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Array-CGH based detection of genomic imbalances in patients with heart defects as part of complex syndromes

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The prevalence of congenital heart defects (CHD) is estimated at 7-9 per 1000 births. Besides single gene mutations chromosomal aberrations are found in a significant number of syndromic and non-syndromic patients affected by CHD. In order to identify novel gene loci associated with CHD we mined clinical and experimental data from a population of patients in which we had performed array comparative genomic hybridization (aCGH) analysis for the detection of constitutional imbalances because of a variety of complex phenotypes. Array CGH had been performed using different BAC (36K) and oligonucleotide (44K, 105K, 180K, 244K) platforms. Well-defined syndromes associated with CHD like microdeletions in 7q11 and 22q11 or Noonan syndrome were excluded. In 28 of 89 (32%) patients aCGH detected chromosomal imbalances which in part were subsequently confirmed by independent techniques like FISH or qPCR. In 8 cases the imbalance has been proven to be de novo whereas in 8 of cases the imbalance has been transmitted from one of the parents. The size of the aberrations ranged between 0.07 Mb and 151.8 Mb (median 4 Mb). Three chromosomal regions were affected in more than one patient: Two patients with discordant cardiac phenotypes had overlapping deletions in 21q22.3 (sizes 6.15 and 6.9 Mb). Overlapping deletions in 1p36.33 (sizes 3.8 and 12.7 Mb) were detected in two patients with aortic coarctation and left ventricular non-compaction cardiomyopathy, respectively. Finally, two almost completely overlapping terminal deletions in 5p15.33 distal of the Cri-du-Chat syndrome critical region of 4.2 Mb respectively 4.4 Mb were detected in two patients with a ventricular septal defect (VSD). In summary, our study showed that in nearly one third of patients presenting with complex phenotypes including CHD a constitutional imbalance can be detected by aCGH. The minimally overlapping regions affected in these patients might point to the position of candidate genes involved in the pathogenesis of CHD.