24 IDENTIFICATION OF NOVEL GENETIC RISK LOCI DETERMINE FETAL OUTCOME IN CONGENITAL HEART BLOCK

Sabrina Görgen,[1] Bo Ding,[2] Stina Salomonsson,[1] Lars Klareskog,[1] Anders Hamsten,[1] Jan Hillert,[1] Lars Alfredsson,[3] Tomas Olsson,[2] The Swedish Congenital Heart Block Study Group, Ingrid Kockum,[3] Marie Wahren-Herlenius[1] *[1]Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [2]Department of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [3]Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden*

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Objective Congenital heart block (CHB) is a life threatening heart condition where the fetal atrioventricular conduction system is disrupted. The block may occur during fetal development after placental transfer of autoantibodies from Ro/SSA positive mothers. The association with maternal Ro/SSA antibodies is well established; however the recurrence risk is only 11-20% despite persisting autoantibodies in the mother, suggesting that additional factors other than the maternal autoantibodies determine disease development and fetal outcome. We hypothesized that the fetal genetic composition is a major factor influencing susceptibility to CHB, and therefore conducted a genome-wide association study to map potential genetic risk loci involved in CHB pathogenesis.

Methods Genotyping of 561,490 SNP markers was accomplished in DNA samples from 389 individuals of 104 Swedish Caucasian families with at least one case of congenital heart block and a maternal serum positive for Ro/SSA autoantibodies. A family-based association analysis was performed using the transmission disequilibrium test (PLINK). The Cochran–Mantel–Haenszel statistical test was used to investigate SNP associations with CHB in index cases (n=88) compared to Swedish Caucasian population-based healthy controls (n=1710).

Results A family-based analysis (n=348) revealed 37 SNP markers with a p value of $P_{GWAS\,family} \leq 9.88 \times 10^{-5}$ (OR 0.18–6.50) associated to congenital heart block. In a case-control analysis between the index cases and population-based healthy controls 6 of the 37 SNP markers were confirmed. The CHB risk loci are located at the chromosomal positions 1p31.3, 2q35 and 3p25.1 and genes encoded within these regions are involved in cellular stress responses, energy metabolism and tissue repair.

Conclusion Our study identifies three novel genetic risk loci associated with development of CHB after exposure to maternal Ro/SSA autoantibodies. Functional exploration of the genes encoded within these risk loci will help to shed light on the cellular mechanisms underlying CHB pathogenesis.