Ultrasonographic measurement of the nuchal translucency (NT, in the second trimester referred to as nuchal skin fold) in the first trimester of pregnancy has become an established method for identifying fetuses at risk for aneuploidy. In the presence of a normal karyotype in fetuses with enlarged NT (>p95), there is still an increased risk of a variety of congenital abnormalities, such as cardiac defects and genetic syndromes. Detailed ultrasound examination may reveal clues as to the underlying cause of increased NT, in some cases enabling DNA analysis to confirm a suspected syndrome. This allows genetic counseling and provides parents the possibility of making an informed decision on whether or not to continue the pregnancy. In fetuses with increased NT and a normal karyotype, Noonan syndrome should be considered, especially in the presence of cystic hygroma, cardiac defects, edema, pleural effusions or polyhydramnion. Noonan syndrome is an autosomal dominant disorder characterized by short stature, congenital heart defects, cardiac hypertrophy, a varying degree of intellectual deficit and distinctive facial characteristics. Also, distended jugular lymphatic sacs (JLS) have been reported in fetuses with Noonan syndrome. A delayed or disturbed jugular lymphatic development results in distension and subsequently ultrasonographic appearance of the JLS. A disturbance in lymphatic development causes nuchal edema and recently has been described as a common denominator in the pathophysiology of the increased NT. With an estimated incidence between 1:1000 and 1:2500 live births, Noonan syndrome is a relatively common cause of increased NT associated with a normal karyotype. Noonan syndrome is caused by mutations in the PTPN11 gene in approximately 50% of cases. In a recent study, PTPN11 testing based on prenatal sonographic abnormalities resulted in detection of a mutation in 16% and 2% of fetuses with cystic hygroma and increased NT, respectively. Recently, mutations in the SOS1-, RAF1-, MEK1 and KRAS- gene have been described to account for a small percentage of Noonan syndrome cases. Approximately 55 pregnancies with increased NT and a normal karyotype are observed annually at our center (111 times during the last two years). After counseling, prenatal analysis was requested 19 times for the PTPN11 gene and 16 times for the KRAS gene. This report covers the 3 cases where analysis of these genes led to detection of a de novo mutation and the prenatal diagnosis of Noonan syndrome.

Case 1: A 37-year old primigravida was referred to our hospital at 13+4 weeks gestation because of an increased NT seen at a routine first-trimester ultrasound scan. Ultrasound examination confirmed the increased NT (14.0mm), and distended JLS and bilateral pelvic dilatation of the kidneys were seen. No other anomalies were detected. Amniocentesis demonstrated a normal male karyotype. Repeated ultrasound at 16+5 weeks gestation showed a nuchal skin fold of 11.4mm, distended JLS and bilateral pelvic dilatation of the kidneys. The renal pelvices were still dilated. Second trimester ultrasonography at 19+1 weeks gestation showed a nuchal skin fold of 10.6mm, distended JLS and unilateral left sided pleural fluid. The bilateral dilated renal pelvices were still visible (right side 9.6mm, left side 7.7mm) with a normal bladder and a normal amount of amniotic fluid. Low set ears were seen with three-dimensional ultrasound scanning. Fetal biometry was normal. No other structural anomalies were observed. Based on the persistence
of increased NT and a normal karyotype, analysis of the PTPN11 was performed. No mutation could be identified. Subsequent sequencing of the KRAS gene was performed. In the third exon of the KRAS gene a de novo heterozygous pathogenic mutation (c.173C>T, p.Thr58Ile) was present, confirming the diagnosis of Noonan syndrome. The parents decided to terminate the pregnancy, which took place at 22+2 weeks' gestation. Autopsy revealed nuchal edema, ocular hypertelorism, low set ears, cardiac hypertrophy of both ventricles and renal pelvic dilatation, in accordance with the prenatal diagnosis of Noonan syndrome.

Case 2: A 34-year old gravida 2 para 1 was referred at 12+2 weeks of gestation because of an increased NT seen at a first trimester ultrasound for Down syndrome screening. Ultrasound examination showed increased NT of 5.2mm and the presence of enlarged JLS in the nuchal region. No other anomalies were detected. Karyotyping revealed a normal male karyotype. Repeat ultrasound examination at 17+5 weeks gestation revealed a nuchal fold of 5.2mm and bilateral visible JLS. Sequence analysis of the PTPN11 gene was initiated. Second trimester ultrasonography at 19+6 weeks gestation showed that the nuchal fold and JLS had disappeared. No other abnormalities were seen. Fetal biometry was normal. Sequence analysis revealed a de novo heterozygous pathogenic mutation (c.417G>C, p.Glu139Asp) in the PTPN11 gene. The parents decided to terminate the pregnancy which took place at gestational age 23 +5 weeks. Autopsy showed loose nuchal skin, ocular hypertelorism, a low set left ear and cardiac hypertrophy mainly of the interventricular septum. These findings were in line with the prenatally diagnosed Noonan syndrome.

Case 3: A 39 year old gravida 4 para 2 was referred to our hospital at 11+3 weeks of gestation because an increased NT was seen at a routine first-trimester ultrasound scan. Ultrasound examination showed an increased NT of 8.2mm and presence of JLS. Detailed ultrasound examination could not be performed, due to the small size and position of the fetus. Chorionic villus sample karyotyping showed a normal male karyotype. Ultrasound examination at 15+2 weeks of gestation showed a nuchal skin fold thickness of 7mm, visible JLS and pericardial effusion (Figure 1). The heart showed a complete atrioventricular septal defect (AVSD). The renal pelvices were dilated. The femora were shortened (<p5). The combination of increased NT, a complete AVSD, and shortening of the femora gave rise to suspicion of Noonan syndrome. PTPN11 mutation analysis revealed a de novo heterozygous pathogenic mutation (c.181G>C, p.Asp61His). The parents decided to terminate the pregnancy at 16 +0 weeks of gestation. Post mortem examination showed webbing of the neck, ocular hypertelorism, posteriorly rotated low set ears and a complete AVSD. These findings were in line with the prenatally diagnosed Noonan syndrome.

Increased NT detected using ultrasound examination is a common phenotypic manifestation of chromosomal abnormalities with a wide range of possible outcomes. The chance of an adverse pregnancy outcome increases with larger size of the NT. Increased NT detected using ultrasound examination is a common phenotypic manifestation of chromosomal abnormalities with a wide range of possible outcomes. The chance of an adverse pregnancy outcome increases with larger size of the NT. Once abnormal karyotype has been excluded and detailed ultrasound examination does not reveal abnormalities at 20 weeks gestation, the chance of having a healthy child is high. However, since euploid fetuses
with increased NT are still at increased risk of a wide range of malformations and genetic syndromes, establishment of a normal karyotype following the observation of increased NT may leave parents with great uncertainty. Therefore, extensive counseling and efforts directed at establishing a diagnosis should be offered. Given the relatively high incidence and the phenotypic variability of Noonan syndrome, this diagnosis should be considered, even in absence of ultrasonographically detectable anomalies. We present three cases illustrating the phenotypic variability of Noonan syndrome. In case 1, the NT at 13+4 was severely increased. The combination of persistent increased NT, dilated renal pelvices, distended JLS and low set ears, detected upon ultrasound investigation, gave rise to a strong suspicion of Noonan syndrome. Upon finding no mutation in the PTPN11 gene, the KRAS gene was sequenced and a pathogenic mutation was found. The establishment of a diagnosis was perceived as helpful by the parents in the decision process on terminating the pregnancy. Sequence analysis of RAS-MAPK genes other than PTPN11 during pregnancy has, to our knowledge, not been reported previously. Mutations in the PTPN11 gene account for the vast majority of detectable Noonan syndrome mutations. However, given the relatively high incidence of Noonan syndrome in pregnancies with increased NT and a normal karyotype, prenatal sequencing of the other Noonan syndrome associated genes (KRAS, RAF1, SOS1) should, in our opinion, be considered. Furthermore, the
less frequently occurring but clinically more severe Costello syndrome (caused by HRAS mutations) and cardio-facio-cutaneous syndrome (caused by mutations in either of the genes BRAF, MEK1, MEK2 or KRAS) are known to be pathogenetically related to Noonan syndrome and have similar prenatal manifestations. In the three presented cases the parents decided to terminate the pregnancy after extensive counseling by a clinical geneticist, gynecologist and psychosocial worker. In case 2, additional counseling by a pediatrician and by a clinical geneticist with particular expertise in the field of Noonan syndrome (dr. I. van der Burgt) was offered. In case 1 and 3 the associated ultrasound abnormalities played a major role in this decision. In both cases the parents were considering termination of pregnancy, but hesitated because there was no diagnosis. In this situation of uncertainty, they preferred to postpone their choice and follow the natural course of the pregnancy for some more time. Certainty of the diagnosis appeared to facilitate their decision. Given the high incidence of Noonan syndrome we strongly advocate that in case of increased NT and a normal karyotype, genetic counseling and Noonan syndrome mutation detection is offered, even in the absence of additional associated abnormalities.
REFERENCES