A previously unreported association between Noonan and related syndromes and anomalous left brachiocephalic vein

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Objective
To report a previously unknown association between Noonan and related syndromes and anomalous left brachiocephalic vein.

Methods
1. Report two consecutive prenatal cases of Noonan and related syndromes and describe the respective types of anomalous left brachiocephalic vein in the two cases. Discuss the possible association between Noonan and related syndromes and anomalous left brachiocephalic vein and the potential diagnostic value of the association.

Results
Both cases showed previously reported ultrasound features of Noonan and related syndromes (NRS) including first trimester increased nuchal translucency, second trimester cystic hygroma, bilateral dilated jugular lymphatic sacs, pleural effusion, and subcutaneous oedema. Case 1 also had ascites and a small ventricular septal defect. Anomalous left brachiocephalic vein (ALBCV) was found in both cases. In Case 1, it was the retroesophageal type and in Case 2, it was retroductal. Chorionic villus sampling for karyotype and chromosome microarray study was normal in both cases. Genetic study with Noonan panel found heterozygous mutation in the RAF1 and BRAF gene in Case 1 and 2, respectively. The association between NRS and ALBCV has not been reported. ALBCV is rare and so its detection in two consecutive prenatal cases of NRS suggests the association is not a chance occurrence. Moreover, the common types of cardiac defects associated with ALBCV like right sided aortic arch and underdevelopment of the pulmonary artery were not found in these two cases. This suggests an alternative mechanism related to NRS for development of ALBCV in our cases. Absence of previous report of the association is probably because the LBCV is seldom assessed during fetal or postnatal echocardiography. Prenatal diagnosis of NRS based on ultrasound findings has been reported but with a low positive predictive value. It is probable that prenatal detection of ALBCV in fetuses with ultrasound signs of jugular lymphatic obstruction may increase the accuracy of prenatal ultrasound diagnosis of NRS.

Conclusion
We speculate that the association between NRS and ALBCV is not coincidental. Further studies are required to evaluate its diagnostic value in prenatal NRS.