Review Article

Prenatal Diagnosis of Euploid Increased Nuchal Translucency on Fetal Ultrasound (I): Noonan Syndrome: Prenatal Diagnosis and Genetic Testing

CME Credits

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Abstract

Prenatal diagnosis of euploid increased nuchal translucency (NT) remains a challenge to obstetricians and genetic counselors although increased euploid NT at prenatal diagnosis can be associated with a favorable outcome. Prenatal diagnosis of euploid increased NT should include a differential diagnosis of pathogenetic copy number variants and RASopathy disorders (RDs) including Noonan syndrome (NS). Therefore, chromosomal microarray analysis, whole-exome sequencing, RD testing, and protein-tyrosine phosphatase, nonreceptor type 11 (*PTPN11*) gene testing may be necessary under such a circumstance. In this report, a comprehensive review of NS with its prenatal diagnosis and genetic testing is presented.

Keywords: Genetic testing, increased nuchal translucency, Noonan syndrome, prenatal diagnosis, RASopathy disorder

Introduction

Prenatal diagnosis of euploid increased nuchal translucency (NT) remains a challenge to obstetricians and genetic counselors although euploid increased NT at prenatal diagnosis can be associated with a favorable outcome. Prenatal diagnosis of euploid increased NT should include a differential diagnosis of pathogenetic copy number variants and RASopathy disorders (RDs) including Noonan syndrome (NS). Therefore, chromosomal microarray analysis (CMA), whole-exome sequencing (WES), RD testing, and protein-tyrosine phosphatase, nonreceptor type 11 (*PTPN11*) gene testing may be necessary under such a circumstance.

Noonan Syndrome and Genetic Heterogeneity

NS1 (OMIM 163950) is an autosomal dominant disorder caused by heterozygous mutation in the *PTPN11* gene (OMIM 176876) and is characterized by short stature, congenital heart defects such as pulmonic stenosis and hypertrophic cardiomyopathy, facial dysmorphism of a broad forehead, hypertelorism, downslanting palpebral fissures, a high-arched palate and low-set ears, and other abnormalities including skeletal defects of chest and spine, webbed neck, mental retardation, and cryptorchidism.[1-6] NS1 caused by *PTPN11* gene accounts for about half of the patients with NS.

PTPN11 (OMIM 176876) located 12q24.13 encodes protein-tyrosine phosphatase, nonreceptor type 11 or SHP-2. Mutations of *PTPN11* have been reported to be associated with juvenile myelomonocytic leukemia and autosomal dominant LEOPARD syndrome 1 (OMIM 151100), metachondromatosis (OMIM 156250), and NS1 (OMIM 163950). Tartaglia *et al*.[1] identified mutations in the *PTPN11* gene in more than 50% of the patients with NS. They found that gain-of-function changes by PTPN11 mutations result in

Received: 09-08-2022 **Accepted:** 11-08-2022 **Available Online:** 09-11-2022

Access this article online

Quick Response Code:

Website: www.jmuonline.org

DOI: 10.4103/jmu.jmu_78_22

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How to cite this article: Chen CP. Prenatal diagnosis of euploid increased nuchal translucency on fetal ultrasound (I): Noonan Syndrome: Prenatal diagnosis and genetic testing. J Med Ultrasound 2022;30:257-60.

excessive SHP-2 activity and cause the pathogenesis of NS. NS has genetic heterogeneity. In addition to the common type of NS1 caused by *PTPN11* gene mutation, other autosomal dominant NS types include NS3 (OMIM 609942) caused by *KRAS* (OMIM 190070) mutations, NS4 (OMIM 610733) caused by *SOS1* (OMIM 182530) mutations, NS5 (OMIM 611553) caused by *RAF1* (OMIM 164760) mutations, NS6 (OMIM 613224) caused by *NRAS* (OMIM 164790) mutations, NS7 (613706) caused by *BRAF* (OMIM 164757) mutations, NS8 (OMIM 615355) caused by *RIT1* (OMIM 609591) mutations, NS9 (OMIM 616559) caused by *SOS2* (OMIM 601247) mutations, NS10 (616564) caused by *LZTR1* (OMIM 600574) mutations, NS11 (OMIM 618499) caused by *MRAS* (OMIM 608435) mutations, NS12 (OMIM 618624) caused by *RRAS2* (OMIM 600098) mutations, and NS13 (OMIM 619087) caused by *MAPK1* (OMIM 176948) mutations. Autosomal recessive forms of NS include NS2 (OMIM 605275) caused by *LZTR1* (OMIM 600574) mutations and NS14 (OMIM 619745) caused by *SPRED2* (OMIM 609292) mutations. Other autosomal dominant NS-like disorders include NSLH1 (NS-like disorders with loose anagen hair-1) (OMIM 607721) caused by *SHOC2* (OMIM 602775) mutations, NSLH2 (NS-like disorder with loose anagen hair-2) (OMIM 617506) caused by *PPP1CB* (OMIM 600590) mutations, NSLL (NS-like disorder with or without juvenile myelomonocytic leukemia) (OMIM 613563) caused by *CBL* (OMIM 165360) mutations, and NFNS (neurofibromatosis-NS) (OMIM 601321) caused by *NF1* (OMIM 162200) mutations.

Noonan Syndrome: Prenatal Diagnosis and Genetic Testing

Prenatal diagnosis of increased NT and/or cystic hygroma associated with chromosomal abnormalities and other genetic disorders such as NS has been well described. As early as in 1982, Cowchock *et al*.[7] found that not all cystic hygromas at prenatal diagnosis occur in Turner syndrome and suggested that cystic hygromas can be a part of a variety of genetic malformation syndromes. In 1992, Nicolaides *et al*.[8] found that the incidence of chromosomal abnormalities (mainly trisomy 21, trisomy 13, trisomy 18, and Turner syndrome) was 35% in fetuses with NT of 3–8 mm, compared with only 1% in fetuses with NT <3 mm. In 1995, Pandya *et al*.[9] reported screening for fetal trisomies by maternal age and fetal NT thickness at 10–14 weeks of gestation and found that NT > 95th centile occurred in 77% of fetuses with trisomy 21 as well as in 78% of those with other chromosomal abnormalities. In 1997, Reynders *et al*.[10] investigated the significance and outcome of first-trimester isolated fetal NT in 44 fetuses and found that 12% had chromosomal abnormalities, whereas in other 36 euploid NT fetuses, 1 fetus had NS, 1 fetus had Joubert syndrome, and 1 fetus had autosomal recessive polycystic kidney disease. In 1999, Adekunle *et al*.[11] investigated the fetal outcome with increased NT in the first trimester. They found a prevalence of 0.8% (n = 53) of increased NT in the first trimester. They also found that in the fetuses with increased NT, 28.3% (15/53) had chromosomal abnormalities. Of the other 38 cases with euploid increased NT, 31 cases had live births, of which 2 had developmental delay, and 1 had NS. In 1999, Nisbet *et al*.[12] reported six cases of NS which prenatally presented with sonographic abnormalities of increased NT, short femora, pleural effusions, hydrops, cardiac anomalies, and renal abnormalities. In 2001, Hiippala *et al*.[13] investigated 50 cases with euploid increased NT and found that 8% (4/50) had major cardiac defects including 1 case with NS, 1 case with cleidocranial dysplasia, and 1 case with developmental delay. In 2009, Lee *et al*.[14] reported PTPN11 analysis for the prenatal diagnosis of NS in 134 fetuses with abnormal ultrasound findings such as cystic hygroma, increased NT, and/or hydrops fetalis and found that 9% (12/134) had *PTPN11* mutations. In their study, in the fetuses with cystic hygroma, 16% had *PTPN11* mutations, whereas in the fetuses with increased NT, 2% had *PTPN11* mutations. In 2011, Pergament *et al*.[15] performed routine screening of five genes associated with NS including *PTPN11*, *SOS1*, *KRAS*, *RAF,* and *MEK1* in 120 cases with euploid increased NT and found that 6.7% (8/120) had NS. In 2017, Gezdirici *et al*.[16] reported two fetuses with cystic hygroma and *PTPN11* mutations and suggested that *PTPN11* gene testing is necessary in euploid fetuses with first-trimester cystic hygroma.

In 2017, Ali *et al*.[17] performed testing for NS with the genetic testing of the genes of *BRAF*, *HRAS*, *KRAS*, *MAP2K1*, *MAP2K2*, *NRAS*, *PTPN11*, *RAF1*, *RIT1*, *SHOC2,* and *SOS1* in 39 fetuses with euploid NT and found that 10.3% (4/39) had NS. In 2020, Schönfeld *et al*.[18] reported rapid detection of *PTPN11* mutation by hydrops panel in a fetus with NS. In 2020, Corsten-Janssen *et al*.[19] reported rapid WES as a diagnostic test for multiple congenital anomalies on fetal ultrasound in 23 euploid fetuses without CMA anomalies and found that 35% (8/23) had genetic diagnosis including 1 fetus with NS and *PTPN11* mutation. In 2020, Sinajon *et al*.[20] applied microarray and RD testing in 226 fetuses with increased NT and found that 51.3% (116/226) had aneuploidy, and 48.7% (110/226) had normal karyotypes, of which microarray detected abnormalities in 8.2% (9/110) of the cases, and RD testing detected pathogenic variants in 2.9% (3/103) of the cases. The RD testing can detect about 80% of RDs caused by germline mutations in the RAS/MAPK pathway.[21] RDs include NS, cardiofaciocutaneous syndrome (CFC), neurofibromatosis type 1 (NF1), NS with multiple lentigines, Costello syndrome, Legius syndrome, SYNGAP1, and central conducting lymphatic anomalies.[21] The RD gene next-generation sequencing (NGS) panel used in the study of Sinajon *et al*.[20] encompassed nine genes including *BRAF, HRAS*, *KRAS*, *MAP2K1*, *MAP2K2*, *PTPN11*, *RAF1*, *SOS1,* and *SHOC2*. In 2022, Weinstock and Sadler[22] reported the detection of *RRAS2* mutation in a fetus with severe NS and hydrocephalus. In 2022, Mellis *et al*.[23] conducted a systematic review and meta-analysis to determine the diagnostic yield of WES for prenatal structural anomalies and found a diagnostic yield of 2% (95% confidence interval [CI]: 0%–5%, $P = 0.04$)

for isolated increased NT. In 2022, Yang and Li[24] used the 23-gene RASopathy panel (*ACTB*, *ACTG1*, *BRAF*, *CBL*, *FGD1*, *HRAS*, *KAT6B*, *KRAS*, *LZTR1*, *MAP2K1*, *MAP2K2*, *MRAS*, *NF1*, *NRAS*, *PPP1CB*, *PTPN11*, *RAF1*, *RIT1*, *RRAS*, *SHOC2*, *SOS1*, *SOS2*, and *SPRED1*) and WES in a fetus with increased NT and a normal array and detected an *FGFR2* mutation.

In 2022, Qiu *et al*.[25] detected *RIT1* mutation by WES in a fetus with increased NT and NS. To date, at least 13 NS fetuses with *RIT1* mutations have been identified.[25-30] Milosavljević *et al*.[26] first reported detection of a *de novo* missense *RIT1* mutation in a fetus with euploid increased NT, cystic hygroma, and hydrops fetalis and a normal CMA result by an NGS NS/RASopathy gene panel encompassing the coding sequences and splice sites of *A2ML1*, *BRAF*, *CBL*, *HRAS*, *KRAS*, *MAP2K1*, *MAP2K2*, *NRAS*, *PTPN11*, *RAF1*, *RIT1*, *SOS1*, *SHOC2*, and *SPRED1*. Yates *et al*.[27] reported the application of WES on 84 deceased fetuses with ultrasound anomalies and found that 20% (17/84) were tested positive, and 9% (7/84) had only candidate gene variants including one fetus with hydrops fetalis, central nervous system malformation, congenital heart defect, NS, and *RIT1* mutation. Normand *et al*.[28] reported clinical WES for fetuses with ultrasound abnormalities and a suspected Mendelian disorder in 146 fetuses and yielded an overall molecular diagnostic rate of 32% (46/146) including five NS fetuses with *PTPN11 (*2 cases), *KRAS* (1 case), *RIT1 (*1 case), and *SOS1 (*1 case) mutations. Lord *et al*.[29] reported prenatal WES analysis in 610 euploid fetuses with fetal structural anomalies detected by ultrasound and found that 8.5% (52/610) had diagnostic genetic variants including six NS fetuses with *PTPN11 (*3 cases), *RIT1 (*2 cases), *KRAS* (1 case), *BRAF* (1 case), and *SOS1 (*1 case) mutations. Petrovski *et al*.[30] reported WES in the evaluation of structural anomalies in 234 euploid fetuses with structural anomalies and found that 10% (24/234) had diagnostic genetic variants including two NS fetuses with *RIT1 (*1 case) and *SOS1 (*1 case) mutations.

In summary, in this review article, a comprehensive review of NS with its prenatal diagnosis and genetic testing is presented, and the information provided is useful for ultrasonographers as well as genetic counselors.

Financial support and sponsorship

This work was supported by research grants MOST-110-2314-B-195-005 from the Ministry of Science and Technology, Taiwan, and MMH-E-111-04 from MacKay Memorial Hospital, Taipei, Taiwan.

Conflicts of interest

Prof. Chih-Ping Chen, an Editorial-in-Chief at *Journal of Medical Ultrasound*, had no role in the peer review process of or decision to publish this article.

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