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## ***IDH1* and *IDH2* mutations in myelodysplastic syndromes and role in disease progression**

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### **Keywords**

MDS; *IDH1*; *IDH2*; outcome; transformation

### **Letter to Editor**

Recurrent pathogenic mutations in *IDH1* and *IDH2* at the conserved amino acid sites *IDH1-R132*, *IDH2-R140* and *IDH2-R172* occur in approximately 20% of patients with acute myeloid leukemia (AML).<sup>(1)</sup> A recent analysis of AML patients at our institution identified *IDH1/2* mutations in 20% (n=167) of 826 AML patients, with *IDH1/2* mutations occurring most frequently in the setting of diploid karyotype or other intermediate-risk cytogenetics, particularly trisomy 8 (77% vs 53%,  $p<0.0005$ ). AML patients with *IDH1/2* mutations were overall less likely to have a diagnosis of therapy-related AML (8% vs 17%,  $p=0.003$ ).<sup>(2)</sup>

Compared to their frequency in AML, *IDH1/2* mutations are less common in myelodysplastic syndromes (MDS), occurring in approximately 5% of MDS patients, although an incidence as high as 12% has been reported.<sup>(3–8)</sup> While *IDH1/2* mutations are thought to represent early “driver” events in leukemogenesis with mutational stability over time, reports of *IDH1/2* acquisition at the time of leukemic transformation in patients with myeloproliferative neoplasms and MDS have been described.<sup>(3, 9, 10)</sup>

The purpose of this analysis is to evaluate the overall prevalence of *IDH1/2* mutations in MDS patients treated at our institution, as well as determine the incidence and frequency of *IDH1/2* mutations identified at the time of leukemic transformation in MDS patients.

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Eligible patients comprised all adults with histologically-confirmed MDS treated at M.D. Anderson Cancer Center from January 2010 to January 2015. A total of 1042 MDS patients with known *IDH1* and *IDH2* status were included. From January 2010 to September 2012, *IDH1/2* molecular analysis was performed by high-resolution melting curve analysis followed by Sanger sequencing confirmation (analytical sensitivity: 10–20%) as has been previously described.<sup>(11)</sup> Beginning in September 2012, *IDH1/2* testing was performed within a CLIA-certified next-generation sequencing (NGS) platform (analytical sensitivity: 2.5–5%). Statistical analyses were conducted in SAS v9.0 and significance defined as  $p < 0.05$ . Overall survival (OS) was measured as the time from presentation to date of death or last follow-up, and Progression-free survival (PFS) from presentation to date of death, last follow-up, or date of progression to AML. Informed consent was obtained following institutional guidelines and in accordance with the Declaration of Helsinki.

Of the 1042 MDS patients, 60 patients (5.7%) had *IDH1/2* mutations identified. Specifically, 17 patients (1.6%) were *IDH1-R132* mutated and 43 patients (4.1%) had *IDH2-R140* ( $n=42$ ) or *IDH2-R172* ( $n=1$ ) mutations, respectively. The clinicopathologic characteristics of patients with and without *IDH1/2* mutations are shown in Table 1. Within this cohort, 701 patients (67%) were untreated and 341 (33%) had received systemic MDS therapy prior to presentation. MDS patients with *IDH1/2* mutations had a lower ANC count ( $1.15 \times 10^9/L$  vs  $1.71 \times 10^9/L$ ,  $p=0.02$ ), higher bone marrow blast percentage (6% vs 4%,  $p=0.001$ ), and a trend for higher platelet counts ( $99 \times 10^9/L$  vs  $75 \times 10^9/L$ ,  $p=0.07$ ).

Of the 60 *IDH1/2* mutations, 17 (28%) were present in the very low or low-risk IPSS-R groups, 15 (25%) intermediate, and 27 (45%) in the high or very-high IPSS-R prognostic score categories (Table 1). While the distribution of IPSS-R categories among *IDH1/2*-mutants versus wild-type patients was similar, we identified a conspicuously different underlying pattern of cytogenetics and bone marrow blasts. Consistent with karyotypic patterns in *IDH1/2*-mutant AML,<sup>(2)</sup> the majority of *IDH1/2*-mutant MDS patients demonstrated favorable or intermediate-risk cytogenetics (93%,  $n=56$ ), with diploid karyotype in 60%, isolated trisomy 8 in 10%, and other intermediate cytogenetics in 23%; significantly different than the cytogenetic distribution in the *IDH1/2* wild-type MDS patients ( $p=0.023$ ) as per Table 1. Of interest, there were no MDS patients with an *IDH1/2*-mutation and isolated del(20q), and no *IDH1/2*-mutated patients with the presence of a del(5q) chromosomal abnormality were identified, as also demonstrated by Papaemmanuil et al.<sup>(12)</sup> Only 5% of *IDH1/2*-mutated patients had chromosome 7 abnormalities or complex cytogenetics, compared to 14% of *IDH* wild-type patients (Table 1).

At presentation, *IDH1/2*-mutated patients had higher bone marrow blast percentage than *IDH* wild-type patients (6% vs 4%,  $p=0.001$ ) and were more frequently classified as RAEB1 or RAEB2 morphology. By WHO classification, 55% of *IDH1/2* mutants were classified as RAEB-1 (32%) or RAEB-2 (23%), compared to 42% *IDH* wild-type ( $p=0.051$ ). Additionally, 17% of *IDH*-mutants were classified as CMML-1 or CMML-2. Interestingly while 10 of the 43 (23%) *IDH2*-mutations occurred in CMML patients, no *IDH1* mutations were detected in CMML patients, suggesting a particular genotype-phenotype correlation with *IDH2*-mutations and CMML. As *SRSF2* mutations, which are not analyzed within our molecular panel, are enriched within CMML patients and also frequently co-occur with

*IDH2* mutations, the *IDH2*/CMML association may be related to underlying *SRSF2* co-mutations.<sup>(13, 14)</sup> Notably also, no patients with the WHO classification of MDS with refractory anemia (RA) were *IDH1/2*-mutated, although RA patients comprised 9% of the total MDS cohort.

The frequency of other somatic mutations among *IDH1/2*-mutated versus wild-type patients is displayed in Table 1. No *IDH1/2*-mutated MDS patient also had a *TP53* mutation at presentation, compared to 17% of the *IDH1/2* wild-type MDS cohort ( $p=0.006$ ). While rare overall, no *IDH1/2*-mutated patients had concomitant *FLT3-ITD* or *FLT3-D835* mutation (0% vs 2%,  $p=0.006$ ). Patients with *IDH1/2*-mutations were also significantly less likely to have a *RUNX1* (13% vs 40%,  $p=0.015$ ), *ASXL1* (21% vs 44%,  $p=0.039$ ), or *TET2* mutation (8% vs 35%,  $p=0.008$ ). While *TET2* mutations are frequently thought to be mutually exclusive with *IDH1/2* mutations, 2 patients with *IDH2-R140* mutations did have concurrent *TET2* mutations identified. While the subsets are small, the distribution of *KRAS*, *NRAS*, *JAK2*, *NPM1*, *DNMT3A*, *EZH2* and *CEBPA* mutations were similar between *IDH1/2*-mutated and wild-type patients.

OS among the 701 treatment-naïve MDS patients (including 45 *IDH1/2*-mutants) was 21.2 months; 22.2 months for *IDH1/2*-mutated patients and 21.1 months for *IDH1/2* wild-type patients ( $p=0.67$ ). [Figure 1] Within *IDH1/2* mutants, survival was not different based on *IDH1* vs *IDH2* mutation status; 22.2 months for *IDH1* and 21.0 months for *IDH2* mutants ( $p=0.44$ ). PFS for treatment-naïve MDS patients was 19.9 months (range 0–47.4 months); 22.2 months for *IDH1/2*-mutated and 19.7 months for *IDH1/2* wild-type ( $p=0.77$ ). PFS among patients with *IDH* mutations was similar, 16.9 months in *IDH1*-mutated patients and 17.4 months *IDH2*-mutated patients ( $p=0.18$ ).

Of the 214 treatment-naïve patients receiving HMA therapy for which response assessments are available, 18 (8.4%) had *IDH1/2* mutations [Supplemental Table 1]. No significant difference in the rate of responses was seen based on the presence of *IDH1/2* mutations, with complete remission (CR) in 7 of 18 *IDH1/2*-mutant (39%) versus 63 of 196 (32%) *IDH* wild-type patients ( $p = 0.56$ ). OS was similarly not dependent on *IDH1/2* mutation status in this HMA-treated group, with a median OS of 20.0 months in *IDH1/2*-mutant patients and 15.0 months in *IDH* wild-type patients,  $p = 0.64$  [Supplementary Figure 1].

During the treatment course of the complete  $n=1042$  cohort, 150 MDS patients transformed to AML. This includes 11 of the 60 patients with *IDH1/2* mutation identified at MDS diagnosis (1 *IDH1* and 10 *IDH2*; 18% of *IDH1/2*-mutated patients), and 138 (14%) *IDH1/2* wild-type MDS patients. Additionally, 7 confirmed *IDH1/2* wild-type patients at MDS diagnosis had an identified *IDH1* or *IDH2* mutation at the time of AML transformation ( $n=5$ ) or progression to RAEB-2 MDS ( $n=2$ ; one subsequently progressed to AML within another 6 weeks), with an allelic frequency ranging from 10–37%. Specific details of these 7 patients are provided in Table 2. Of interest, patient #5 had both an *IDH1-R132H* and *IDH2-R140Q* mutation at the time of AML transformation. In the patients with apparent *IDH1/2* acquisition, *IDH1/2*-mutations were detected a median of 1.3 years from original presentation, at the time of disease progression. In these 7 patients, OS was universally poor, with 3 month median OS from time of *IDH1/2* detection. Thus of the 150 MDS patients

transforming to AML, 17 (11.3%) were identified to have an *IDH1/2*-mutation at the time of AML progression.

We acknowledge several study limitations. Given the limits of sequencing technology, we cannot fully rule out the presence of a small *IDH1/2* clone in some MDS patients at presentation, undetected at diagnosis which increased in size at the time of progression, thus more accurately representing clonal expansion rather than molecular acquisition. Additionally, selection bias, including more frequent molecular testing among MDS patients with transformation and proliferative disease in this retrospective study may have exaggerated the overall frequency of *IDH1/2* acquisition. However this is unlikely the case, as only 42 of 150 (28%) MDS patients transforming to AML had repeat comprehensive molecular sequencing performed within 8 weeks of transformation, and thus the frequency of *IDH1/2* acquisition or expansion, particularly in MDS patients with diploid or intermediate cytogenetics, may be even higher than reported.

We have previously reported on the dynamic acquisition of *FLT3* and *RAS* mutations in lower-risk patients at the time of MDS disease progression,<sup>(15)</sup> specifically in 20 of 278 IPSS low or intermediate-1 risk MDS patients, of whom 18 (90%) then transformed to AML. Our findings suggest we can also consider *IDH1/2*-mutations as molecular “drivers” of leukemic transformation in some MDS patients. It will be most interesting to evaluate the efficacy of targeted *IDH*-inhibitors in the secondary/transformed AML setting, specifically whether responding patients revert back to a prior MDS state, or whether complete remissions with full count recovery are attainable. This further advocates a role for rational combination studies of *IDH*-inhibitors with other effective MDS strategies such as hypomethylating agents for these patients.

To conclude, *IDH1/2* mutations were found in 5.7% of MDS patients at presentation; 1.6% *IDH1-R132* and 4.1% *IDH2*-mutated. Only one MDS patient with an *IDH2-R172* mutation was identified, the *IDH2-R140* mutation comprised all other *IDH2*-mutants. The notable low frequency of *IDH1-R132* and *IDH2-R172* mutations is consistent with recent data by Molenaar et al, suggesting *IDH1-R132* and *IDH2-R172* mutations are less frequently involved in the ancestral neoplastic clone.<sup>(10)</sup> *IDH1/2*-mutations occurred more frequently in patients with diploid or other intermediate-risk cytogenetics and RAEB classification by WHO, and were less frequent in patients with *TP53*, *RUNX1*, *ASXL1*, or *TET2* mutations. At the time of leukemic transformation/secondary AML, 11.3% of MDS patients had an *IDH1/2*-mutation identified, suggesting the importance of molecular profiling at the time of progression for optimal characterization and treatment decisions for our patients.

## Supplementary Material

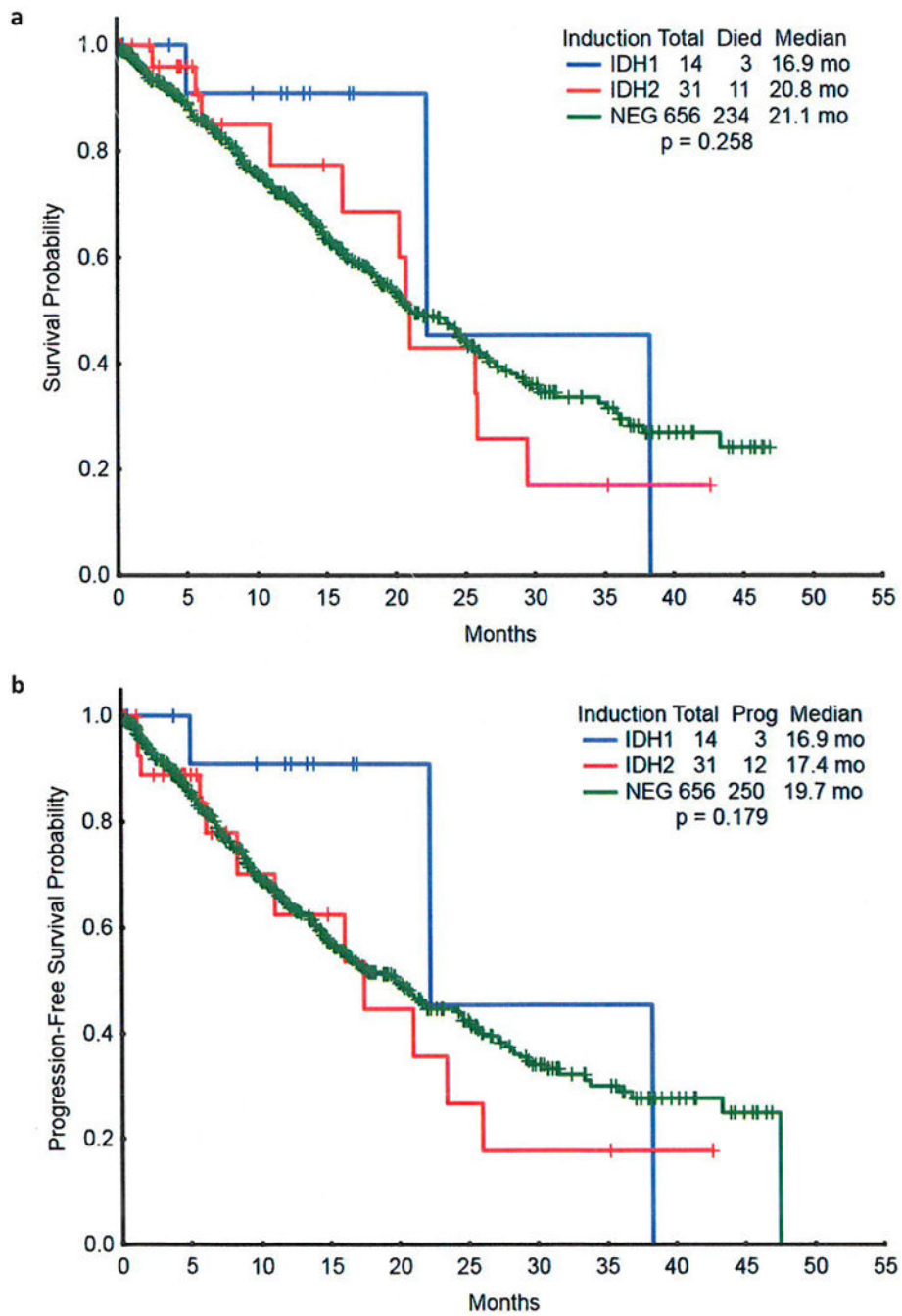
Refer to Web version on PubMed Central for supplementary material.

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**Figure 1.**  
**a:** OS of treatment-naïve MDS patients by *IDH1/2*-mutant versus wild-type  
**b:** PFS of treatment-naïve MDS patients by *IDH1/2*-mutant versus wild-type



**Table 1**

Clinicopathologic characteristics of MDS study cohort (n=1042)

Characteristic	IDH wild-type [n=982]	IDH-mutated [n=60]	p-value	IDH1 Mutated [n=17]	IDH2-Mutated [n=43]	p-value <sup>2</sup>
Median age (range)	70 (17–90)	68 (32–85)	0.36	68 (57–78)	68 (32–85)	0.84
Male sex (%)	642 (65)	44 (73)	0.21	14 (82)	30 (70)	0.32
WBC count (×10 <sup>9</sup> /L)	3.6 (0.4 – 223.1)	2.5 (0.7 – 67.5)	0.12	2.1 (1.2 – 67.5)	3.2 (0.7 – 58.6)	0.08
ANC (×10 <sup>9</sup> /L)	1.71 (0.008–118.3)	1.15 (0.064–60.07)	0.02	0.97 (0.098–60.075)	1.23 (0.064–33.9)	0.31
PLT count (×10 <sup>9</sup> /L)	76 (3–1552)	99 (11–441)	0.07	99 (30–194)	101 (11–441)	0.98
BM Blasts (%)	4 (0–38)	6 (1–18)	0.001	5 (1–18)	7 (1–18)	0.41
PB Blasts (%)	0 (0–29)	0 (0–14)	0.12	0 (0–3)	1 (0–14)	0.006
LDH /	536 (24–9329)	550 (278–2321)	0.37	534 (322–963)	580 (278–2321)	0.37
<b>Cytogenetics: n (%)</b>			0.023			0.97
Diploid or -Y	420 (43)	36 (60)		10 (59)	26 (60)	
Isolated del(5q)	23 (2)	0 (0)		0 (0)	0 (0)	
Double del(5q)	14 (1)	0 (0)		0 (0)	0 (0)	
Complex del(5q)	56 (6)	0 (0)		0 (0)	0 (0)	
Trisomy 8	73 (7)	6 (10)		2 (12)	4 (9)	
-7/7q or complex	135 (14)	3 (5)		1 (6)	2 (5)	
Isolated del(20q)	29 (3)	0 (0)		0 (0)	0 (0)	
Other intermediate	174 (18)	14 (23)		4 (24)	10 (23)	
-Not done, Inad.	58 (6)	1 (2)		0 (0)	1 (2)	
<b>WHO category: n (%)</b>			0.330			0.073
5q-	19 (2)	0 (0)		0 (0)	0 (0)	
CML Ph-	8 (1)	0 (0)		0 (0)	0 (0)	
CMM1-1	100 (10)	6 (10)		0 (0)	6 (14)	
CMM1-2	36 (4)	4 (7)		0 (0)	4 (9)	

Characteristic	IDH wild-type [n=982]	IDH-mutated [n=60]	p-value	IDH1_Mutated [n=17]	IDH2_Mutated [n=43]	p-value <sup>2</sup>
<b>MDS/MPD</b>	23 (2)	1 (2)		1 (6)	0 (0)	
<b>MDS-U</b>	39 (4)	1 (2)		1 (6)	0 (0)	
<b>RA</b>	88 (9)	0 (0)		0 (0)	0 (0)	
<b>RAEB-1</b>	215 (22)	19 (32)		5 (29)	14 (33)	
<b>RAEB-2</b>	199 (20)	14 (23)		4 (24)	10 (23)	
<b>RARS</b>	35 (4)	3 (5)		0 (0)	3 (7)	
<b>RCMD</b>	196 (20)	11 (18)		5 (29)	6 (14)	
<b>RCMD-RS</b>	24 (2)	1 (2)		1 (6)	0 (0)	
<b>IPSS-R</b>			0.792			0.334
<b>Very high</b>	188 (19)	13 (22)		4 (24)	9 (21)	
<b>High</b>	195 (20)	14 (23)		1 (6)	13 (30)	
<b>Intermediate</b>	195 (20)	15 (25)		6 (35)	9 (21)	
<b>Low</b>	247 (25)	12 (20)		4 (24)	8 (19)	
<b>Very low</b>	91 (9)	5 (8)		2 (12)	3 (7)	
<b>N/A</b>	66 (7)	1 (2)		0 (0)	1 (2)	
<b>Molecular</b>						
<b>KRAS/NRAS</b>	73 (8)	7 (12)	0.25	1 (6)	6 (14)	0.37
<b>JAK2</b>	25 (3)	2 (3)	0.76	1 (6)	1 (2)	0.50
<b>FLT3-ITD or D835</b>	21 (2)	0 (0)	0.006	0 (0)	0 (0)	n/a
<b>NPM1</b>	9 (1)	1 (2)	0.54	0 (0)	1 (3)	0.54
<b>TP53</b>	73 (17)	0 (0)	0.006	0 (0)	0 (0)	n/a
<b>RUNX1</b>	24 (40)	3 (13)	0.015	1 (25)	2 (10)	0.41
<b>ASXL1</b>	37 (44)	5 (21)	0.039	2 (50)	3 (15)	0.12
<b>TET2</b>	53 (35)	2 (8)	0.008	0 (0)	2 (10)	0.51
<b>DNMT3a</b>	26 (6)	3 (7)	0.89	1 (7)	2 (6)	0.93
<b>CEBPA</b>	52 (6)	4 (8)	0.64	1 (7)	3 (8)	0.93
<b>EZH2</b>	13 (1)	0 (0)	0.36	0 (0)	0 (0)	n/a

<sup>1</sup> Institutional normal reference range for LDH is 313 to 618 IU/L

<sup>2</sup> p-values < 0.1 are depicted in bold font



Table 2

Clinicopathologic details of patients with IDH1 or IDH2 mutations at progression (n=7)

Age/ Sex	Initial WHO Dx	Cyto	Molecular Testing at Dx	WHO Dx at Progression	Time from Dx to Progression	Genetics at Progression	Status
1 65/M	RAEB-2 (15% blasts)	Diploid	Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2	AML (67% blasts)	2.5 years	IDH2-R1420Q (37% AF) FLT3-ITD DNMT3A R882H Same cyto	Died 3.6 mo from AML dx
2 70/M	RCMD (6% blasts)	+8	Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2	RAEB-2 (15% blasts)	2.1 years	IDH2-R140Q (30% AF) Same cyto	Died 2.7 mo from RAEB-2 dx
3 77/F	RAEB-1 (7% blasts)	Del(5)(q13q33), +6	Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2	AML (28% blasts)	2.3 years	IDH1-R132G (17% AF) TP53-S240R Same cyto	Died 3.0 mo from AML dx
4 81/M	RAEB-1 (7% blasts)	Del(12)(p11.2p13), r(7)(p12q11.2)	Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2	RAEB-2 (10% blasts) (further progressed to AML within 6 wks)	1 year	IDH2-R140Q (10% AF) TP53-E339K Also acquired Del(20)(q11.2q13.3)	Died 3.3 mo from RAEB-2 dx
5 65/F	CMML-2 (15% blasts)	+21	Mutant: NPM1 W288fs *NRAS G12D Wild-type: FLT3, CEBPA, IDH1/2, JAK2	AML (60% blasts)	1.3 years	IDH1-R132H (<10% AF) IDH2-R140Q (12% AF) NPM1 and NRAS still present Same cyto	Died 12 months from AML dx
6 60/M	CMML-1 (6% blasts)	Diploid	Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2, DNMT3A	AML (24% blasts)	6 months	IDH1-R132C (11% AF) JAK2 V617F Same cyto	Died 1.1 mo from AML dx
7 63/F	RAEB-1 (7% blasts)	Complex 50,XX,+2, add(5)(q22),-7,+11,+13,-15,+22	Mutant: TP53 Y234C Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2, DNMT3A	AML (60% blasts)	6 months	IDH2-R140Q (18% AF) TP53 Y234C still present Same cyto	Died 2.0 months from AML dx

\* AF = allelic frequency