# RIMD–IPR Joint Seminar

## “Insight into the functions of the CRK gene family from a view of DiGeorge Syndrome”


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DiGeorge syndrome, also known as *del22q11* syndrome, is the most prevalent deletion syndrome, as microdeletions are localized most frequently to 22q11. Patients affected by this syndrome exhibit a broad spectrum of congenital malformation frequently in anterior tissues including craniofacial tissues, heart, and pharyngeal tissues such as thymus and parathyroid, often associated with growth retardation and neurological/psychiatric disorders. In addition, approximately 30% of the patients are known to extend a range of malformation into more posterior tissues in the genitourinary (GU) system. While most patients have a 3Mb deletion referred to Typically Deleted Region (TDR) or Common Deletion, a small but significant number of individuals have smaller deletions that do not overlap with a 1.5 Mb so-called “critical” region nested proximally within the TDR. We originally identified *CRKL* (*CRK-like*) as a DiGeorge candidate gene localized distally to the critical region, based on a set of anterior malformations in mice lacking the mouse homolog of this gene. Our recent multicenter study has identified nonsense or missense point mutations within the CRKL protein coding sequence among a large cohort of patients with genitourinary defects without a microdeletion. Furthermore, we have shown that mouse ortholog is essential for normal genitourinary development. Previous reports identified the essential role of *TBX1*, a gene encoding a transcription factor, in the 22q11 critical region. We showed that compound heterozygosity of mouse *Crkl* and *Tbx1* was sufficient to produce a synergistic synthesis of a stable syndromic phenotype. However, mouse embryos deficient for *Tbx1* alone do not show GU defects. Therefore, these results supply a definitive piece of evidence that DiGeorge syndrome is a true contiguous gene syndrome in which *CRKL* and *TBX1* are involved in most patients, while heterozygosity of *TBX1* or *CRKL* alone with point mutations or in small nonoverlapping deletions may affect syndromic patients possibly with other modifiers. Interestingly, we have also found that *Tbx1* heterozygosity can also synergize with heterozygosity of *Crk*, the paralog of *Crkl*, to produce DiGeorge-like anomaly in mice. As the *CRK* gene family encode adapter proteins consisting of SH2 and SH3 domains, we suggest that the genetic or signaling network affected in this syndrome is sensitive to function shared in the *CRK* gene family. I will also discuss recent unpublished results to shed light onto shared functions identified by omics approach.


**日時：2017年3月28日(火) ~~16:00～~~ 15：00～**

**Date : Tuesday, March 28th 2017, ~~16:00～~~ 15：00～**

**会場：微生物病研究所本館1階 微研ホール**

**Venue : BIKEN Hall ,RIMD**

※講演は英語で行われます This seminar will be held in English


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