Increased Nuchal Translucency (NT). Can We Do More?

Prenatal trio exome sequencing revealed unexpected findings in fetuses with increased NT.

AUTHORS

Gabriel H.[1], Ritthaler M.[1], Battke F.[2], von Kaisenberg C.[3], Lebek H.[4], Entezami M.[5], Wüstemann M.[6], Schröer A.[5], Biskup S.[1,2]

[1]Praxis f. Humang. Tübingen, [2]CeGaT Tübingen, [3]Klinik f. Frauenheilk. u. Geburtshilfe, MH Hannover, [4]Pränatale Diag. Berlin, [5]Zentrum f. Pränataldiag. u. Humang. Berlin, [6]Zentrum f. Pränatalm. Hannover

Background

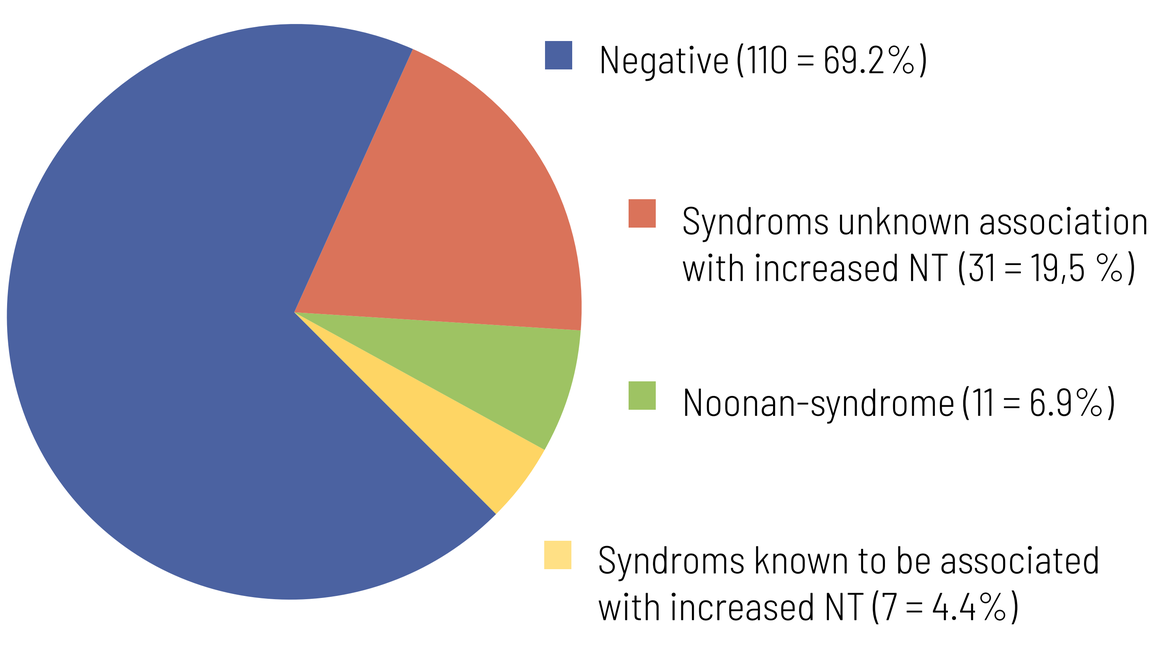
Ultrasound diagnosis allows for the detection of half of all major structural anomalies. As a soft marker, nuchal translucency (NT) is associated with a spectrum of structural anomalies. Mostly, NT measurement is offered as part of screening for chromosomal abnormalities. About 20% of fetuses with increased NT will have a chromosomal abnormality. Noonan syndrome is considered the most frequently reported syndrome associated with increased NT. Prenatal panel testing for Noonan syndrome genes is nowadays widely offered in cases with increased NT. Aside from these Noonan syndrome genes, there are only a limited number of gene for which increased NT is documented.

Methods

In this study, we performed prenatal trio exome sequencing in cases with increased NT. A cohort of 159 fetuses with increased NT were analysed by trio exome sequencing. The mean turn-around-time (TAT) was 12 days, with a shortest TAT of 5 days.

Gene	Type	No. found in study
PTPN11	Noonan-syndrome 1	4x
LZTR1	Noonan-syndrome 2, 10	2x
KRAS	Noonan-syndrome 3	1x
SOS1	Noonan-syndrome 4	1x
RAF1	Noonan-syndrome 5	1x
NRAS	Noonan-syndrome 6	-
BRAF	Noonan-syndrome 7	1x
RIT1	Noonan-syndrome 8	1x
SOS2	Noonan-syndrome 9	-
MRAS	Noonan-syndrome 11	-
RRAS2	Noonan-syndrome 12	-
MAPK1	Noonan-syndrome 13	-
SPRED2	Noonan-syndrome 14	-

Tab 1: Noonan-syndrome genes found in this study



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Gene	Type	OMIM	No. found in study
EPHB4	Lymphatic malformation 7	616362	3x
MYRF	Cardiac-urogenital syndrome	618280	2x
SMAD4	Myhre syndrome	139210	1x
NUP93	Nephrotic syndrome 12	616892	1x
FOXC2	Lymphedema-distichiasis syndrome	153400	1x
SEC23B	Cowden syndrome 7	616858	1x
SCN8A	Developmental and epileptic encephalopathy 13	614558	1x
UPS7	Hao-Fountain syndrome	6166863	1x
RASA1	Capillary malformation-arteriovenous malformation 1	608354	1x
GJA1	Atrioventricular septal defect 3	600309	1x
GBA	Gaucher disease	230800	1x
ACTA1	myopathy, actin, congenital, with cores	161800	1x
PPP2R1A	Mental retardation, autosomal dominant 36	616800	1x
ACTB	Baraitser-Winter syndrome 1	243310	1x
SMAD3	Loeys-Dietz syndrome 3	613795	1x
PHF6	Borjeson-Forssman-Lehman syndrome	301900	1x
SOX9	Campomelic dysplasia	114290	1x
KMT2D	Kabuki syndrome 1	147920	1x
EHMT1	Kleefstra syndrome 1	610253	1x
TMEM260	Structrual heart defects and renal anomalies syndrome	617478	1x
FLT4	Lymphatic malformation 1	153100	1x
ACTG1	Baraitser-Winter syndrome 2	614583	1x
PHGDH	Neu-Laxova syndrome 1	256520	1x
ANKRD11	KBG syndrome	148050	1x
CTSA	Galactosialidosis	256540	1x
KMT2C	Kleefstra syndrome 2	617768	1x
RBM10	TARP syndrome	311900	1x

Tab 2: List of genes in which pathogenic variants were detected in cases with increased NT. Association of these genes/syndromes with increased NT was not described so far.

Results

Among the 159 tested fetuses we were able to detect pathogenic or likely pathogenic variants in 49 cases (diagnostic yield: 30.8%). Noonan syndrome genes were found in 11 cases (incl. 4x PTPN11). In 15 cases we detect a causative variant in genes, which are known to be associated with increased NT (incl. 3 pathogenic copy number variants). In all other cases (31x) pathogenic variants were found in genes, which are not to be known to be associated with increased NT so far.

Ø 4.64 mm (negative testing result)
Ø 6.27 mm (positive testing result)

Average NT in mm in cases with a positive genetic result and without genetic findings.

Conclusion

Our data clearly demonstrated that prenatal testing should be not limited to structural or numeric chromosomal aberrations and RASopathies in cases with fetal increased NT. Increased NT can be found in different syndromic conditions and increased NT might be one of the earliest detectable phenotypic features in the first trimester. Therefore, increased NT is a significant marker for wide range of genetic disorders. We could show the value of trio exome sequencing for the prenatal genetic diagnosis of fetuses with increased NT and trio exome testing should be standard approach in fetuses with increase NT.