-year period, 124 fetuses with a hypoplastic nasal bone were detected on ultrasound between 16-37 weeks' gestation. There were 118 fetuses (117 pregnancies, one dichorionic twin pregnancy contributed two fetuses) that met the criteria for inclusion. Six cases were excluded because genetic or newborn information were not available. Fifty-eight fetuses were assessed during the pre-CMA era and sixty fetuses were assessed during the CMA era (Figure 2).

<Figure 2>

The maternal demographics and pregnancy characteristics were similar during the two practice eras (Table 2). The median maternal age (33 vs 32, $p=0.50$) was not statistically different between the two eras. Our referral population was predominantly high-risk, with the indications for ultrasound being high risk aneuploidy screening result, advanced maternal age, abnormal previous ultrasound or significant family history.

<Table 2>

Genetic testing

Genetic testing was performed in 83% and 90% of fetuses with hypoplastic nasal bone in the two respective practice eras. Genetic testing was predominantly performed in the prenatal period (Table 3).

During the transition to CMA, there was a small proportion of women who had G-band karyotype performed when a common aneuploidy was suspected according to the ultrasound findings or prior screening. Thus, a CMA was performed in 72% (43/60) of fetuses with a hypoplastic nasal bone during the CMA era. A pathogenic or potentially pathogenic genetic result was detected more frequently in the CMA era (31/60, 52% vs 19/58, 33%); 25 cases (42%) had common aneuploidies and 6 cases (10%) had clinically relevant CNVs (Table 4). Further details of genetic results according to the type of genetic test and the timing, can be found in Table S1.

Among the 16 cases with no genetic testing performed prenatally or during the short-term postnatal follow-up, there was one case of known hypoplastic left heart syndrome with an atrial septal defect and aberrant right subclavian artery. This baby did not have further evidence of a syndromic diagnosis. The remaining 15 cases did not have any congenital anomalies identified at birth.

<Table 3>

<Table 4>

Outcomes according to aneuploidy screening

An abnormal genetic result was most frequently seen in women with a high risk screen result (21/36, 58.3%), followed by women with no aneuploidy screening (16/31, 51.6%); and least frequently in women with a low risk screen result (13/51, 25.5%). The mix of genetic abnormalities differed between women according to their screening result. In women with high risk screening, all pathogenic findings comprised of trisomy 21 and 18. In contrast, for women with low risk results or no screening, a clinically relevant CNV occurred in 5.9% (3/51, 95% CI 2.0-15.9%) and 9.7% (3/31, 95% CI 3.3-24.9%) respectively. Outcomes of these pregnancies according to aneuploidy screening are shown in Figure 3.

<Figure 3>

Copy number variants

Of the clinically relevant CNVs detected during the CMA era, 2 cases presented with isolated hypoplastic nasal bone but both subsequently developed fetal growth restriction and one also ventriculomegaly (Table 5, cases 1-2). In the other 4 cases, structural anomalies or additional soft markers were evident on initial ultrasound (Table 5, cases 3-6). Three pregnancies with a clinically relevant CNV resulted in a livebirth: two were diagnosed on postnatal CMA, performed in view of facial dysmorphism and multiple anomalies (Table 5, cases 1 and 5); one was diagnosed with multiple anomalies at birth that could be related to the novel but potentially

pathogenic CNV detected on prenatal CMA (Table 5, case 2). The remaining CNVs were likely to be benign based on their small sequence size and/or inheritance from a healthy parent (Table 5, cases 7-10).

Considering only fetuses that had CMA testing for the overall study period, a clinically relevant CNV was detected in 12% (6/47, 95% CI 6.0-25.2%). For the 10 cases of isolated hypoplastic nasal bone investigated with CMA, 20% (2/10, 95% CI 5.7-50.1%) were found to have a clinically relevant CNV. For the 37 cases of non-isolated hypoplastic nasal bone investigated with CMA, 11% (4/37, 95% CI 4.3-24.7%) were found to have a clinically relevant CNV.

<Table 5>

Discussion

A hypoplastic nasal bone is most strongly associated with trisomy 21 but also with other syndromes that can present with facial dysmorphism (3-5). There is paucity of evidence as to whether the prevalence of less frequent genetic abnormalities would justify invasive testing in pregnancies with a hypoplastic nasal bone if at low risk for trisomy 21. In this ten-year audit of fetuses presenting with hypoplastic nasal bone, we report our experience of using CMA for this indication. A pathological genetic result was detected more frequently in the CMA era (31/60, 52% vs. 19/58, 33%) when compared to the Pre-CMA era. Of these, 25 cases (42%) had common aneuploidies and 6 cases (10%) had clinically relevant CNVs. Two clinically relevant CNVs were detected in fetuses with isolated hypoplastic nasal bone at presentation. On subsequent ultrasounds, both fetuses developed fetal growth restriction and one also ventriculomegaly; final diagnoses were Wolf-Hirshhorn syndrome and multiple minor dysmorphisms at birth (case 1 and 2). These two cases highlight the importance of detailed follow-up ultrasound and consideration of further investigation such as invasive testing irrespective of aneuploidy screening results. In fact, in this study population the yield for a pathogenic CNV following the detection of a hypoplastic nasal bone was 5.9% in those who had a previous low risk screening result.

Nasal bone length has been reported to show ethnic variation (17, 18). The mean nasal bone length of Caucasian and African American fetuses reported by Sonek et

al., differed from the means reported in Japanese and Korean populations (14, 18). Our referral population consisted of a large proportion of women of Asian ethnicity (28% in the CMA era). During the same period, the proportion of Asian women in our general maternity population was 21%. If a hypoplastic nasal bone is indeed shorter in Asian populations, then our study may have underestimated the frequency of clinically relevant CNVs by including a higher proportion of false positive cases, as we have used a nasal bone length cut-off derived from a predominantly Caucasian population. Nonetheless, the impact of ethnicity on biometric markers like the nasal bone length needs to be considered. The rationale to use the reference range reported by Sonek et al. is mainly practical as it covers the widest range of gestational ages. Furthermore, a significant difference in nasal bone length between Asian and Caucasian groups was not demonstrated in a study conducted in an Australian population (19). Counselling of non-Caucasian women with a fetus identified with an isolated hypoplastic nasal bone will remain complex due to the ethnicity-related normal variation and this should be taken into account during genetic counselling.

Other limitations to our study include its retrospective nature and the small number of cases with isolated hypoplastic nasal bone having undergone CMA testing. The yield of further testing via CMA in this subset of cases should be the subject of larger studies, particularly focusing in those who had an overall low risk result on screening for the common chromosomal anomalies.

It is important to note that a pathogenic CNV could not be excluded in those who only had G-band karyotyping or newborn examinations. Considering only fetuses that had CMA testing, a clinically relevant CNV was detected in 12% overall and 20% when the hypoplastic nasal bone was an isolated finding on initial ultrasound. Despite the study's limitations, our estimated frequency for clinically relevant CNVs in this scenario is at least 5-6%, not dissimilar to the rate of pathogenic CNVs in a fetus with other ultrasound abnormalities, and significantly higher than the 1% seen in a structurally normal fetus (9, 10). Therefore, we believe that until further data is available, our results caution against the abandonment of nasal bone assessment in women with a low risk aneuploidy screening result. Our observation also supports the Society for Maternal-Fetal Medicine's statement (8) that ultrasound findings such as hypoplastic nasal bone and ventriculomegaly should be further evaluated clinically and not be considered as a soft marker per se.

Detection rates of additional ultrasound findings could reflect the different levels of ultrasound expertise and the evolution of findings as the pregnancy advances; these factors should be taken into account in clinical practice.

We believe genetic counselling is appropriate at the initial detection of a hypoplastic nasal bone and this is routine practice in our unit. Counselling should also include the benefits and limitations of CMA, including the type and range of results such as

variants of uncertain significance (VOUS); and findings which increase susceptibility to autism and other late-onset disorders (20). Parental studies may be required to clarify the origin of abnormal results and to aid counselling in cases of VOUS. Knowing the possible outcomes of CMA, women are more likely to choose broader coverage testing in alignment with their personal values (21).

This study demonstrates the potential value of using hypoplastic nasal bone beyond the first trimester as an objective marker of facial dysmorphism associated with pathogenic CNVs. Therefore women with isolated or non-isolated fetal hypoplastic nasal bone should receive appropriate assessment, followed by a discussion of benefits and risks of invasive testing irrespective of prior aneuploidy screening.

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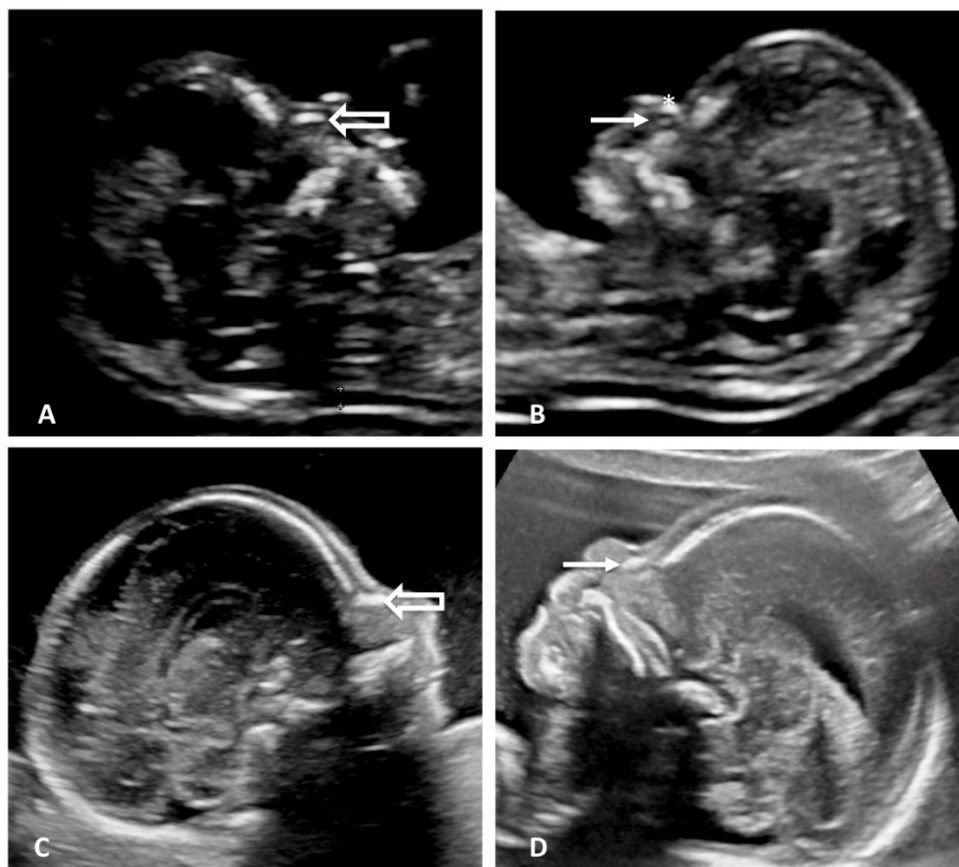


Figure 1. Examples of ultrasound images during the first and second trimesters showing: (A) normal nasal bone (unfilled arrow) and (B) absent nasal bone (arrow points to a structure which is thinner and less echogenic than the overlying skin, highlighted by the *) in the first trimester; (C) normal nasal bone (unfilled arrow) and (D) hypoplastic nasal bone (arrow) at mid-trimester.

Figure 2. Fetuses identified with hypoplastic nasal bone during the ten-year period

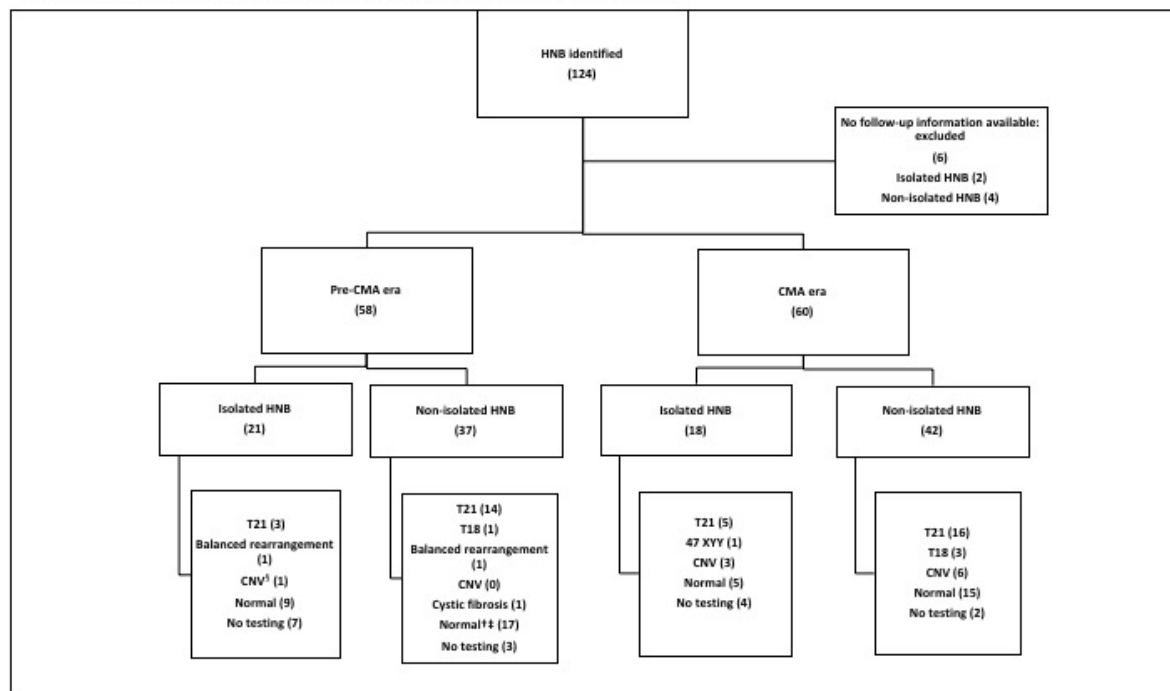


Figure 2. Fetuses identified with hypoplastic nasal bone during the ten-year period
Legend:

[†] 2 terminations of pregnancy for multiple fetal anomalies (normal G-band karyotypes); 1 with early fetal growth restriction, hypoplastic cerebellum, ventricular septal defect and hypoplastic nasal bone; 1 with tricuspid atresia, ventricular septal defect, upper body oedema and hypoplastic nasal bone.

[‡] 1 termination for suspected fetal alcohol syndrome (normal CMA) based on fetal growth restriction, hypoplastic nasal bone and maternal history of alcohol use.

[§] CNV of uncertain significance detected on postnatal CMA

HNB, hypoplastic nasal bone; CMA, chromosomal microarray analysis; T21, trisomy 21; T18, trisomy 18; CNV, copy number variant

Figure 3. Outcomes according to aneuploidy screening

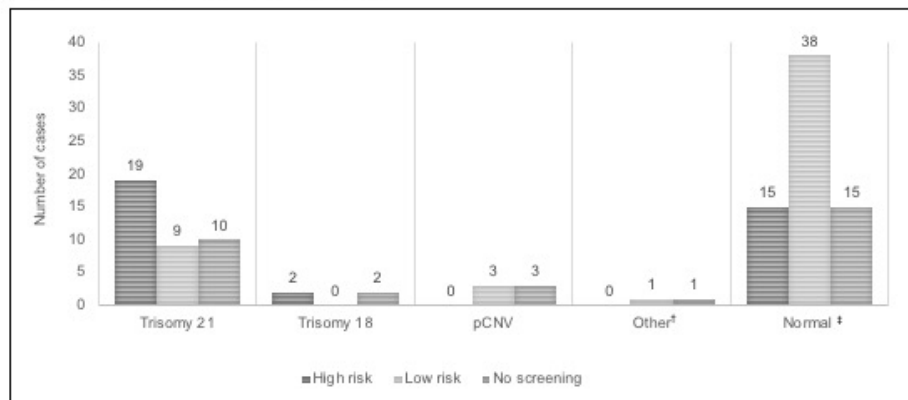


Figure 3 Outcomes according to aneuploidy screening

[†] 1 Cystic fibrosis (low risk), 1 47 XYY (no screening)

[‡] Normal cases include balanced rearrangements, likely benign CNVs and those with normal newborn examinations

pCNV, pathogenic or potentially pathogenic copy number variants

Table 1 Context in which our study was performed

Pre-CMA era	• Prior to January 2012, FISH and G-band karyotype were the standard choice for genetic testing • CMA was available for postnatal testing from 2007 • Prenatal CMA was introduced but only available through participation in a local clinical study protocol for fetal structural anomalies in 2009-2011 • Resolution 5-10Mb
CMA era	• Whole-genome single nucleotide polymorphism array was available from January 2012 • During a transitional period between 2012-2014, CMA was requested depending on the clinical findings • CMA became the routine first-tier test in 2015 • Resolution 0.2Mb

FISH, fluorescent in-situ hybridisation; CMA, chromosomal microarray analysis

Table 3. Details of genetic testing for the 118 fetuses

	Overall N=118	Pre-CMA era N=58	CMA era N=60
Genetic testing			
Performed	102 (86.4)	48	54
G-band	55	44	11
CMA	47	4	43 [†]
Not performed	16 (13.6)	10	6
Timing of testing[‡]			
Prenatal	84 (82.4) [‡]	38	46
Postnatal	18 (17.6)	10	8 [†]

[†] 1 fetus had both prenatal G-band karyotype and postnatal CMA; only the postnatal CMA was counted (see Table 5, case 1).

[‡] For 102 fetuses who had testing CMA, chromosomal microarray

Table 4. Comparison of diagnoses between the two clinical eras

Diagnosis	Overall n (%)	Pre-CMA era n (%)	CMA era n (%)
Copy number variant	10 (8.5)	1 (1.7)	9 (15.0)
Pathogenic	4	0	4
Potentially pathogenic	2	0	2
Benign/uncertain significance	4	1	3
Common aneuploidy	43 (74.1)	18 (31.0)	25 (41.7)
Trisomy 21	38	17	21
Trisomy 18	4	1	3
47 XYY	1	0	1
Structural rearrangements	2 (1.7)	2 (3.4)	0 (0)
Balanced	2	2	0
Unbalanced	0	0	0
Monogenic disorder[†]	1 (0.8)	1 (1.7)	0 (0)
Normal karyotype	46 (39.0)	26 (44.8)	20 (33.3)
G-band karyotype	27	23	4
CMA	19	3 [‡]	16
Genetic testing not performed	16 (13.6)	10 (17.2)	6 (10.0)
Total	118	58	60

[†] Cystic fibrosis diagnosed on targeted gene testing for fetal echogenic bowel

[‡] Two prenatal CMA performed within a research protocol, one postnatal CMA

Table 5. Clinical details of pregnancies diagnosed with copy number variants

Cas e	Age	Ethnicit y	GA †	Aneuploid y screening	Ultrasou nd findings	Subsequent ultrasound findings	CMA	Diagnosis, prevalence	Outcome
1	29	Maori	19	NT 0.7mm Low risk cFTS	Isolated hNB	FGR from 24 weeks	Arr[hg 18] 4p16.3p16.1(38,283- 7,979,941)x1 dn, 9p24.3(36,587-339,518)x3 dn [‡]	Wolf- Hirshhorn syndrome 1/50,000	LB, 1620g, 34+5 weeks GA. NND day 12. Dysmorphic facies, encephalopathy with intractable seizures. Ponto-cerebellar hypoplasia on MRI.
2	41	African	17	-	Isolated hNB	VM at 29 weeks and FGR at 37 weeks	Arr[hg19] 1p31.3(66,713,050- 67,912,259)x1dn, 6q21q22.1(114,588,463- 116,788,453)x1dn	CNV of potential significance	LB, 2250g at 37+4 weeks GA. Dysmorphic facies, anteriorly placed anus, polysyndactyl of both fifth toes, bifid distal phalanx of left thumb, multiple wormian bones, 11 pairs of ribs. Hypoplastic corpus callosum and bifrontal paraventricular cysts on MRI.

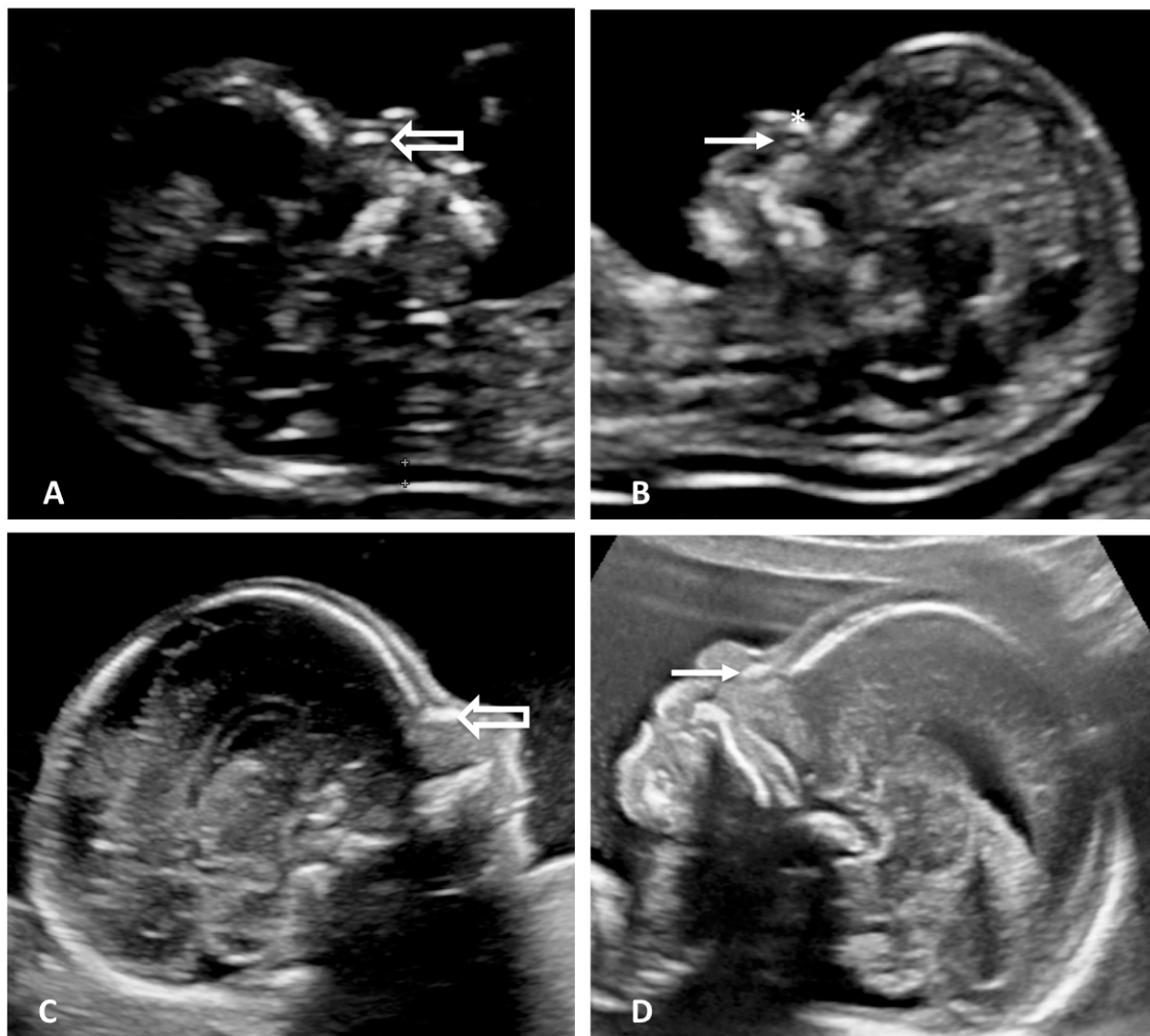
3	35	Cauc	20	NT 1.2mm Low risk cFTS	hNB, thick NF, hypoplastic cerebellum, oligohydramnios	-	Arr[hg 19] 5p15.33p14.3(113,576-21, 973,894)x1 dn, 5q35.3(176,843,832- 180,715,096)x3 dn	Cri-du-chat syndrome 1/15-50,000	ToP
4	31	Cauc	20	-	Absent NB, hypoplastic corpus callosum	-	Arr[hg19]17p11.2(16,745,6 00-20,499,811)x1dn	Smith- Magenis Syndrome 1/25-50,000	ToP
5	31	Asian	20	-	hNB, short long bones	No additional findings on 2 subsequent ultrasounds	Arr[hg19]17q23.3q25.3(62, 464,807-78,335,034)x3	Pathogenic, rare	LB, 3560g at 38+6 weeks GA. Dysmorphic facies, sensorineural hearing loss, developmental delay. Enlarged pre-axial space, under-opercularisation of Sylvian fissures, dilated lateral and third ventricles, dysplastic hippocampi on MRI.
6	21	Asian	23	NT 1.0mm Low risk cFTS	hNB, RAA	FGR at 33 weeks	Arr[hg19] 9q31.2(108,350,181- 111,123,697)x1 dn	CNV of potential significance	LB, 1680g, 34+3 weeks GA. RAA, ALSA, left eye ptosis

7	32	Cauc	18	NT 1.6mm Low risk cFTS	Isolated absent NB	Absent right kidney at 29 weeks and FGR at 33 weeks	Arr[hg18] 9q34.13(133,100,286- 133,328,423)x3	CNV of uncertain significance	LB, 1620g, 35+3 weeks GA. Right pelvic kidney.
8	41	Cauc	21	NT 1.0mm Low risk cFTS	Isolated absent NB	No additional findings on 2 subsequent ultrasounds	Arr[hg 19] 19q12(31,709,481- 32,107,103)x3 paternally inherited	Likely benign CNV	Newborn information not available.
9	27	Asian	20	NT 1.3mm Low risk cFTS	hNB, ICEF	No additional findings on 2 subsequent ultrasounds	Arr[hg19] 9p24.3(291,480- 660,922)x3-?4 maternally inherited	Likely benign CNV	LB, 3268g, 39+4 weeks GA. Normal newborn examination.
10	23	Middle- Eastern	19	Low risk MSST	hNB, FGR, echogeni c bowel	No additional findings on 14 subsequent ultrasounds	Arr[hg 19] 9q33.1(117,976,150- 118,609,807)x3 maternally inherited	Likely benign CNV	LB, 1616g, 37 weeks GA Normal newborn examination. Placental massive perivillous fibrin deposition.

[†] Gestational age at tertiary ultrasound

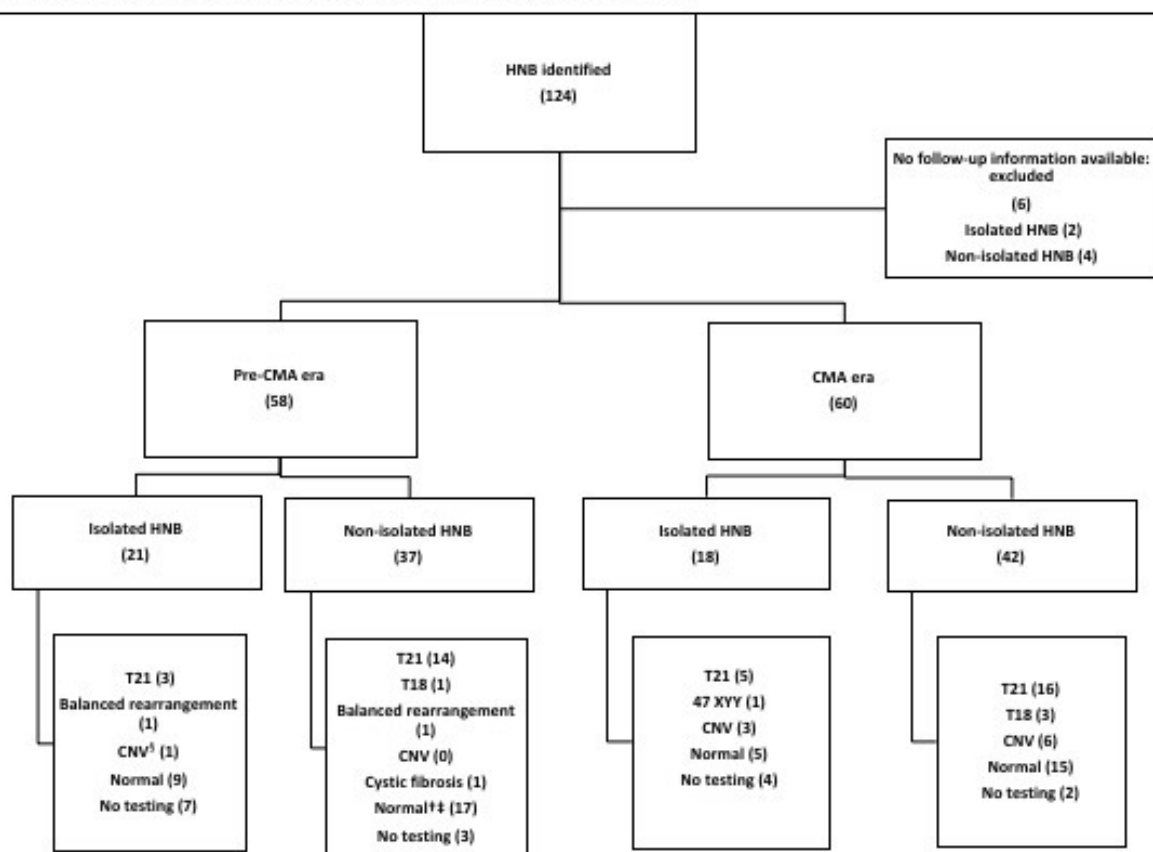
[‡] De novo terminal deletion from 4p16.1 and terminal duplication from 9p24.3. This case occurred in the CMA era but a G-band karyotype was requested prenatally. The diagnosis was made on postnatal CMA.

Cauc, Caucasian; GA, gestational age; CMA, chromosomal microarray, NT, nuchal translucency; cFTS, combined first trimester screen; NB, nasal bone; hNB, hypoplastic nasal bone; ToP, termination of pregnancy; LB, livebirth; NND, neonatal death; NF, nuchal fold; FGR, fetal growth restriction; VM, ventriculomegaly; RAA, right aortic arch; ALSA, aberrant left subclavian artery; ICEF, intracardiac echogenic focus; MSST, maternal serum screen test.



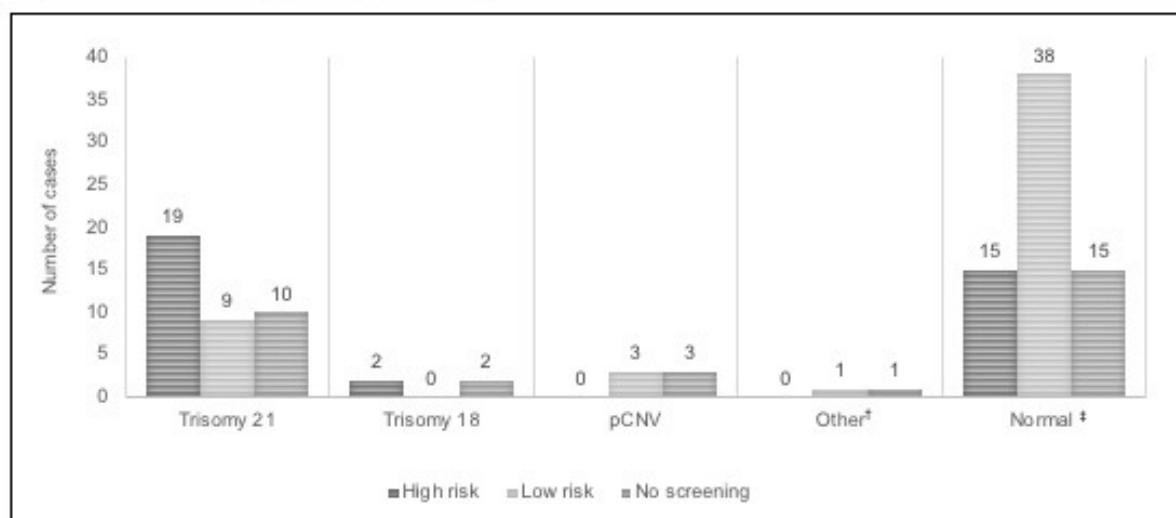
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Figure 2. Fetuses identified with hypoplastic nasal bone during the ten-year period



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Figure 3. Outcomes according to aneuploidy screening



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