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Germline Variants Associated with Cancer Predisposition and Bone Marrow Failure Are Common in KMT2A-r Infant Acute Lymphoblastic Leukemia Patients

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Leukemias in infants (<12 months) are extremely rare, ~40 cases/million infants diagnosed in the US each year.

- Of these, infant acute lymphoblastic leukemia is the most common

Prognosis remains poor with an overall survival of less than 50%.

Approximately 70% of cases are characterized by a chromosomal rearrangement of $KMT2A$ ($KMT2A-r$) on chromosome 11q23.

- >100 partner genes, many of which are known transcriptional elongation factors
- Strongest independent predictor of a poor prognosis

Figure 1. *Event free survival of infants with ALL separated by MLL status. Redrawn after Hilden et al.9 Please note that the data correspond to event free survival (a more stringent criterion) and do not include children older than one year.*
Background

- Aside from KMT2A-r itself, studies examining somatic variation have demonstrated a low mutational frequency.
- Germline mutations in cancer predisposition genes are found in 8.6% of pediatric malignancies (Zhang J et al., *N Engl J Med* 2015).
• We hypothesize that germline variants may play a role in the development of \textit{KMT2A-r} ALL in infants.
Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD¹, Nazneen Aziz, PhD²,¹⁶, Sherri Bale, PhD³, David Bick, MD⁴, Soma Das, PhD⁵, Julie Gastier-Foster, PhD⁶,⁷,⁸, Wayne W. Grody, MD, PhD⁹,¹⁰,¹¹, Madhuri Hegde, PhD¹², Elaine Lyon, PhD¹³, Elaine Spector, PhD¹⁴, Karl Voelkerding, MD¹³ and Heidi L. Rehm, PhD¹⁵; on behalf of the ACMG Laboratory Quality Assurance Committee

<table>
<thead>
<tr>
<th>Benign</th>
<th>Likely Benign</th>
<th>Variants of Uncertain Significant</th>
<th>Likely Pathogenic</th>
<th>Pathogenic</th>
</tr>
</thead>
</table>

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Predicting Pathogenicity of a Gene Variant

- Type of gene variant
  - Missense, nonsense, frameshift, splice site → how will it effect function?
- Population data
  - prevalence in control populations
- Computational and predictive data
- Functional data
  - In vitro or in vivo studies supporting damaging effect on gene/gene product
- Segregation/familial data
- Allelic data
- Phenotypic data
Methods

• We performed whole genome sequencing (WGS) and whole exome sequencing (WES) on DNA isolated from peripheral blood at time of remission from 36 KMT2A-r infant ALL cases enrolled on COG trial AALL15P1.

• Sequencing was performed using Illumina Hiseq 4000 or 2500 to a minimum depth of 90Gb (WGS) and 15Gb (WES). Alignment and variant calling were performed using the Dragon Bio-IT platform (v 3.2.8, Illumina)

• We compiled a list of 346 genes associated with cancer predisposition, bone marrow failure, and cancer driver genes (as identified in somatic variant analysis by Ma X et al., Nature 2018)

• Variants meeting the following criteria were interpreted using ACMG/AMP 2015 guidelines for sequence variants:
  • Variant allele frequency ~50%
  • Minor allele frequency <1% in our Children’s Mercy internal variant warehouse database
Results

• 351 germline variants were identified (mean 9.75 variants per patient sample)
  • Benign/Likely Benign (B/LB) = 199
  • Variants of Uncertain Significance (VUS) = 143
    • Likely Pathogenic (LP) = 3
    • Pathogenic (P) = 6

• 19.4% of unique patient samples displayed at least one LP/P variant
Results

Characterization by possible causative pathway

- Bone Marrow Failure Genes
- Driver Genes
- Tumor Suppressor Genes
- Tyrosine Kinase Genes
- Inherited Leukemia Genes
- Other

- Pathogenic
- Likely Pathogenic
- VUS
## Results

### Likely Pathogenic/Pathogenic Germline Variant Characterization in *KMT2A-r* infant ALL

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Gene</th>
<th>Nucleotide Change</th>
<th>Amino Acid Change</th>
<th>Transcript</th>
<th>Clinical Disorder</th>
<th>Inheritance</th>
<th>ACMG Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ERCC2</td>
<td>c. 466C&gt;T</td>
<td>p. R156*</td>
<td>NM_000400.3</td>
<td>Xeroderma Pigmentosum (early onset skin cancer)</td>
<td>AR</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>1</td>
<td>FANCI</td>
<td>c.3853C&gt;T</td>
<td>p. R1285*</td>
<td>NM_001113378.1</td>
<td>Fanconi anemia (BMF)</td>
<td>AR</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>3</td>
<td>CTC1</td>
<td>c.724_727 del</td>
<td>p. KA242*</td>
<td>NM_025099.5</td>
<td>Coats plus syndrome, Dyskeratosis congenita (BMF)</td>
<td>AR</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>12</td>
<td>ATM</td>
<td>c.8988-1G&gt;A</td>
<td>p. ?</td>
<td>NM_000051.3</td>
<td>Ataxia-telangiectasia syndrome (lymphoma and leukemia)</td>
<td>AR</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>18</td>
<td>MITF</td>
<td>c.952G&gt;A</td>
<td>p. E318K</td>
<td>NM_000248.3</td>
<td>Increased risk of melanoma and renal cell carcinoma</td>
<td>AD</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>18</td>
<td>HOXB13</td>
<td>c.251G&gt;A</td>
<td>p. G84E</td>
<td>NM_006361.5</td>
<td>Hereditary prostate Cancer</td>
<td>Unknown</td>
<td>Pathogenic</td>
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<tr>
<td>21</td>
<td>CHEK2</td>
<td>c.707T&gt;C</td>
<td>p. L236P</td>
<td>NM_007194.3</td>
<td>Increased risk of breast cancer and colorectal cancer</td>
<td>AD</td>
<td>Likely Pathogenic</td>
</tr>
<tr>
<td>30</td>
<td>RAG1</td>
<td>c.994C&gt;T</td>
<td>p. R332*</td>
<td>NM_000448.2</td>
<td>Severe Combined Immunodeficiency, Alpha/Beta T-cell lymphopenia</td>
<td>AR</td>
<td>Likely Pathogenic</td>
</tr>
<tr>
<td>33</td>
<td>ERCC2</td>
<td>c.2150C&gt;G</td>
<td>p. A717G</td>
<td>NM_000400.3</td>
<td>Xeroderma Pigmentosum (early onset skin cancer)</td>
<td>AR</td>
<td>Likely Pathogenic</td>
</tr>
</tbody>
</table>
Conclusion

• Our KMT2A-r infant ALL cohort presents a higher mutation rate of 19.4% in germline variants in cancer predisposition and bone marrow failure genes than has been previously reported, however the significance of this finding is unclear.
• Variants in ERCC2, which encodes a protein involved in DNA repair mechanisms, were found to be recurrent within our cohort.
• We have continued this investigation, exploring germline analysis of other infant and non-infant ALL samples to determine the frequency of this recurrent ERCC2 variant in relation to other pediatric leukemias.
Acknowledgements

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• Patrick A. Brown
Thank you for your time.

Please contact me at semcdermott@cmh.edu with any questions.