A comparison of the genetic feature in Down syndrome-ALL and non-Down syndrome-ALL

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Down syndrome (DS), also known as trisomy of chromosome 21 (Chr21), has an increased risk of developing leukemia, which include both acute myeloid and lymphoblastic leukemia (ALL). Instead, Chr 21 is the most frequent gained chromosome in pediatric hyperdiploid ALL, and sometimes it becomes tetrasomy or pentasomy. Although previous studies have shown that DS-ALL differs clinically and genetically from non-DS-ALL, but comparison of DS-ALL and hyperdiploid ALL, which have common genetic basis of a gain of chromosome 21, remains to be elucidated. In this study, we focused on the difference of the genetic features between DS-ALL and non-Down ALL with a gain of Chr 21. Thus we performed target amplicon deep sequencing and copy number analysis for 31 samples, including 7 DS-ALL and 24 non-DS-ALL samples. We could divided non-Down ALL into three groups, group A (21trisomy), group B (21tetrasomy), and group C (no hyperdiploidy) based on gene alteration patterns. There were few copy number changes in DS-ALL and group C. 1q gain, 9p LOH and 12p LOH were concentrated in group C. RAS mutations were more frequently in group A (83.3%) and group B (80.0%) than DS-ALL (42.9%) and group C (37.5%). CRLF2-P2RY8 fusion was detected in only 1 case of DS-ALL without RAS mutation. Intriguingly, DCAF7 mutations, known as recurrent mutations in DS-AMKL, were also presented in DS-ALL (57.1%), group A (50%) and group B (30%), but not in group C. Our results were concordant to that of previous studies, and we confirmed that somatic +21 played a different role in pathogenesis of ALL from germline +21.

GATA2 and secondary mutations in familial myelodysplastic syndromes and pediatric myeloid malignancies

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Background: GATA2 plays critical roles in hematopoiesis. Germline GATA2 mutations cause hematological disorders, including familial myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML). The rare GATA2-related disorders have various clinical presentations, even within a single family, ranging from lymphedema without hematological malignancy to early-onset childhood MDS/AML. However, the molecular pathogenesis of GATA2-related familial MDS/AML remains poorly characterized.

Methods: We performed target gene sequencing of 90 hematological malignancy-related genes in six patients with familial MDS/AML using a SureSelect Custom (Agilent) and a MiSeq next-generation sequencer (Illumina).

Results: All patients carried germline GATA2 mutations. Furthermore, we identified at least 20 somatic driver mutations in myeloid malignancy-related genes, including RUNX1, ASXL1, STAG2, NRAS, TP53, and SETBP1. No somatic mutations were detected in two patients who remained alive without hematopoietic stem cell transplantation (HSCT). In contrast, in the remaining four patients who required HSCT, 2-7 somatic driver mutations were detected.

Conclusions: To the best of our knowledge, this is the first study revealing the secondary mutations in GATA2-related disorders. Our data strongly suggest that serial clonal evolution is at least partly responsible for the variation observed in the clinical presentation of familial MDS/AML. As in case of adult MDS, the detection of driver mutations may be useful in predicting the clinical course and prognosis of GATA2-related disorders.
Identification of in-frame tandem duplication of BCOR in clear cell sarcoma of the kidney

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Clear cell sarcoma of the kidney (CCSK) is the most common pediatric renal sarcoma, which comprise 5% of pediatric renal tumors. Its associated genetic abnormalities are largely unknown. We have reported that CCSK shows characteristic DNA hypermethylation. Since the DNA methylation is reportedly associated with histone modification, we focused on histone modifiers and found the BCL6 corepressor (BCOR), which encodes a component of non-canonical polycomb repressive complexes1 (PRC1), was highly expressed and its promoter CpG sites were hypomethylated. During analyzing the expression, we found abnormalities in the 3’ part of BCOR in all 20 tumors analyzed. These abnormalities are duplications of 89 to 114 bases in exon 16, with or without small insertions between duplicated sequences. All sequence alterations result in duplication of 30 to 38 amino acids. The minimally overlapping region is within the PCGF Ub-like Fold Discriminator (PUFD) domain, necessary for PCGF1 binding. The BCOR is localized to Xp11.4 and only aberrant BCOR allele was identified in male tumors and aberrant and normal BCOR were identified in female tumors. In addition, only aberrant BCOR allele was overexpressed in both male and female tumors. The BCOR aberration is found in all CCSK tumors but none of other pediatric renal tumors (0/193) and could be utilized as a diagnostic marker. Since the aberration we identified in this study is involved in PUFD, important in forming PRC1 complex, BCOR partial duplication could promote CCSK tumorigenesis via epigenetic aberration.
KIR ligand incompatible allogeneic cord blood transplantation for high risk neuroblastoma

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Background: Venstrom et al. reported that superior survival was strongly associated with “missing KIR ligand” in patients with neuroblastoma. We evaluated KIR ligand incompatible allogeneic cord blood transplantation (CBT) as a salvage therapy for high risk neuroblastoma. Methods: We chose KIR ligand incompatible donor and planned tandem transplantation using high dose chemotherapy followed by autologous SCT and allogeneic CBT with reduced intensity conditioning regimens. Reduced intensity conditioning regimen for CBT were used either BU, Flu and L-PAM or Flu, L-PAM and low dose TBI 2Gy. Eligibility criteria of this study was stage IV neuroblastoma patients with either of following 1) relapse, 2) MIBG positive metastases after 4 courses of induction chemotherapy 3) over 10 years old at diagnosis 4) MYCN amplification over 10. Results: Fifty five patients received KIR ligand incompatible CBT. Median age at diagnosis was 2 (0-10) years old. Median follow-up period was 30(3-78) months. Multivariate analysis revealed KIR3DL2 mismatch and disease status at transplant was significant covariate factor for relapse. In the subgroup analysis of 45 patients excluded non remission of relapsed patients or KIR3DL2 mismatch donors exhibited 78.2% three year PFS. The group of Flu, L-PAM and low dose TBI regimen showed significantly better PFS than BU regimen group (88.7% vs 54.2%, p=0.028). Conclusions: Allogeneic CBT from KIR ligand incompatible donor for neuroblastoma was feasible and related to less relapse rate and better progression free survival.