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Abstracts

Molecular medicine and development

Program/Abstract # 80
Identification of potential Tbx1 targets in a mouse model of DiGeorge syndrome

Kelly Lammerts van Bueren [1], Sarah Ivins [1], Catherine Roberts [1], Amelie Calmont [1], Kerra Pearce [1], Elizabeth Lindsay [2], Baldini [2], Peter Scambler [1]

[1] *Institute of Child Health, London, UK*

[2] *University Federico II, Naples, Italy*

DiGeorge syndrome is characterised by craniofacial, cardiovascular and thymic and parathyroid defects resulting from a heterozygous 3Mb deletion of chromosome 22q11 in most patients. Haploinsufficiency of the *TBX1* transcription factor is considered to be the major underlying cause of this syndrome. Heterozygous mouse models in which a region of MMU16 homologous to HSA22q11 is deleted (*Df1*) and $Tbx1^{+/-}$ mice exhibit aortic arch, thymic and parathyroid defects; $Tbx1^{-/-}$ mice display more severe defects of pharyngeal development. In order to more clearly define cell autonomous effects of *Tbx1* and circumvent problems associated with tissue loss, we have developed a novel method of comparing *Tbx1* cells. The *Tbx1* null allele was generated by knocking in a lacZ reporter gene into exon 5. Using a fluorescent lacZ substrate, we have isolated specific *Tbx1* cells by FACS and compared the expression profile of $Df1/Tbx1^{lacZ}$ cells to $Tbx1^{+/lacZ}$ cells by microarray. Down-regulation of hemizygous *Df1* genes confirmed the sensitivity of the microarray experiment and novel potential transcriptional targets of *Tbx1* have been identified including *Nkx2.6*, *Dab2* and *Hes1*, a downstream effector of Notch signalling. Analysis of *Hes1* mouse mutants has led to the characterisation of DiGeorge-like craniofacial, heart and glandular defects. The genetic interaction between *Hes1* and *Tbx1* is currently being investigated by crossing transgenic mouse mutants and conducting morpholino knockdown studies in zebrafish.

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Program/Abstract # 81
Chd7 mutant mice phenocopy CHARGE and DiGeorge syndromes in the pharyngeal arch region of the developing embryo

Victoria A. Randall, Catherine Roberts, Peter Scambler

Molecular Medicine Unit, Institute of Child Health, UCL, London, UK

CHARGE syndrome is a multiple malformation syndrome, with characteristic anomalies including inner and outer ear defects and cardiovascular malformations. The *CHD7* gene on chromosome 8q12.1 was recently identified as a candidate gene and mutations are found in approximately 60% of patients. We show that insertion of a genetrap cassette within the murine *Chd7* gene results in a mouse model of the syndrome with a heart phenotype consistent with that observed in the human condition. We have analysed the expression of the *Chd7* gene throughout embryonic development. Homozygous embryos do not survive beyond 10.5 dpc. In heterozygous embryos early growth and remodelling defects in the pharyngeal arch arteries are detected explaining the later complex heart phenotype consisting of rearrangements in the aortic arch and great vessels. The heart phenotype overlaps with that seen in DiGeorge syndrome, another congenital disease where many of the associated defects are due to abnormal patterning of the pharyngeal arches as shown in the *Tbx1* mouse model. Examination of $Chd7^{+/-}/Tbx1^{/+/-}$ trans-heterozygous embryos reveals an increased penetrance of anomalies resulting from defective pharyngeal arch development, suggesting an epistatic interaction between the two genes in this region. We also demonstrate that *Wnt1* driven restoration of *Chd7* expression in neural crest cells in an otherwise heterozygous embryo does not rescue the arch artery defects, contrary to hypotheses proposing the syndrome is due to irregularities in this population of cells.

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Program/Abstract # 82
Dissecting DiGeorge Syndrome: The interaction between *Tbx1* and the retinoic acid pathway

Catherine Roberts [1], Sarah Ivins [1], Andrew C. Cook [2], Kelly Lammerts van Buren [1], Antonio Baldini [3], Peter J. Scambler [1]

[1] *Molecular Medicine Unit*

[2] *Cardiac Unit, Institute of Child Health, 30 Guilford St, London, WC1N 1EH, UK*

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