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The incidence of genetic abnormalities in fetuses with severe congenital heart defects

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Objectives
Overall survival of children with congenital heart defects (CHD) has improved significantly. Knowledge on additional morbidity, in particular genetic abnormalities, has become more important, as this is influences the prognosis of these cases. The aim of this study was to gather up-to-date information on the incidence of genetic abnormalities in fetuses with severe CHD to aid prenatal counselling.

Methods
The regional PRECOR database was used to identify all severe CHD cases (2012-2016). Aneuploidy cases were excluded from the study. Pre- and postnatal files and post-mortem reports were assessed to collect data on the presence of genetic abnormalities. The American College of Medical Genetics (ACMG)'s categories of clinical significance (pathogenic, likely pathogenic, uncertain significance, likely benign or benign) were used to interpret all genetic anomalies encountered. We assessed the incidence of genetic anomalies amongst all CHD subjects, specific types of CHD and the association with extra-cardiac malformations (ECM).

Results
Genetic abnormalities were encountered in 178/710 (25.1%) of subjects with severe CHD. In 27.5% genetic testing was not performed, as there was no clinical suspicion for a genetic syndrome. Pathogenic alterations, likely pathogenic alterations and variants of uncertain significance (VOUS) were observed in 13.8%, 1.8% and 5.6% of all CHD subjects respectively. Common genetic anomalies comprised 22q11 deletion (4.2%), CHARGE (0.7%), Kabuki (0.4%) and Noonan syndrome (0.4%). Genetic abnormalities were most frequently encountered amongst common arterial trunk (37.5%), atrioventricular septal defect (35.7%) and Tetralogy of Fallot (27,6%) cases. The risk of genetic abnormalities was significantly lower for isolated cases (21.2%) compared to cases with additional ECMs (38.8%) ($p<0.001$).

Conclusions
The yield of genetic and syndromic abnormalities amongst fetuses with severe CHD and a normal karyotype was 25.1%, of which 15.6% comprised pathogenic or likely pathogenic anomalies. This information is valuable for prenatal counselling and postnatal care management in these subjects, especially in the presence of ECMs.