Mutational profile and cytogenetic characteristics of myelodysplastic syndrome, chronic myelomonocytic leukemia, and acute myeloid leukemia with myeloplasiasis-related changes.

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Introduction
The heterogeneity of myelodysplastic syndromes (MDS) is well-known from morphological, genetic, and clinical studies, which guided the creation of classification, and prognostic scoring systems. To generate more therapeutically relevant disease classifications, the most recent WHO classification included classification of Tumors of the Hematopoietic and Lymphoid Systems. Tissues included multiple updates to emphasize the significance of genomic profiling in AML not only at the gross chromosomal level, but also at the molecular level. Approximately a half of MDS cases lack structural chromosomal abnormalities and instead exhibit normal karyotypes, in which instance correlation with molecular studies can allow for more accurate stratification and inform clinical management. Recently, inexpensive high-throughput next-generation sequencing (NGS) technology studies have established the panel of MDS relevant gene mutations. Thus, targeted gene panels composed of relevant MDS driver genes may have utility in establishing a diagnosis of MDS and be of interest for gaining additional knowledge about the prognostic and therapeutic significance of these gene mutations potentially leading to further refinement of the prognostic scoring system.

Materials & Methods
All samples were obtained from the Pathologist Biomedical Laboratories and the Baylor Scott White Medical System (November of 2016 through October 2017). The study cohort consisted of 40 cases, including 21 cases lacking cytogenetic abnormalities (8 MDS, 4 CMML, 7 AML-MRC/AML), and 21 cases with cytogenetic abnormalities (17 MDS, 2 CMML, 2 AML-MRC). The mean age was 72 years with a male predominance in both groups (male-female ratio = 25:15). Abnormal Cytogenetics and FISH

Mutated 10.1 MCHC was the most commonly mutated gene in WBC. AML, MDS, CEBPA being the most commonly mutated 5 (45%) 2 (20%) 2 (20%)

CEBPA Mutation Detection The assay is performed using PCR/Sanger sequencing of the entire coding region of the CEBPA gene. The expected size of the mutation in the background of normal cells. Detected sequence variants are classified as a mutation or a variant of uncertain clinical significance based on the clinical importance of the mutation published by Behdad et al. J Molecular Genetics 17, 76-84.

Statistical Analysis Statistics was performed using the χ2 test to compare categorical variables. A two-tailed t test was used to compare mutation burden (mean number of mutations) between different groups. A P value less than .05 was considered statistically significant.

Results

<table>
<thead>
<tr>
<th>Table 3. Distribution of Mutations and Cytogenetic Abnormalities Across Different Subgroups</th>
<th>Table 4. Single vs Multiple (&gt;3) Mutations Across Different Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>CMML</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>8</td>
</tr>
<tr>
<td>Abnormal karyotype</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
</tr>
</tbody>
</table>

Overall, our mutation frequencies in MDS, CMML, and AML-MRC/AML are in agreement with prior studies. Given that a selected panel of genes was tested, differences in mutation burden may in part be due to gene selection. The distribution of mutations in MDS, MDS, CMML, and AML is depicted in Figure 1. Data from NGS facilitated an accurate primary diagnosis in cases of CMML or MDS with normal cytogenetics. MDS. As shown in Figure 2, no significant difference was found in the number of mutated genes between low grade MDS and AML-MRC

Conclusions
• In our cohort most cases of MDS (97.5%) contain at least one mutation while only 68% of cases of MDS, 33% of CMML, and 22% of AML-MRC revealed abnormal cytogenetics.
• Solitary mutations were more often found in those with abnormal cytogenetics (47%) and in CMML (83%), but only 19% of those with normal cytogenetics had solitary mutations.
• Three or more mutated genes are found more often in cases with cytogenetics abnormalities (47%) and in CMML (83%), but only 19% of those with normal cytogenetics had solitary mutations.

References

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