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THE RELEVANCE OF GENETIC PREGNANCY TESTS IN THE DIAGNOSIS OF SEVERE BIRTH DEFECTS

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ABSTRACT
We report one clinical case of a 33-year-old, Caucasian woman who is pregnant for the first time. Ultrasound examination showed a singleton fetus with multiple malformations: unilateral cleft and lip palate, spina bifida and congenital heart abnormality with tricuspid valve regurgitation. Amniocentesis was done, and the fetal chromosomal analysis revealed a fetus with normal male karyotype: 46,XY. After a personalized post-procedure genetic counselling the parents opted to terminate the pregnancy. The autopsy confirm the prenatal ultrasound diagnosis.

KEYWORDS: birth defects, cleft lip/palat, spina bifida, ultrasound examination, prenatal diagnosis.

INTRODUCTION
Birth defects, also known as congenital anomalies, congenital disorders or congenital defects have been defined as anomalies of the structure and/or function of an organ and/or a system in the body, detectable prenatally (by ultrasound examination), at birth or during infancy.[1, 2]

Birth defects are an important cause of infant death, worldwide.[2] In the European Region, the World Health Organization (WHO) estimated that up to 25% of neonatal deaths are attributable to congenital anomalies.[3]

Neural tube defects, a multifactorial condition resulting from the failure of embryonic neural tube closure, are the most common birth defect of the central nervous system and they occur at a range of 0.5–10 or more in 1,000 live births worldwide.[4]

Spina bifida is a congenital malformation in which the spinal column is split (bifid) as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization.[5]

The reported frequency of spina bifida occulta ranges greatly among researchers and populations; it varies also across gender, ethnicity and geographic location. However, its actual frequency seems to range from 1 to 5 cases per 1,000 live births.[6]

Accurate and timely prenatal diagnosis of spina bifida is a major goal of modern antenatal care.[7]

Cleft lip and cleft palate, important human congenital malformations with a complex multifactorial etiology, can occur as part of a syndrome involving multiple organs or as isolated clefts without other detectable defects.[8]

The etiology of nonsyndromic cleft lip with or without cleft palate is complex with both environmental and genetic factors causally implicated.[9, 10]

Recently, Michigan State University and Children's National Health System researchers are the first to link mutations in a gene known as "Interferon Regulatory Factor 6," or IRF6, which cause cleft palates, to spina bifida and other neural tube defects.[11]

MATERIALS AND METHODS
A 31-year-old, Caucasian woman, pregnant for the first time, was referred to a private medical center, from Bucharest, Romania, at 13 weeks' gestation for a routine prenatal ultrasound investigation. The couple was non-consanguineous and clinically healthy.[12]

Ultrasound examination at 13 weeks of pregnancy, selective ultrasonography for detection of fetal abnormalities, 2D, 3D and 4D Real Time scan with General Electric Echograph Voluson, amniocentesis,

fetal chromosomal analysis and genetic counselling was done.

RESULTS

Ultrasound examination revealed a singleton live fetus with multiple congenital malformations: increased nuchal translucency (Figure 1, 2), unilateral cleft lip and cleft palate (Figure 3 - 6), spina bifida (Figure 7, 8), and congenital heart abnormality with moderate tricuspid valve regurgitation (Figure 9, 10).

Genetic amniocentesis and the fetal chromosome analysis revealed a karyotype of 46,XY (Figure 11).

After the prenatal noninvasive testing (ultrasound examination) and genetic invasive testing (genetic amniocentesis) the following diagnosis was established: Pregnancy 17 weeks in evolution. Increased nuchal translucency. Unilateral cleft lip and cleft palate. Spina bifida. Congenital heart malformation with moderate tricuspid valve regurgitation.

After a personalized genetic counselling the parents opted to terminate the pregnancy. The prenatal diagnosis was confirmed by fetal autopsy.

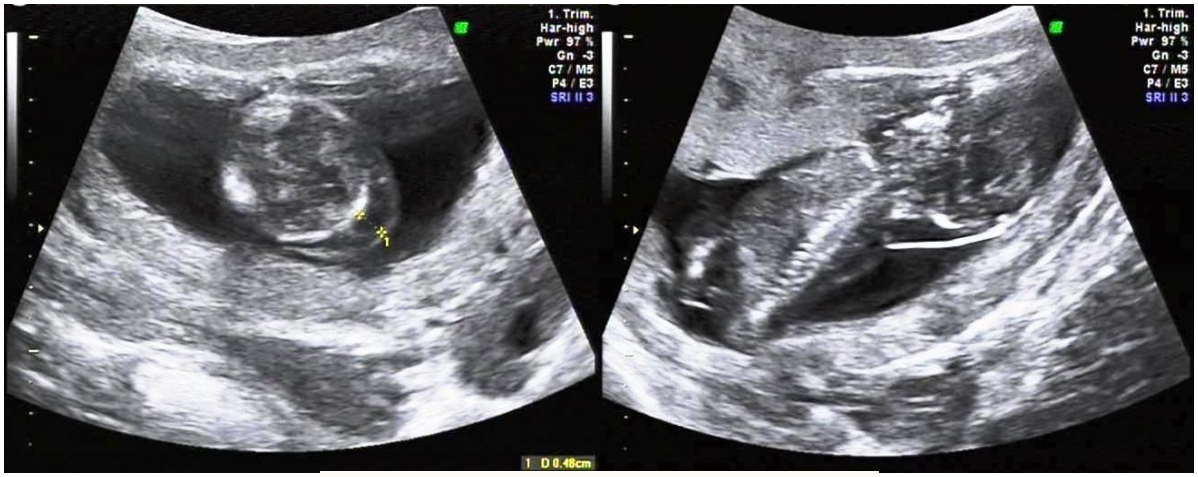

Figure 1 **Figure 2**

Figure 1 and Figure 2 – Nuchal translucency 2D Ultrasound examination.

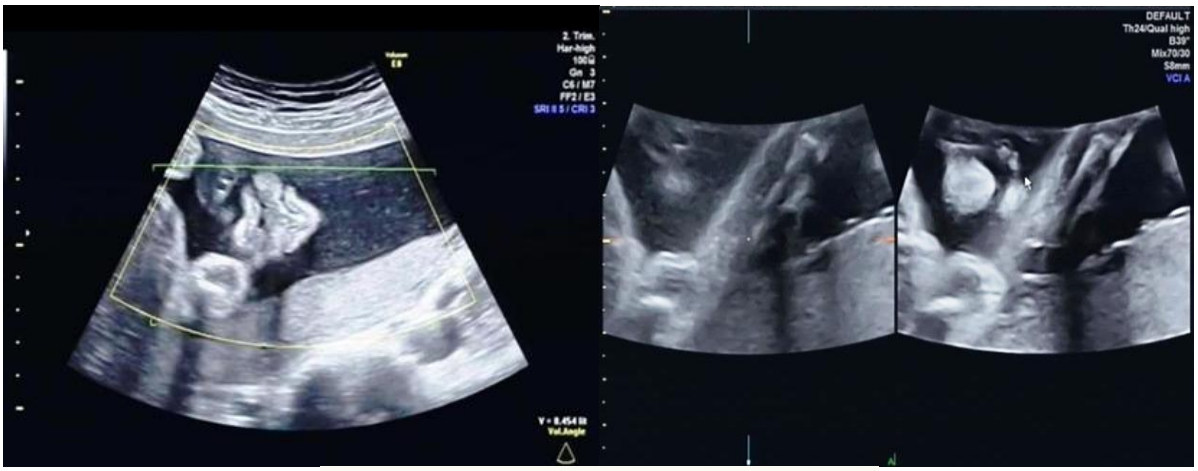

Figure 3 **Figure 4**

Figure 3 and Figure 4 – Unilateral cleft lip/palate 2D Ultrasound examination.

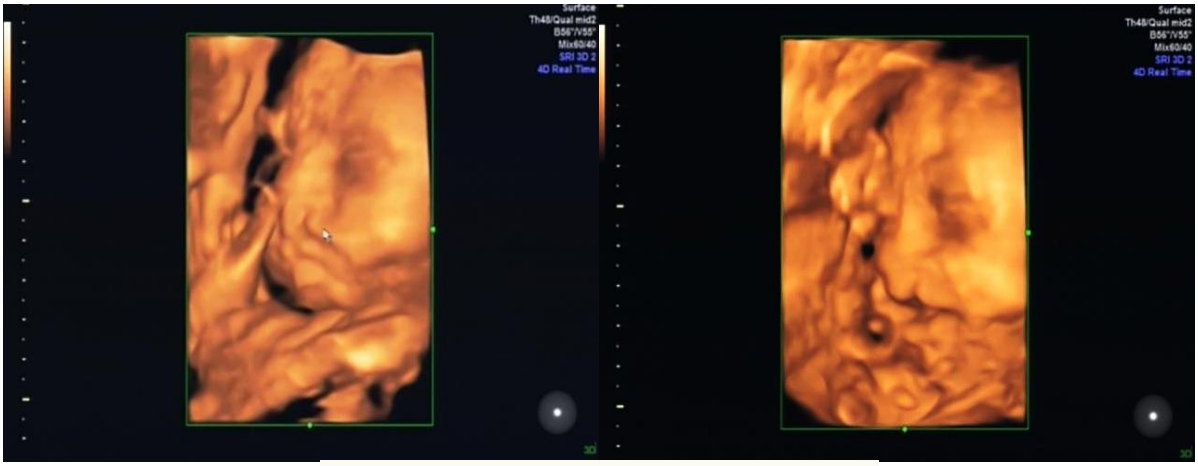

Figure 5 **Figure 6**

Figure 5 and Figure 6 – Unilateral cleft lip/palate 4D Real Time Ultrasound examination.

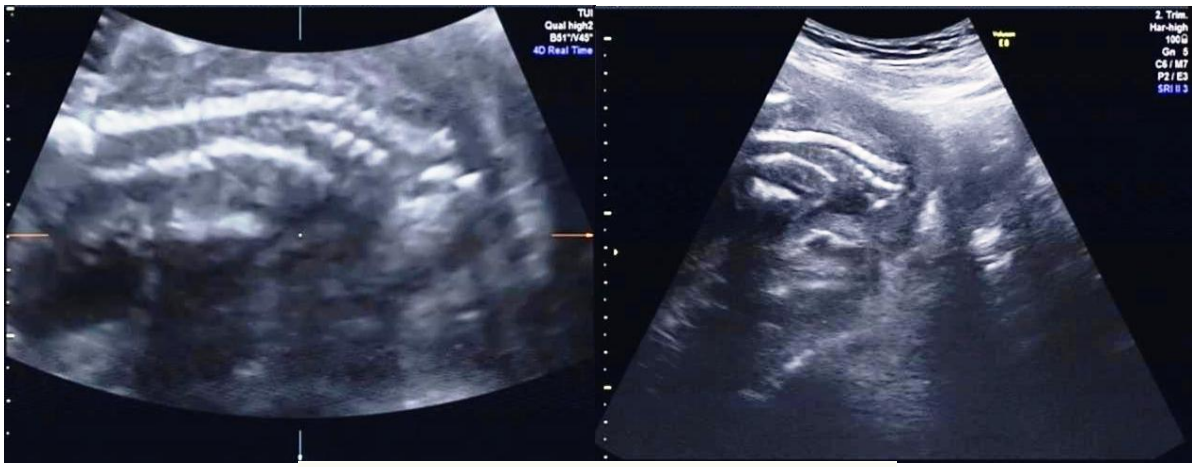

Figure 7 **Figure 8**

Figure 7 and Figure 8 – Spina bifida 4D Real Time and SRI II 3 Ultrasound examination.

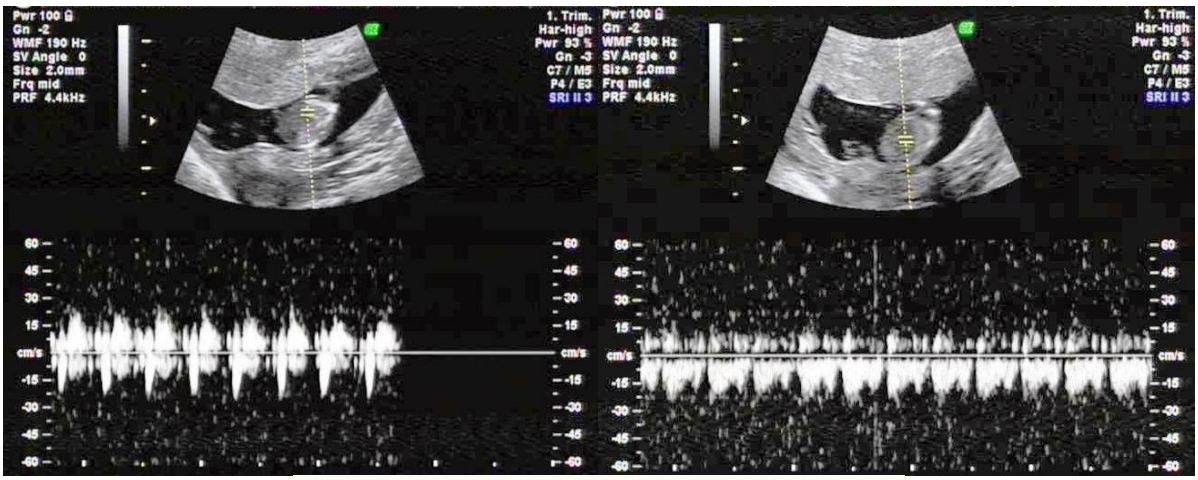

Figure 9 **Figure 10**

Figure 9 and Figure 10 – Tricuspid valve regurgitation.
SRI II 3 Ultrasound examination.

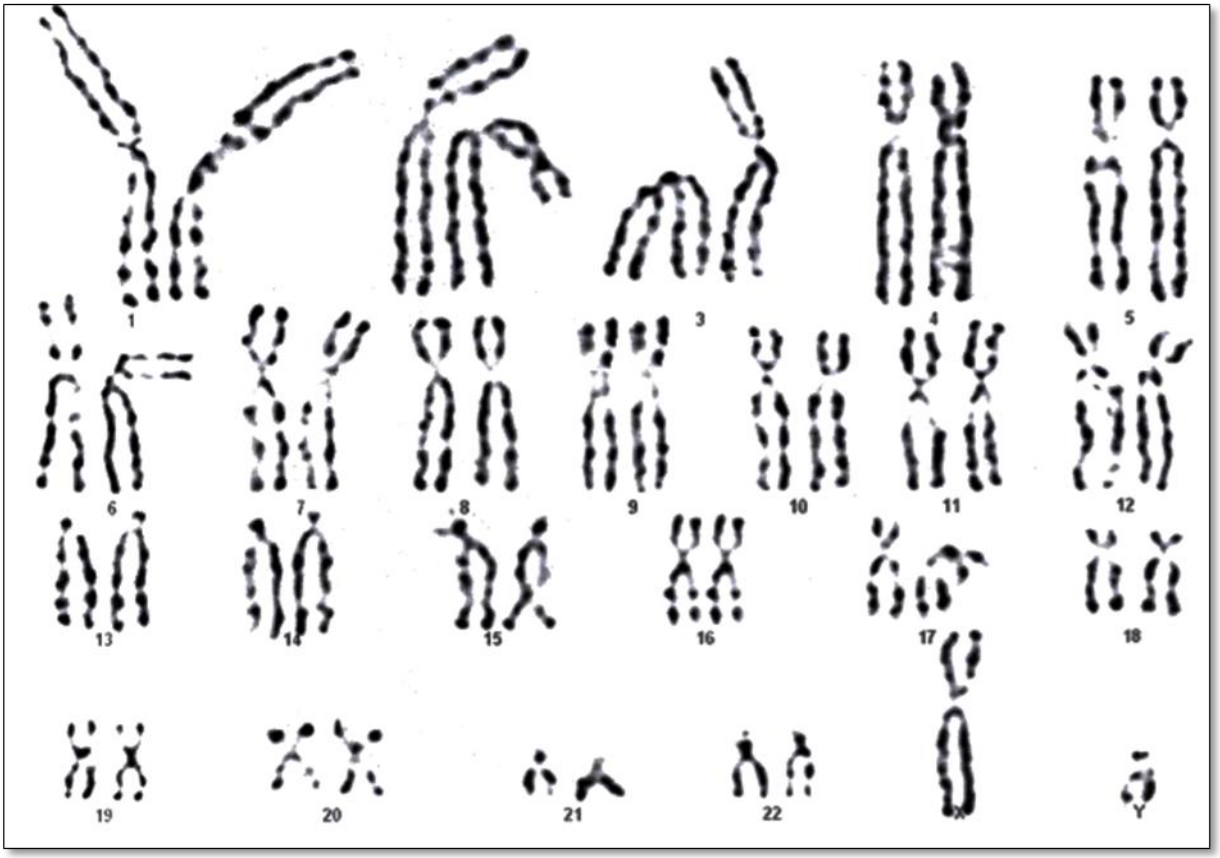

Figure 11 – Fetal karyotype: 46,XY.

DISCUSSION

Congenital malformations occur in 2-4% of all birth defects and remain a significant source of worldwide morbidity and mortality.[13, 14]

A major goal of obstetric sonography is the detection of associations of the most frequent patterns of anomalies in order to make a diagnosis, or to determine which pregnant women should be offered invasive testing.[15]

Neural tube defects such as spina bifida, where a part of the spinal cord fails to close, may be caused by the same genes that lead to cleft lip and palate, according to Human Molecular Genetics (January 25, 2019).[16]

Brian Schutte, associate professor of microbiology and molecular genetics in pediatrics and human development, is the first to link gene mutations, which cause cleft palates, to spina bifida and other neural tube defects.[11]

Prenatal diagnosis of congenital disease provides information for decisions during pregnancy and appropriate treatment perinatally (timed delivery in tertiary care centers) and it is assumed to improve perinatal and long term outcome.[13]

CONCLUSION

Prenatal genetic testing is absolutely necessary for the early prenatal detection and management of severe structural congenital malformations.

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