Objective: Conventional karyotyping and, more recently, chromosomal microarrays support a substantial role for genetic factors as a cause of non-isolated CDH. However, causal genes responsible for isolated CDH remain elusive. We propose that chromosomal microarray analysis will identify copy number variations (CNVs) associated with isolated CDH. In the absence of pathogenic CNVs, exome sequencing is an attractive approach for causal variant identification in both isolated and syndromic CDH.

Method: A prospective prenatal study of 75 isolated CDH fetuses was undertaken using a high-resolution genome-wide microarray. Exome sequencing was performed in: (1) a family with 2 siblings affected with isolated CDH; (2) a family with 2 male siblings with multiple congenital anomalies (MCA) including microphthalmia, CDH, spinal bifida, and cardiac defects; (3) a consanguineous family with a single fetus affected with MCA including bilateral CDH, cardiac and renal anomalies, dysmorphism, cleft palate and oligodactyly.

Results: Pathogenic CNVs were revealed by microarray analysis in 9% of isolated CDH patients (n=7), and rare inherited variants in 4% of patients (n=3). Exome sequencing revealed pathogenic variants in 2PAN2 as a cause of isolated CDH, and in PIGN and PORCN as causes of syndromic CDH.

Conclusions: The CNV screen highlights chromosomal microarray analysis as a valuable tool for investigation of isolated CDH patients. In the absence of pathogenic CNVs, we show that exome sequencing identifies causal variants in several cases of both isolated and syndromic CDH.