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A nonsense mutation of *IDH1* in myelodysplastic syndromes and related disorders

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Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are tricarboxylic acid cycle enzymes that catalyze conversion of isocitrate to α-ketoglutarate, operating in the cytosol and mitochondria, respectively. Recently, Parsons *et al.*[1] described that *IDH1* is mutated in 12% of glioblastomas, followed by the Yan *et al.*'s[2] report showing a high frequency (80%) of *IDH1* mutations at the R132 residue and less frequent *IDH2* mutations at the R172 residue in grade II–III gliomas and secondary glioblastomas. *IDH1* and *IDH2* were shown to be also mutated in 7.7–9.9% and 15.4% of acute myeloid leukemia (AML) cases, respectively, especially those having normal karyotypes. More recently, both gene mutations were found in other myeloid neoplasms, including myeloproliferative neoplasms and myelodysplastic syndrome (MDS), and were associated with a high rate of MDS–AML transformation and poor prognosis.[3–5] In hematopoietic neoplasms, all reported *IDH1* mutations involved the R132 residue, while *IDH2* mutations involve either the R172 or the R140 residue.

These mutations are thought to result in loss-of-function of these enzymes and prevent α-ketoglutarate production from isocitrate in a dominant-negative manner, which in turn leads to activation of the HIF-1α pathway.[6] On the other hand, Dang *et al.*[7] and Ward *et al.* demonstrated that mutant *IDH1* and *IDH2* also showed gain-of-function that promotes production of 2-hydroxyglutarate (2HG) from α-ketoglutarate, which is thought to be oncogenic. However, the relative contribution of loss-of-function and gain-of-function to oncogenesis is still unclear.

Conflict of interest

The authors declare no conflict of interest.

Here, we report mutations of both *IDH1* and *IDH2* in a series of 171 cases with MDS or related myeloid neoplasms, where the complete status of genome-wide copy numbers and mutations of major MDS-related genes, including *c-CBL, RUNX1, TP53, FLT3ITD, JAK2, NRAS* and *KRAS* genes, were previously investigated.[8] Our series included 28 cases with AML, 35 with chronic myelomonocytic leukemia (CMML), 3 with refractory anemia (RA), 69 with RA with excess of blasts (RAEB), 1 with RA with ringed sideroblasts (RARS), 25 with refractory cytopenia with multilineage dysplasia (RCMD), 4 with MDS-unclassified (MDS-U), and 6 with 5q-syndrome, according to the new World Health Organization classification. Mutations of *IDH1* and *IDH2* were examined with genomic DNA isolated from bone marrow by direct sequencing of the PCR-amplified exon 4 of both genes as previously described.[2] This study was performed under the regulation of the ethics committee at the Faculty of Medicine, University of Tokyo.

In total, 9 *IDH1* (5.2%) and 7 *IDH2* (4.2%) mutations were identified (Table 1). *IDH1/2* mutations were most frequently found in RAEB (14.4%), followed by RCMD (8%), transformed AML (7.1%) and CMML (5.7%). There were conflicting reports regarding the frequencies of *IDH2* mutations in MDS. While similar frequencies of *IDH1* and *IDH2* mutations were observed by Kosmider *et al.*,[5] Thol *et al.*[3] reported no *IHD2* mutations in their 193 MDS cases showing 3.6% mutation rate for *IDH1.* In our series, on the other hand, *IDH2* mutations were found to have a frequency comparable to that of *IDH1* mutations, although all *IDH2* mutations were R140Q, with no R172 mutations that are common in brain tumors, and also have been reported in the previous literatures on AML, myeloproliferative neoplasm and MDS. All mutations were heterozygous and no sample had both mutations occurring simultaneously. All but one of the *IDH1* mutations corresponded to amino-acid conversions previously reported in AML and glioblastoma, including four R132C, three R132 and one R132L mutations. The remaining one was a nonsense mutation (CGA>TGA) at the R100 residue (Figure 1). The R100X mutation was most likely to result in loss-of-enzymatic function of *IDH1*, because it truncates all the enzymatically active domains of the protein.

IDH1/2 mutations were found in 8 out of 72 cases with normal karyotypes (cases 2, 3, 5, 8, 10, 12, 13 and 16), but 5 of them showed abnormalities in SNP array analysis, although none of them had poor-prognosis karyotypes such as complex chromosomal abnormalities. Pardanani *et al.*[9] reported frequent *IDH* mutations in cases with simple del(5q) (4/16, or 25%), but in our series none of four such cases had the mutations. Coexisting mutations of other genes were found in 5 of the 16 cases with *IDH* mutations, including mutations in *c-CBL* in one case, *RUNX1* in two cases, *TP53* in another and *JAK2* in the other case. *RAS* mutations were found in 13 cases, but none of them coexisted with *IDH* mutations. No statistical difference in the clinical outcomes was observed between cases with and without *IDH* mutations.

In the past reports, *IDH1* mutations were confined to the R132 residue. It is predicted that the consequences of these mutations at this position will be the structural alteration of the protein to a closed, active conformation, which has a higher affinity to $NADPH^+$, loss of three hydrogen bonds with isocitrate, and reorganization of the active sites via the positional shift of Y139 and K212′.[7] These are thought to facilitate the synthesis of 2HG from α-

ketoglutarate (gain of function) rather than conversion of isocitrate to α-ketoglutarate. However, the R100X mutation truncates most amino-acid residues that contact substrates, including R100 and R132, and, thus, is thought to abrogate all enzymatic activities without side effects, such as the synthesis of 2HG from α-ketoglutarate. This is the first example that represents pure loss-of-function of IDH1. Our findings will provide an interesting insight into the mechanism by which *IDH1* mutations promote the development of human cancers.

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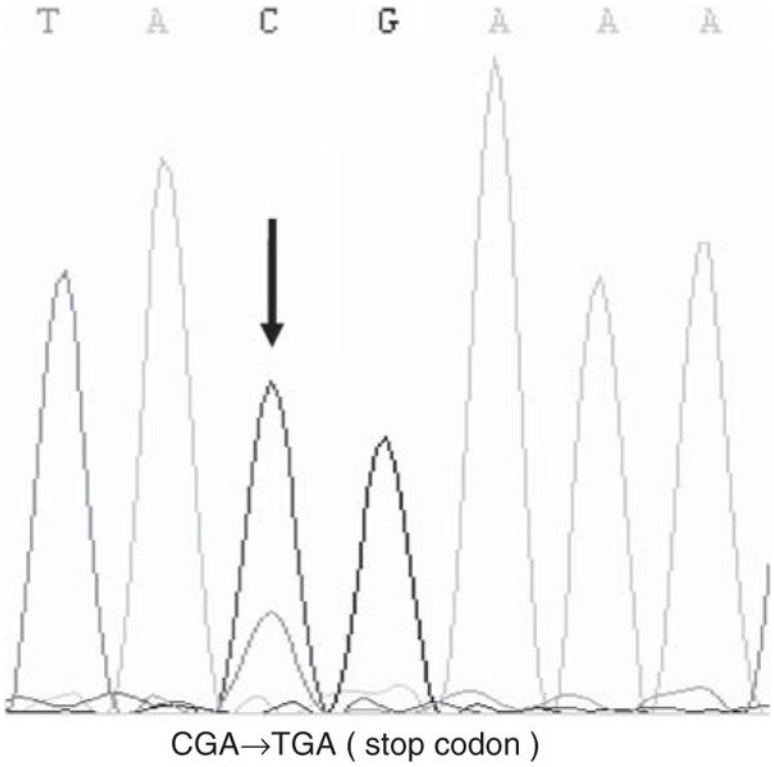

Figure 1.
Sequence of *IDH1* R100 mutation (case 9). The arrow indicates the mutated nucleotide.

Table 1

Mutational status of 16MDS or MDS-related disease with *IDH* mutations

Patient number	Sex/age	Type (WHO)	Cytogenetics	Results by 50k	IDH	cbl	RUNX1	p53	FLT3ITD	JAK2	NRAS	KRAS
1	F/71	RAEB1	ND	Normal	*IDH1* R132H	wt	wt	mut	wt	wt	wt	wt
2	M/75	RAEB2	46,XY	+1q,der(1;7)	*IDH1* R132H	wt	wt	wt	wt	wt	wt	wt
3	M/66	RAEB1	46,XY	9p UPD	*IDH1* R132H	wt	wt	wt	wt	mut	wt	wt
4	M/65	RAEB2	ND	+8	*IDH1* R132C	wt	wt	wt	wt	wt	wt	wt
5	M/51	RAEB2	46,XY	Normal	*IDH1* R132C	wt	mut	wt	wt	wt	wt	wt
6	M/75	RCMD	46,XY,del(20)(q11)	add(3)(p26.3-24.3), del(20)(q11.21-13.13)	*IDH1* R132C	wt	wt	wt	wt	wt	wt	wt
7	M/82	RCMD	46,XY,del(20)(q11)	del(20)(q11.21-13.2), 3qUPD	*IDH1* R132L	wt	wt	wt	wt	wt	wt	wt
8	M/64	RAEB2	46,XY	del(8)(q21.3)	*IDH1* R132C	wt	wt	wt	wt	wt	wt	wt
9	M/—	AML with MLD	46,XY[7] 49,XY,+4,+8,+10[12]	Normal	*IDH1* R100X	wt	wt	wt	wt	wt	wt	wt
10	M/77	RAEB2	46,XY	Normal	*IDH2* R140Q	wt	wt	wt	wt	wt	wt	wt
11	M/80	CMML2	47,XY,+8	11q UPD	*IDH2* R140Q	mut	wt	wt	wt	wt	wt	wt
12	M/57	AML with MLD	46,XY	+8	*IDH2* R140Q	wt	wt	wt	wt	wt	wt	wt
13	M/63	RAEB2	46,XY	Normal	*IDH2* R140Q	wt	mut	wt	wt	wt	wt	wt
14	F/74	RAEB1	45,XX,del(5)(q23q32), der(11;12)(q10;q10), del(20)(q11)	del(5)(q23.2-35.3), del(20)(q11.22-13.2)	*IDH2* R140Q	wt	wt	mut	wt	wt	wt	wt
15	M/76	CMML2	46,XY,+1, der(1;7) (q10;p10)	+1q,der(1;7)	*IDH2* R140Q	wt	wt	wt	wt	wt	wt	wt
16	M/63	RAEB2	46,XY	7q UPD	*IDH2* R140Q	wt	wt	wt	wt	wt	wt	wt

Abbreviations: AML with MLD, acute myeloid leukemia with multilineage dysplasia; CMML, chronic myelomonocytic leukemia; *IDH*, isocitrate dehydrogenase; MDS, myelodysplastic syndrome; mut, mutation; RAEB, refractory anemia with excess blasts; RCMD, refractory cytopenia with multilineage dysplasia; wt, wild type.