CHD7 and Epigenetics, CHARGE and 22q11.2 Syndromes

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Occasionally patients present with features of 22q11.2DS but where no deletion or *TBX1* mutation are found. *CHD7* has been reported in some of these cases, and this gene is haploinsufficient in CHARGE syndrome. The mouse model with heterozygous *Chd7* mutation has IAA-B, a malformation relatively specific for 22q11.2DS. Notably, double heterozygosity for *Tbx1* and *Chd7* has a severe phenotype. Given recent work showing TBX1 protein modifies chromatin and CHD7 is a component of a chromatin remodelling "machine" we have examined whether there is convergent regulation of the genes and pathways affected by loss of these proteins.

Methods

Conditional mutagenesis was used to ablate *Chd7* in various tissues vital for cardiac and pharyngeal development, and for which data was available in *Tbx1* mutants. Genome-wide transcriptomic analysis was undertaken after FACS or dissection. These data were then compared with *Tbx1* datasets. Small molecules were administered to pregnant mice to examine whether there was rescue of fourth pharyngeal arch artery hypoplasia in *Chd7* heterozygote embryos.

Results

Chd7, unlike *Tbx1*, was required in the first heart field in addition to the second heart field. This is explained by earlier expression of *Chd7* in the anterior mesoderm. Transcriptional changes in cardio-pharyngeal mesoderm revealed that the majority of genes were altered in opposite directions in the two models. This can be rationalized by the earlier and broader requirements for *Chd7*. When effects on cardiomyocyte differentiation genes are accounted for, there were alterations in the retinoic acid signalling pathway that mirror what is seen in *Tbx1* mutants.

Conclusion

It is clear there is no simple co-regulation of target genes in mesoderm that accounts for the TBX1-CHD7 genetic interaction data. However, specific signalling pathways may be common targets and even if affected at different embryonic stages these pathways may be susceptible to similar small molecule interventions.