Gene Mutations in Cases Suspected of MDS with Loss of the Y Chromosome as the Sole Abnormality

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ABSTRACT

MDS and loss of the Y chromosome are both observed in older patients. Currently loss of the Y chromosome in >75% of the cells from unstimulated cultures is used as the cut off to suggest the possibility of existence of a neoplastic process. The recent characterization of the molecular abnormalities underlying the biology of MDS should provide objective biomarkers to confirm the diagnosis of MDS in cases with loss of the Y chromosome as the sole abnormality. Retrospective analysis of next generation sequencing data of 30 genes was performed on 100 cases of suspected MDS – 50 with loss of the Y chromosome as the sole abnormality and 50 cases with a normal karyotype. Hematologic profiles of the 50 cases with loss of the Y chromosome were also reviewed. Mutations were observed in 18 cases with loss of the Y chromosome (36%); 9 of 20 cases (45%) with >75% cells with -Y and in 9 of 30 cases (30%) with <75% cells with -Y. The proportions of cases with mutations are not significantly different from the proportion of cases with a normal karyotype (25 of 50 cases; 50%). There was also no significant difference in the hematologic profiles (WBC, HGB, MCV, RDW, PLT, lymphocytes, monocytes, neutrophils and CD45 dim) of cases with loss of the Y chromosome in <75% cells and >75% cells. Based on data from a limited number of cases, loss of the Y chromosome does not appear to be associated with presence of mutations observed in MDS. The data also suggests that <75% of cells with loss of the Y chromosome should not be interpreted as merely an age related factor and be the basis for excluding from consideration of a diagnosis of MDS. While 5 of 9 cases (56%) with loss of Y in >75% had mutations in more than one gene, 1 of 9 cases (11%) with loss of Y in <75% cells and 7 of 25 (28%) cases with a normal karyotype had mutations in more than one gene. The higher proportion of cases with loss of Y in >75% cells with more than one mutation may reflect greater rate of proliferation of cells with more mutations. In this respect, a higher proportion of cells with loss of the Y chromosome in patients with MDS may indicate the existence of mutations in multiple genes. Additional studies are essential to confirm this relationship between multiple mutations and rate of proliferation of the abnormal cells.

Figure 1. Mutation profile of cases with loss of the Y chromosome in <75% cells



INTRODUCTION

Myelodysplatic syndrome (MDS) is a disorder in the older individuals. In some male patients, cytogenetic studies show loss of the Y chromosome as the sole abnormality. Loss of the Y chromosome is also observed in older males in the absence of MDS. Currently, based on differences in the frequency of cells with loss of the Y chromosome in disease and control populations, loss of the Y chromosome in >75% of the cells from unstimulated cultures is used as the cut off to suggest the possibility of existence of a neoplastic process. Recent characterization of the molecular abnormalities underlying the biology of MDS should provide objective biomarkers to confirm the diagnosis of MDS in cases with loss of the Y chromosome as the sole abnormality.

ETV6					
ZRSR2					

Figure 2. Mutation profile of cases with loss of the Y chromosome in >75% cells



Figure 3. Comparing cases with normal karyotype and cases with loss of Y chromosome – not significant (p=0.16)

Figure 4. Comparing cases with >75% and <75% -Y cells – Not significant (p=0.12)

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SAMPLE AND METHOD

- 100 cases suspected of MDS
- 50 with loss of the Y chromosome as the sole abnormality
- 50 with a normal karyotype
- Retrospective analysis of next generation sequencing data of 30 genes
- Review of hematologic profiles of the 50 cases with loss of the Y chromosome.

RESULTS

- Mutations were observed in 18 of 50 (36%) cases with loss of the Y chromosome.
- 9 of 30 (30%) of cases with loss of Y in <75% of cells (Figure 1).
- 9 of 20 (45%) of cases with loss of Y in >75% of cells (Figure 2).
- 25 of 50 cases (50%) of cases with a normal karyotype showed mutations.
- 5 of 9 cases (56%) with loss of Y in >75%, (Figure 2) 1 of 9 cases (11%) with loss of Y in <75% cells (Figure 1) and 7 of 25 (28%) cases with a normal karyotype had mutations in more than one gene.

DISCUSSION

- Loss of the Y chromosome does not appear to be associated with presence of mutations observed in MDS (Figure 3).
- The proportion of cells with loss of the Y chromosome (<75% vs >75%) does not appear to be associated with the presence of mutations in MDS (Figure 4).
- The higher proportion of cases with loss of Y in >75% cells with more than one mutation may reflect greater rate



CONCLUSION

- Loss of the Y chromosome is likely an age related abnormality, independent of a neoplastic process.
- Loss of Y chromosome in <75% of cells should not be interpreted as merely an age related factor and be the basis for excluding from consideration of a diagnosis of MDS.
- Presence of multiple mutations may be related to increased proliferation, resulting in detection of a higher proportion of cells with loss of the Y chromosomes.
- Additional studies are essential to confirm the relationship between multiple mutations and rate of

of proliferation of cells with more mutations.



• A higher proportion of cells with loss of the Y chromosome in patients with MDS may indicate the existence of



• Molecular profiling may be informative in confirming the diagnosis of MDS in cases suspected of MDS with

loss of the Y chromosome as the sole abnormality.