CRKL and mammalian structural birth defects

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Background:
The *CRKL* gene maps to the LCR22C-D region on 22q11.2. *CRKL* encodes a CRK like proto-oncogene adaptor protein that is expressed within the cytoplasm of all mammalian cells. Its main roles are to transduce signals from the extracellular environment to the nucleus or cell membrane. This presentation includes a review of the literature on *CRKL* and its requirement for the formation of the brain, heart and genitourinary tract. *CRKL* is part of a gene family that includes the *CRK* gene, mapping to human chromosome 17p13.3. Both *CRK* and *CRKL* can serve unique and also redundant functions in embryonic development.

Methods:
This review also includes preliminary data generated by using mouse models to understand the function of *Crkl* and *Crk* in the development of the cardiovascular system. We performed global and tissue specific inactivation of *Crkl* and *Crk* floxed alleles using *Mesp1-Cre* (mesoderm) and *Wnt1-Cre* (neural crest) expressing mice.

Results:
Inactivation of *Crk* or *Crkl* results in mid-gestational lethality due to severe cardiac defects. Surprisingly, tissue specific inactivation of *Crk* or *Crkl* alone did not lead to any defects. On the other hand, inactivation of three *Crk/Crkl* alleles (two of *Crkl* and one of *Crk* or vice versa) in the mesoderm led to severe peripheral vascular defects resulting in early embryonic lethality. Inactivation of three alleles in neural crest cells resulted in a persistent truncus arteriosus and peripheral vascular smooth muscle defects.

Conclusions:
Patients with LCR22C-D deletions also have risk to structural birth defects, we suggest that *CRKL* is a strong candidate gene for some of these defects. Studies of *Crkl/Crk* together may shed new light on this important gene adaptor family in human embryonic development.