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Mutational profiling of a MonoMAC syndrome family with *GATA2* deficiency

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We performed whole genome and exome sequencing of a family with high risk myelodysplastic syndrome (MDS). Based on the sequencing results, the affected family members were diagnosed as having MonoMAC syndrome with a heritable germline *GATA2* mutation (R396Q) as the causative factor of the disease (Fig. 1).

MonoMAC is an autosomal-dominant syndrome and manifests as a deficiency of monocytes, B lymphocytes and NK cells. It is often accompanied with mycobacterial, fungal and viral infections[1]. This rare genetic disorder was initially described a few years ago[2] and subsequent studies then revealed mutation of the transcription factor *GATA2* as the cause of the syndrome[3-7]. Although targeted sequencing or exome sequencing has been performed recently and a number of cooperating mutations has been found in several studies[3, 4, 6, 8], to our knowledge, the entire spectrum of genomic changes of this disease has not yet been characterized.

The studied family includes two disease-affected patients (father and son) and a disease-free daughter. Both father and son experienced repeated infections and were diagnosed with MDS at ages 18 and 17, respectively. They remained healthy after receiving hematopoietic stem cell transplantation from unrelated donors. Genomic DNA was extracted from the father's malignant paraffin embedded bone marrow before transplantation as well as from a swab of the mouth mucosa (germline control), the son's paraffin embedded bone marrow before transplantation and his mouth swab, as well as the healthy daughter's bone marrow together with her normal cells from the mouth swab. Whole genome sequencing was

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performed on the above samples using Illumina HiSeq X Ten (mean >30× coverage). Exome sequencing of the son's bone marrow sample was also performed using Illumina Hiseq 4000 (mean >200× coverage) to enhance the identification of potential subclonal mutations. The sequencing reads were aligned to the standard human genome (hg19) using BWA, and mutations were called using Mutect (for single nucleotide variants, SNVs), VarScan (for SNVs and indels), Pindel (for indels) and Delly (for structural variants). Results were filtered with dbSNP 131,1000 genome (cutoff >0.001), Esp5400 database (cutoff >0.001), and the repetitive and low complexity regions(repeats and genomic SuperDups track, UCSC Genome Browser). Inactivating germline mutations (nonsense, frameshift and splicing-site mutations) were further analyzed. All the germline variants of *GATA2* gene, including coding region, intron, UTR and upstream/downstream were called and filtered with dbSNP 131, 1000 genome, Esp5400 database and further examined using ExAC exome database (http://exac.broadinstitute.org/).

The disease was featured with a paucity of somatic mutation. We found a germline missense variant R396Q within the *GATA2* gene in all of the specimens of both the father and son (both swab and bone marrow), but not in the healthy daughter. This variant was previously reported as a mutation hotspot associated with MonoMAC disease[4]. The father's bone marrow (cytogenetic: 47XY, +8) also carried the well-appreciated inactivating mutations of MDS/acute myeloid leukemia (AML) genes: *BCOR* (stop-gain R342X, variant allele frequency (VAF)=92%, X-chr gene), *STAG2* (splicing site, exon 6:C.289-2A>C, VAF=80%, X-chr gene), *FANCA* (indel, G755fs, Fanconi Anemia Complementation Group A, involved in DNA repair), as well as a missense mutation of *MLL2* (P187S) (Fig. 1, Supplementary Table 1). Potential MDS related missense mutations include *KDM4B* (Histone H3K9 demethylase), *DGKG* (diacylglycerol kinases) and *APIP* (functions in the methionine salvage pathway).

We found 2 somatic mutations in the son's bone marrow sample (*STAG2, RYR2,* cytogenetic 46XY, der(16)t(1; 16)(q21; q22)). A *STAG2* splicing-site mutation (exon 19:C.1821+1G>A) was found with low VAF (=22%), indicating its presence as a minor subclone. Notably, the *STAG2* mutations found in father and son occurred in different position, indicating that these mutations were acquired independently, suggesting *STAG2* may act as a cooperating-gene with *GATA2* in the development of the disease. Collectively, our observation indicates that MonoMAC syndrome is a disease that develops with low mutational burden, emphasizing the crucial role of *GATA2* mutation in this syndrome.

GATA2 encodes a hematopoietic transcription factor that controls the differentiation of myeloid lineage and is crucial for the proliferation and maintenance of hematopoietic stem cells and multipotential progenitors[9, 10]. Mutation of *GATA2* has been found in AML and MDS and was discovered as a predisposing gene for familial and pediatric AML/MDS[4, 11-15]. Notably, analysis of the ExAC database (containing protein-coding genetic variation in 60,706 normal humans) revealed that GATA2 is strongly intolerant towards loss of function (LOF), with a probability of LOF intolerant (pLI) value 0.98 (pLI> 0.9 indicates an extreme intolerance to loss of function). Indeed, no frameshift or nonsense mutation can be found in the entire ExAC cohort (60,706 individual). This observation suggests that *GATA2* is involved in the essential pathway of embryonic/developmental growth and

survival and is indispensable for normal development. It will be interesting to follow-up those individuals who carry rare missense variant of *GATA2* (around 110 individuals in ExAC cohort) to determine whether they display any indolent hematopoietic abnormality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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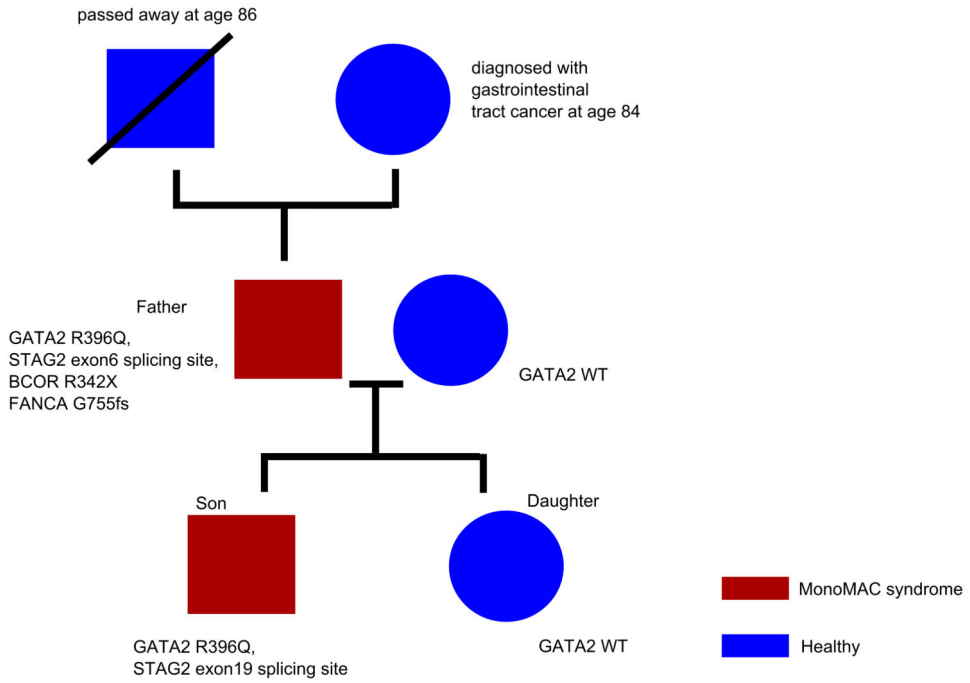

Fig 1.

Pedigree of family affected by the MonoMAC syndrome. Squares represent the male family members and circle represent the female family members.