Fetal exome sequencing for isolated increased nuchal translucency

Mellis, R; Eberhardt, Ruth Y; Hamilton, S; McMullan, D; Kilby, Mark; Maher, ER; Hurles, M; Giordano, JL; Aggarwal, V; Goldstein, D; Wapner, R. J.; Chitty, LS

DOI:
10.1111/1471-0528.16869

Table 1. Diagnostic variants identified after trio ES and review by the PAGE/CUIMC study clinical review panel in fetuses initially presenting with non-isolated increased NT at 11-14 weeks of gestation. †Variants previously published.

Study Identifier	NT(mm)	Additional findings at presentation	Variant(s)	Findings at later scans	Pregnancy outcome	Postnatal follow-up	Final diagnosis
PP0342	8.0	Hydrops; dysmorphic facies; abnormal hand position, fixed flexures with skin webbing - ?arthrogryposis	†*CHRNG* c.1010_1011del p.(His337Leufs*60) †*CHRNG* c.459dup p.(Val154Serfs*24) (Compound het, Biparental inh)	N/A	ToP	nil	Multiple pterygium syndrome
PP3174	4.1	Rhizomelic long bone shortening	*TRIP11* c.757C>T p.(Arg253*) (Hom, Biparental inh)	N/A	Miscarriage	nil	Achondrogenesis, type IA
PP1780	8.6	Encephalocele, hypoplastic thorax; tricuspid regurgitation; bilateral polycystic dysplastic kidneys; hand polydactyly; bilateral talipes; short long bones	†*TCTN2* c.1506-2A>G (Hom, Biparental inh)	As at presentation	NND	nil	Joubert syndrome
PP2567	9.7	Mild ascites	†*PTPN11* c.922A>G p.(Asn308Asp) (Het, Mat inh) *SOS1* pathogenic variant (Het, Pat inh) additionally detected on a postnatal RASopathy panel, independent of PAGE study.	CCAM of right lung, pleural effusions and worsening hydrops	NND	Premature delivery at 33/40 – born in poor condition; hydropic; PPHN refractory to maximal ventilator support. Deceased at 25 days of age due to respiratory insufficiency. No PM	Noonan syndrome
PP2000	9.3	Bilateral talipes; clenched hands	†*RYR1* c.7826C>A p.(Ser2609*)	N/A	Miscarriage	nil	Minicore myopathy

			(Mat inh) †*RYR1* c.10177_10198delCTGGTGCGGGACGAGTTCTCTG p.(Leu3393CysfsTer25) (Pat inh) (Compound het)				with external ophthalmoplegia
PP4147	5.0	Cystic hygroma; skin oedema; post-axial polydactyly; enlarged echogenic kidneys; posterior encephalocele	*TCTN3* c.628-13_643delATATTTTATTCAGGCTGGGGACCCCATTC (Hom, Biparental inheritance)	N/A	ToP	nil	Joubert syndrome
PP3324	6.1	Septated cystic hygroma; severe hydrops (bilateral pleural effusion, ascites, generalised skin oedema)	*BRAF* c.1782T>G p.(Asp594Glu) (Het, De novo)	N/A	ToP	nil	Noonan syndrome
PP1843	11.3	Hydrops (bilateral pleural effusions)	†*KMT2D* c.6295C>T p.(Arg2099*) (Het, De novo)	Echogenic horseshoe kidney (19/40); Borderline ventriculomegaly; mid-face hypoplasia (21/40)	ToP	PM: flat face, low set posteriorly rotated ears); loose neck skin, partial intestinal malrotation, horseshoe kidney;	Kabuki syndrome
PP3732	19.0	Cystic hygroma and fixed flexed extremities; stomach and bladder not visible	420bp deletion 19: 38965858 – 38966278 encompassing exon 29 of *RYR1* (Hom, Biparental inh)	N/A	ToP	No PM	Minicore myopathy with external ophthalmoplegia
PP3393	5.1	Disproportion of Ao>PA; Suspected overriding aorta (possible Tetralogy of Fallot)	*GPC3* c.677delC p.(Thr226Ilefs*8) (Hemi, Mat inh)	Small pericardial effusion (16/40); Moderate perimembranous VSD (22/40)	LTFU after 32/40	nil	Simpson-Golabi-Behmel syndrome, type 1

PP4393	Not specified	Cystic hygroma; hydrops; fixed flexed extremities; fetal akinesia sequence	*RYR1* c.8342_8343delTA p.(Ile2781Argfs*49) (Pat inh) *RYR1* c.2045G>A p.(Arg682Gln) (Mat inh) (Compound het)	N/A	ToP	Limited PM consisting of external examination and micro-CT: Hydrops; facial dysmorphism (flat nose, low-set ears); severe nuchal oedema; reduced muscle bulk; severe flexion deformities; skin webs at large joints; prominent heels. CT: no internal structural abnormalities	Minicore myopathy with external ophthalmoplegia
Fetal0183	3.5	Lethal skeletal dysplasia: micromelia, abnormal profile, micrognathia, talipes; ambiguous genitalia	†*COL2A1* c.1358G>T p.(Gly453Val) (Het, De novo)	N/A	ToP	nil	Type II collagenopathy

Table 2. Diagnostic variants identified after trio ES and review in fetuses presenting with initially isolated increased NT at 11-14 weeks of gestation, then other anomalies detected later. †Variants previously published.

Study Identifier	NT(mm)	Additional findings at presentation	Variant(s)	Findings at later scans	Pregnancy outcome	Postnatal follow-up	Final diagnosis
PP2904	9.5	None	†*EPHB4* c.759dupC p.(Ser254Glnfs*10) (Het, De novo)	Hydrops; ASD (20/40)	IUD	No PM	EPHB4-related lymphatic malformation
PP1726	8.0	None	†*TAB2* c.1311_1312delTC p.(Pro438Glnfs*2) (Het, De Novo)	Narrowing of aorta – suspected coarctation (25/40)	Live birth	Postnatal echocardiogram: mild tapering of aortic arch without coarctation; dysplastic tricuspid and pulmonary valves; bicuspid aortic valve. At 4 and 12 months old: Hypotonia (mild); broad, upturned nose; prominent forehead; protruding tongue; webbing of toes; short stature.	TAB2-related congenital heart defect
PP0503	4.5	None	†*PTPN11* c.922A>G p.(Asn308Asp) (Het, Mat inh)	AVSD (15/40)	Live birth	-	Noonan syndrome
PP0692	6.0	None	*RAF1* c.786T>G p.(Asn262Lys) (Het, De novo)	Short limbs (24/40); polyhydramnios (26/40)	Live birth	-	Noonan syndrome
PP1864	7.4	None	†*KMT2D* c.673+1G>A (Het, De novo)	Hypoplastic left heart syndrome with DORV, transposition of great arteries and pulmonary atresia (16/40)	ToP	PM: hypoplastic left heart with DORV, transposition of great arteries and pulmonary atresia	Kabuki syndrome
PP2033	6.5	None	†*CHD7* c.656dupG p.(Leu220Profs*67) (Het, De novo)	Hypoplastic left heart syndrome with DORV (17/40)	ToP	No PM	CHARGE syndrome

PP1462	8.9	None	†*BRAF* c.770A>G p.(Gln257Arg) (Het, De novo)	Short femurs (16/40); cystic dilatation of lymphatics extending from neck to upper aspect of chest bilaterally (19/40); bilateral renal pelvis dilatation (25/40)	NND	Premature delivery at 26/40. Subtle dysmorphic features; low-set ears; single palmar crease; severe pulmonary stenosis; PDA; ASD; short femurs. Deceased due to sequelae of prematurity. No PM.	Noonan syndrome
PP1807	4.7	None	†*MID1* c.1102C>T p.(Arg368*) (Hemi, De novo)	Hypoplastic right heart; VSD (20/40)	ToP	-	Opitz GBBB syndrome, type I
Fetal0116	Not specified	None	†*FLVCR2* c.1509+1G>A †*FLVCR2* c.1001dupT p.(Met334Ilefs*37) (Compound het)	Hydrocephalus; hyperflexed feet NB: Couple had previous pregnancies similarly affected	ToP	-	Proliferative vasculopathy and hydranencephaly-hydrocephaly syndrome (PVHH)
Fetal0222	5.2	None	†*SOS1 c.1132A>G* p.(Thr378Ala) (Het, Pat inh)	Pleural effusion; ascites	Live birth	-	Noonan syndrome
Fetal0307	4.7	None	*NR2F2* c.1091delT p.(Leu364Cysfs*15) (Het, De novo)	Shones complex	Live birth	-	NR2F2-related congenital heart defect
Fetal0385	4.7	None	*FGD1* c.2026_2028delGAG p.(Glu676del) (Hemi, Mat inherited [XLR, male proband])	Suspected skeletal dysplasia-short long bones <5%, flattened facies, short nasal bone, possible hypospadias versus ambiguous genitalia	Livebirth	-	Aarskog-Scott syndrome

Table 3. Diagnostic variants identified after trio ES and review in fetuses presenting with initially isolated increased NT at 11-14 weeks of gestation which remained isolated or resolved later in pregnancy. †Variants previously published.

Study Identifier	NT(mm)	Additional findings at presentation	Variant(s)	Findings at later scans	Pregnancy outcome	Postnatal follow-up	Final diagnosis
PP0602	4.8	None	†Chr15 UPD	NAD	Live birth	No abnormalities detected at birth	Chr15 UPD
Fetal0045	3.5	None	†*RERE c.248dupA* p.(Ser84Valfs*4) (Het, De novo)	NAD	Live birth	No abnormalities detected at birth but at 8 months of age, length 25th centile, weight 5th centile, occipital frontal circumference (OFC) 25th centile. Dysmorphic features including bifrontal narrowing, low anterior hairline, mild hypertelorism, bilateral epicanthal folds, downslanting palpebral fissures, synophrys, mild hypoplastic helices, redundant nuchal skin; spasticity of all four extremities with upper limbs more affected than lower lilmbs.	Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart (NEDBEH)

Table 4. Diagnostic variants identified after trio ES and review in fetuses presenting with initially isolated increased NT at 11-14 weeks of gestation where later pregnancy follow up was not possible. †Variants previously published.

Study Identifier	NT(mm)	Additional findings at presentation	Variant(s)	Findings at later scans	Pregnancy outcome	Postnatal follow-up	Final diagnosis
PP3321	9.9	None	*PTPN11* c.214G>A p.(Ala72Thr) (Het, De novo)	N/A (pregnancy ended)	ToP	PM: cystic hygroma	Noonan syndrome

PP2039	6.2	None	†*NIPBL* c.1435C>T p.(Arg479*) (Het, De novo)	N/A (pregnancy ended)	Miscarriage	PM: Small limbs. Characteristic facial gestalt appearance of Cornelia de Lange syndrome. No polydactyly.	Cornelia de Lange syndrome

Table 5. Details of cases with non-diagnostic but potentially clinically relevant variants, as judged by the PAGE study clinical review panel. † Variants previously published.

Study Identifier	NT(mm)	Additional findings at presentation	Variant(s)	Findings at later scans	Pregnancy outcome	Postnatal follow-up	Final diagnosis
PP0722	6.7	None	†*KMT2D* c.15535C>T p.(Arg5179Cys) (Het, De novo, Class 4)	NAD	Live birth	NAD at birth. Follow up at 18m: fetal finger pads; sacral dimple; arched eyebrows	Kabuki syndrome
PP1723	5.0	None	†*KMT2A* c.6526delG p.(Val2176Serfs*3) (Het, De novo, Class 4)	Nil structural (Ectopic heart beats only, not requiring treatment)	Live birth	Sacral dimple (no underlying neurological defect on MRI) No hypertrichosis or dysmorphic features reported.	
PP1369	8.7	None	†*NRAS* c.34G>A p.(Gly12Ser) (Het, De novo, Class 4)	Micrognathia (20/40)	IUD	PM: Dysmorphic facial features, prominent orbits, down-slanting palpebral fissures, low set ears, micrognathia, short neck, skin webs, petichiae of visceral pleura	
PP1528	9.3	Hydrops (generalised oedema)	†*PTPN11* c.1530G>T p.(Gln510His) (Het, De novo, Class 3)	N/A (pregnancy ended)	ToP	Nil	
PP3285	7.1	Hypoplastic left heart	†*ACTB* c.193C>G p.(Leu65Val) (Het, De novo, Class 5)	-	-	-	
PP0312	4.8	Hypoplastic left heart; DORV; transposition of great arteries; mega cisterna magna	†*KIAA0586* c.1310A>T p.(Asp437Val) (Hom, Biparental inh, Class 3)	N/A (pregnancy ended)	ToP	Nil	
PP0206	11.3	Hydrops; Cardiac ventricular disproportion R>L	†*SLC9A6* 375bp deletion (Hemi, De novo)	Bilateral talipes; abnormal fixed flexion of extremities; reduced fetal activity; coarctation of aorta; possible VSD (16/40)	ToP	PM: Large cystic hygroma; widespread oedema; coarctation of aorta; small perimembranous VSD	

PP0585	4.6	Generalised oedema	†*ROBO1* c.1985delA (Het, De novo, Class 3)	-	Live birth	-	

Table 6. Number of diagnostic variants identified by trio ES in relation to size of isolated NT at presentation.

NT (mm)	**Number of cases**	**Diagnostic variants detected (%)**
3.5 - 4.4	63	1 (1.6)
4.5 – 5.4	42	6 (14.2)
5.5 – 6.4	22	2 (9.1)
6.5 – 7.4	11	2 (18.2)
≥7.5	14	4 (28.6)
Not specified	7	1 (14.3)
Total	159	16 (10.1)

Figure 1. Natural history of pregnancies presenting with increased NT below 14 weeks' gestation.