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Mutation Profile of Well-Differentiated Thyroid Cancer in Asians

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Recent advances in molecular diagnostics have led to significant insights into the genetic basis of thyroid tumorigenesis. Among the mutations commonly seen in thyroid cancers, the vast majority are associated with the mitogen-activated protein kinase pathway. B-Raf proto-oncogene (*BRAF*) mutations are the most common mutations observed in papillary thyroid cancers (PTCs), followed by *RET/PTC* rearrangements and *RAS* mutations, while follicular thyroid cancers are more likely to harbor *RAS* mutations or *PAX8*/peroxisome proliferator-activated receptor γ (*PPARγ*) rearrangements. Beyond these more common mutations, alterations in the telomerase reverse transcriptase (*TERT*) promoter have recently been associated with clinicopathologic features, disease prognosis, and tumorigenesis in thyroid cancer. While the mutations underlying thyroid tumorigenesis are well known, the frequency of these mutations is strongly associated with geography, with clear differences reported between Asian and Western countries. Of particular interest is the prevalence of *BRAF* mutations, with Korean patients exhibiting the highest rate of *BRAF*-associated thyroid cancers in the world. Here, we review the prevalence of each of the most common mutations in Asian and Western countries, and identify the characteristics of well-differentiated thyroid cancer in Asians.

Keywords: Mutation; Thyroid neoplasms; Asia; Proto-oncogene proteins B-raf; Ret-PTC fusion oncoproteins; Oncogene proteins ras; PPAR gamma; Telomerase

INTRODUCTION

A number of genetic alterations have been shown to play a role in the development of follicular cell-derived thyroid cancer. These point mutations and translocations occur in genes of several important signaling pathways, particularly that of the mitogen-activated protein kinase (MAPK) pathway. The MAPK signaling pathway is a master regulator of numerous cellular processes including division, proliferation, differentiation, adhesion, migration, and apoptosis. B-Raf proto-oncogene (*BRAF*) mutations, *RET*/papillary thyroid cancer (*PTC*) rearrangements, and *RAS* mutations are the most common activators of the MAPK signaling pathway, with significant implications for thyroid tumorigenesis.

BRAF mutations are the most common mutations observed in PTCs, followed by *RET*/*PTC* rearrangements and *RAS* mutations, while follicular thyroid cancers (FTC) are more likely to harbor *RAS* mutations or *PAX8*/peroxisome proliferator-activated receptor γ (*PPARγ*) rearrangements. While all four of these mutations are common worldwide, the prevalence of each mutation type in thyroid cancer varies significantly, particularly between Asian and Western countries, with the prevalence of PTC significantly higher in Asian countries.

Beyond these more common mutations, alterations in the

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telomerase reverse transcriptase (*TERT*) promoter may be predictive of clinicopathologic features, as well as disease prognosis and tumorigenesis in thyroid cancer. Like other common thyroid cancer mutations, the frequency of *TERT* promoter mutations also appear to differ among countries, though the significance of this observation remains limited due to the small number of studies on this mutation having been conducted to date.

In this article, we review the prevalence of each of the most common mutations in Asian and Western countries, and identify the characteristics of well-differentiated thyroid cancer (DTC) in Asians.

BRAF MUTATION

BRAF, located in chromosome 7, is the most commonly mutated gene in thyroid cancers, resulting in potent activation of the MAPK pathway. The most common mutational hotspot in *BRAF* is T1799A in exon 15, conferring a glutamate to valine substitution at amino acid 600 (V600E) in the BRAF protein. *BRAF* V600E is the most common genetic alteration in PTC, exhibiting high prevalence in classic PTC and the tall cell variant, although it is generally rare in the follicular variant. Because *BRAF* mutations can be detected preoperatively in fine needle aspiration biopsy (FNAB) specimens, it is often used in the diagnosis of PTC, and may inform initial treatment strategies. Furthermore, this mutation has emerged as a promising prognostic factor for PTC [1,2], although the prognostic value of this mutation is still inconclusive [3,4].

The overall prevalence of *BRAF* mutations is ~45% (range, 27.3% to 87.1%) [5,6], with prevalence significantly higher in

Table 1. The Prevalence of *BRAF* Mutations in Papillary Thyroid Cancers

Study	Country	Year	PTC
Asian total			6,108/8,884 (68.7)
Hong et al. (2014) [8]	Korea	1995–2003	120/193 (62.2)
Jo et al. (2006) [10]	Korea	2004–2005	102/161 (63.4)
Kim et al. (2009) [6]	Korea	2005–2006	88/101 (87.1)
Kim et al. (2015) [11]	Korea	2008–2012	2,497/3,019 (82.7)
Hong et al. (2014) [8]	Korea	2009–2012	1,792/2,431 (73.7)
Takahashi et al. (2007) [12]	Japan	1956–1993	38/64 (59.3)
Ito et al. (2009) [3]	Japan	1996–2000	242/631 (38.4)
Xing et al. (2013) [2]	Japan	-	33/49 (67.4)
Ito et al. (2014) [13]	Japan	1996–2001	281/766 (36.7)
Guan et al. (2009) [7]	China	1990–2007	639/1,032 (61.9)
Liu et al. (2014) [14]	China	2011–2014	110/182 (60.6)
Lu et al. (2015) [15]	China	2013–2014	121/150 (80.6)
Liu et al. (2005) [16]	Taiwan	1997–2002	49/105 (46.7)
American total			559/1,243 (45.0)
Jung et al. (2014) [9]	USA	1974–2000	81/160 (50.6)
Kim et al. (2006) [17]	USA	2000–2003	34/103 (33.0)
Jung et al. (2014) [9]	USA	2009	70/169 (41.4)
Xing et al. (2013) [2]	USA	-	316/691 (45.7)
Oler et al. (2009) [18]	Brazil	2000–2007	58/120 (48.3)
European total			1,470/3,475 (42.3)
Frasca et al. (2008) [19]	Italy	2002–2005	125/323 (38.6)
Lupi et al. (2007) [20]	Italy	2006	219/500 (43.8)
Basolo et al. (2010) [21]	Italy	2006–2009	473/1,060 (44.6)
Xing et al. (2013) [2]	Italy	-	266/551 (48.3)
Riesco-Eizaguirre et al. (2006) [22]	Spain	2000–2003	28/67 (41.8)
Xing et al. (2013) [2]	Spain	-	28/66 (42.4)
Sykorova et al. (2010) [23]	Czech Republic	1960–2007	81/242 (33.5)
Xing et al. (2013) [2]	Czech Republic	-	71/222 (32.0)
Goutas et al. (2008) [5]	Greece	-	15/55 (27.3)
Musholt et al. (2010) [24]	Germany	1988–2010	122/290 (42.1)
Xing et al. (2013) [2]	Poland	-	42/99 (42.4)

Values are expressed as number/total number (%).
PTC, papillary thyroid cancer.

Asia, especially Korea, relative to Western countries (Table 1) [2,3,5,6,7-24]. Although the mechanisms underlying this difference in *BRAF* mutation frequencies are not well understood, a recent theory suggests that these differences may be associated with higher iodine intake in the Asian populations. Average iodine intakes were 138 to 353 μg/day in the United States [25], 45.3 μg/day in Germany [26], and 226 and 163 μg/day for women and men, respectively, in the United Kingdom [27]. Meanwhile, Japanese and Korean iodine intakes far exceed that of most other countries: 1,565 μg/day in Japan [28] and 479 μg/day in Korea [29]. Furthermore, high iodine intake has been shown to be significantly associated with the occurrence of *BRAF* mutation [7], though exceptions do exist, including lower *BRAF* mutation rates in Japan relative to Korea. One possible explanation for this discrepancy may be that of chronic thyroiditis, which is more prevalent in the Korean population. Incidence of Hashimoto's thyroiditis is strongly correlated with the development of PTC [30]. Because the prevalence of Hashimoto's thyroiditis is high in Korea, this positive correlation may provide an explanation for the high incidence of PTC in this country. However, as Hashimoto's thyroiditis is associated with genetic alterations other than *BRAF* mutations, such as rearrangements of *RAS*, *ERK,* and *RET*/*PTC* [31], the relationship between *BRAF* mutations in PTC and chronic thyroiditis requires further assessment.

While geographic differences in the incidence of *BRAF* mutations are well established, the prevalence of these mutations has changed over time. A recent publication from our laboratory revealed an increase in *BRAF*-associated thyroid cancers from 62.2% to 73.7% over the last two decades in Korea [8]. Similarly, in the United States, the overall prevalence of *BRAF* mutations remained stable for an extended period of time (~46%) but increased sharply from 50.0% to 76.9% in the classic papillary form of PTC over the last four decades [9]. More studies on the changes in the mutational rates and its clinical significance will be needed.

Table 2. The Prevalence of *RAS* Mutations in Well-Differentiated Thyroid Cancers

Study	Country	Year	PTC	FVPTC	FTC
Asian total			9/208 (4.3)	53/193 (27.5)	103/226 (45.6)
Park et al. (1998) [34]	Korea	1995–1996	0/37 (0.0)	-	1/3 (33.3)
Jang et al. (2014) [35]	Korea	1998–2012	-	-	39/85 (45.9)
Kim et al. (2012) [36]	Korea	1999–2004	-	-	11/37 (29.7)
Park et al. (2013) [37]	Korea	2000–2011	-	35/132 (26.5)	-
Jeong et al. (2015) [38]	Korea	2002–2013	-	-	16/35 (45.7)
Lee et al. (2013) [39]	Korea	2011–2012	-	18/54 (33.3)	-
Naito et al. (1998) [40]	Japan	-	2/24 (8.3)	-	-
Fukahori et al. (2012) [33]	Japan	1990–2005	-	-	33/58 (56.9)
Kikuchi et al. (2013) [41]	Japan	-	2/34 (5.9)	-	-
Guo et al. (2014) [42]	China	2010–2011	0/61 (0.0)	0/7 (0.0)	-
Naito et al. (1998) [40]	Taiwan	-	5/10 (50.0)	-	-
Liu et al. (2004) [43]	Taiwan	-	0/42 (0.0)	-	3/8 (37.5)
American total			62/408 (15.2)	68/198 (34.3)	19/52 (36.5)
Namba et al. (1990) [44]	USA	-	3/14 (21.4)	-	-
Garcia-Rostan et al. (2003) [32]	USA	-	-	-	2/19 (10.5)
Nikiforova et al. (2003) [45]	USA	-	-	-	17/33 (51.5)
Zhu et al. (2003) [46]	USA	-	13/76 (17.1)	13/30 (43.3)	-
Jung et al. (2014) [9]	USA	1974–2000	4/149 (2.7)	4/33 (12.1)	-
Rivera et al. (2010) [47]	USA	1980–2002	-	12/47 (25.5)	-
Jung et al. (2014) [9]	USA	2009	42/169 (24.9)	39/88 (44.3)	-
European total			9/81 (11.1)	6/24 (25.0)	17/58 (29.3)
Lemoine et al. (1989) [48]	UK	-	-	-	4/10 (40.0)
Esapa et al. (1999) [49]	UK	-	-	-	4/9 (44.4)
Basolo et al. (2000) [50]	Italy	-	3/31 (9.7)	-	2/5 (40.0)
Vasko et al. (2003) [51]	France	-	-	-	7/34 (20.6)
Di Cristofaro et al. (2006) [52]	France	-	6/50 (12.0)	6/24 (25.0)	-

Values are expressed as number/total number (%).
PTC, papillary thyroid cancer; FVPTC, follicular variant papillary thyroid cancer; FTC, follicular thyroid cancer.

RAS MUTATION

RAS mutations are the second most common genetic alteration in thyroid cancer. The *RAS* gene encodes a family of three isoforms: *NRAS, HRAS,* and *KRAS*. Thyroid neoplasms have been associated with mutations in all three isoforms of the *RAS* gene, although most studies have reported a predominance of *NRAS61*. *RAS* point mutations are commonly observed in FTC, as well as the follicular variant PTC. The frequency of *RAS* mutations in FTC ranges from 10.5% to 56.9% [32,33], and is slightly more common in Asia (45.6%) than in Western countries (36.5% in the Americas, and 29.3% in Europe). In contrast, the frequency of *RAS* mutations in PTC is much lower in Asia (Table 2) [9,32-52]. This low frequency of *RAS* mutations has remained relatively stable over time, which is likely to be due to the lower prevalence of follicular variant PTC in this population. In contrast, a study from the United States reported an increase in the proportion of *RAS* mutation-positive from 2.7% between 1974 and 2000 to 24.9% in 2009, due in part to an increase in the percentage of patients presenting with the follicular variant histology [9].

RAS mutations have been reported in the full spectrum of thyroid neoplasms, limiting the clinical diagnostic value of these mutations. Because it is difficult to differentiate specific types of follicular lesions in thyroid FNAB samples, the diagnostic use of *RAS* mutations in FNAB specimens remains controversial. The prognostic value of *RAS* mutations is also unclear, although some evidence suggests that *RAS*-positive thyroid cancers may be at risk for tumor dedifferentiation, a less favorable prognosis, and metastatic behavior, particularly with regard to bone metastasis [32,33].

RET/PTC REARRANGEMENT

Rearrangements of the *RET* proto-oncogene are commonly seen in PTC, and have been shown to play a role in disease pathogenesis. To date, 13 different types of *RET*/*PTC* rearrangements have been reported, though *RET*/*PTC1* and *RET*/*PTC3* account for more than 90% of all rearrangements. The relationship between radiation exposure and *RET*/*PTC* rearrangement has been established [53,54], with *RET*/*PTC* rear-

Table 3. The Prevalence of *RET/PTC* Rearrangements in Papillary Thyroid Cancers

Study	Country	Year	PTC[a]
Asian total			46/279 (16.5)
Park et al. (1998) [34]	Korea	1995–1996	0/24 (0.0)
Chung et al. (1999) [61]	Korea	1996–1999	4/31 (12.9)
Ishizaka et al. (1989) [62]	Japan	-	1/11 (9.1)
Namba et al. (1991) [56]	Japan	-	0/10 (0.0)
Wajjwalku et al. (1992) [63]	Japan	-	1/38 (2.6)
Motomura et al. (1998) [64]	Japan	1987–1994	4/11 (36.4)
Nibu et al. (2005) [65]	Japan	-	12/40 (30.0)
Lee et al. (1998) [57]	Taiwan	1995–1996	6/11 (54.5)
Lam et al. (1998) [66]	Hong Kong	1996–2000	17/40 (42.5)
Guo et al. (2014) [42]	China	2010–2011	1/63 (1.6)
American total			166/622 (26.7)
Tallini et al. (1998) [67]	USA	-	81/201 (40.3)
Rhoden et al. (2004) [58]	USA	-	18/25 (72.0)
Jung et al. (2014) [9]	USA	1974–2000	12/141 (8.5)
Jung et al. (2014) [9]	USA	2009	4/169 (2.4)
Sugg et al. (1999) [68]	Canada	-	51/86 (59.3)
European total			71/403 (17.6)
Mayr et al. (1998) [59]	Germany	-	8/99 (8.1)
Musholt et al. (2000) [69]	Germany	1988–1999	17/119 (14.3)
Di Cristofaro et al. (2005) [60]	France	1994–2003	9/21 (42.9)
Cinti et al. (2000) [70]	Italy	-	13/69 (18.8)
Elisei et al. (2001) [54]	Italy	-	11/47 (23.4)
Puxeddu et al. (2003) [71]	Italy	1995–1999	13/48 (27.1)

Values are expressed as number/total number (%).
PTC, papillary thyroid cancer.
[a]Post-chernobyl papillary thyroid cancers were excluded.

rangements frequently observed in PTC patients who have received significant doses of external radiation, such as those affected by the Chernobyl nuclear accident. Elevated levels of childhood PTC are well documented in post-Chernobyl contaminated areas, accompanied by a high prevalence of *RET*/*PTC* rearrangements. Rapid proliferation of thyroid cells may account for the high sensitivity to radiation-induced *RET*/*PTC* rearrangements among children, although *RET*/*PTC* rearrangements also occur more frequently in children and young adults not exposed to radiation [55].

The prevalence of *RET*/*PTC* rearrangements in PTC varies widely in different populations (range, 0% to 86.8% [34,53,56]), with significant variability in mutational frequency even within the same geographical regions (0% to 54.5% in Asia [34,56,57], 2.4% to 72.0% in the Americas [9,58], and 8.1% to 42.9% in Europe [59,60]). These discrepancies may be due to the small size of the studies; when this variability is taken into account, the prevalence of *RET*/*PTC* rearrangements in Asia is generally low (16.5%) (Table 3) [9,34,42,54,56-71].

This wide range of the prevalence rates seen in these studies may reflect not only the geographic variability but also the effect of different detection methods. A variety of methods have been used to identify *RET*/*PTC* rearrangements, including reverse transcription polymerase chain reaction methods, Southern blot analysis, and fluorescence *in situ* hybridization. Zhu et al. [72] demonstrated that different detection methods could result in significant variability in the detection of *RET*/*PTC* rearrangement.

PAX8/PPARγ REARRANGEMENT

PAX8/*PPARγ* rearrangements occur as a result of an intrachromosomal translocation between most of the coding sequence of PAX8 (2q13) and the entire coding exons of PPARγ1 (3p25). The fusion gene appears to be an oncogene, and results in production of a *PAX8*/*PPARγ* fusion protein (PPFP). The *PAX8*/*PPARγ* fusion gene is most commonly found in FTC, the follicular variant PTC, and benign follicular adenomas, though the prevalence of these rearrangements varies significantly among studies. The mean frequency in FTC is 5.6% in Asia, 43.8% in the Americas, and 27.4% in Europe (Table 4) [36,38,45,46,73-84]. The low frequency of *PAX8*/*PPARγ* rearrangements in Asia is particularly noteworthy, with one Japanese study failing to identify a single *PAX8*/*PPARγ* rearrangement in FTC [73].

No evidence exists linking *PAX8*/*PPARγ* rearrangements with clinical outcomes in FTC. Multiple studies have reported no correlation between *PAX8*/*PPARγ* rearrangements and clinical variables such as gender, age, tumor size, lymph node me-

Table 4. The Prevalence of *PAX8/PPARγ* Rearrangements in Well-Differentiated Thyroid Cancers

Study	Country	Year	PTC	FVPTC	FTC
Asian total			0/12 (0.0)	-	4/72 (5.6)
Kim et al. (2012) [36]	Korea	1999–2004	-	-	3/31 (9.7)
Jeong et al. (2015) [38]	Korea	2002–2013	-	-	1/35 (2.9)
Hibi et al. (2004) [73]	Japan	1989–2000	0/12 (0.0)		0/6 (0.0)
American total			0/106 (0.0)	0/30 (0.0)	74/169 (43.8)
Nikiforova et al. (2002) [74]	USA	-	-	-	8/15 (53.3)
Nikiforova et al. (2003) [45]	USA	-	-	-	13/33 (39.4)
French et al. (2003) [77]	USA	-	-	-	11/42 (26.2)
Zhu et al. (2003) [46]	USA	-	0/46 (0.0)	0/30 (0.0)	-
Sahin et al. (2005) [75]	USA	1996–2000	-	-	31/54 (57.4)
Giordano et al. (2006) [78]	USA	-	0/51 (0.0)	-	7/13 (53.8)
Nakabashi et al. (2004) [79]	Brazil	-	0/9 (0.0)	-	4/12 (33.3)
European total			0/20 (0.0)	16/89 (18.0)	46/169 (27.4)
Dwight et al. (2003) [80]	Sweden	-	-	-	10/34 (29.4)
Lacroix et al. (2005) [81]	France	-	-	-	4/23 (17.4)
Di Cristofaro et al. (2006) [82]	France	-	0/20 (0.0)	1/12 (8.3)	9/21 (42.9)
Castro et al. (2006) [83]	Portugal	-	-	15/40 (37.5)	12/27 (45.5)
Boos et al. (2013) [76]	Germany	-	-	0/37 (0.0)	6/49 (12.2)
Sahpaz et al. (2015) [84]	Turkey	2001–2012	-	-	5/15 (33.3)

Values are expressed as number/total number (%).
PPARγ, peroxisome proliferator-activated receptor γ; PTC, papillary thyroid cancer; FVPTC, follicular variant papillary thyroid cancer; FTC, follicular thyroid cancer.

tastasis, recurrence, or mortality [74-76].

Despite the lack of clinical associations, *PPARγ* remains an attractive therapeutic target in thyroid cancer. Although PPARγ agonists have shown promising results in both *in vitro* and *in vivo* studies [85,86], the results of these studies have been inconclusive. Larger studies with long-term follow-up will be needed to clarify the efficacy and availability of PPARγ agonists in PPFP thyroid cancer.

TERT PROMOTER MUTATION

Somatic mutations in the *TERT* promoter have been identified in many human malignancies including thyroid cancer. Mutations in the *TERT* promoter have been shown to increase telomerase activity, which protects the telomere repeats from erosion and plays a key role in cellular immortality and tumorigenesis [87]. *TERT* promoter mutations were mainly found in two hotspots, located −124 (chr5: 1,295,228C>T) and −146 bp (chr5: 1,295,250C>T) upstream of the gene transcription starting site. These mutations were recently shown to be more prevalent in aggressive thyroid cancers, and were associated with poor prognosis as well as high-risk clinicopathologic features [88-90]. Therefore, *TERT* promoter mutation has received considerable attention as a novel prognostic biomarker. *TERT* promoter mutations have been shown to coexist with other tumorigenic alterations, such as *BRAF* or *RAS* mutations. Indeed, the coexistence of *BRAF* mutations and *TERT* promoter mutations has been identified as an indicator of the worst prognosis [88,91].

The prevalence of *TERT* promoter mutation exhibits significant variability among countries ranging from 4.2% to 25.5% [89,92] of PTC and 5.9% to 36.4% [91,92] of FTC (Table 5) [88-97]. Among these, the Korean prevalence was noticeably lower than other countries. We analyzed 551 patients with DTC in our institution, with *TERT* promoter mutations identified in 4.5% of patients [92]. Among 222 DTCs treated at the Catholic University of Korea, the overall prevalence of *TERT* promoter mutations was 5.4% [93]. The relatively large proportion of small-size tumors in Korea may account for the low frequency of these mutations relative to other countries. *TERT* promoter mutation assays are difficult to use in routine prognostic testing of DTC, especially in areas where its prevalence is low. Therefore, further studies identifying an optimal subset of *TERT* promoter mutations may be warranted.

CONCLUSIONS

Recent advances in molecular diagnostics have led to significant insights into the genetic basis of thyroid tumorigenesis, including a number of genetic alterations involved in the development of follicular cell-derived cancers having been reported. The frequency of each of these mutations varies significantly among populations, with Asian residents exhibiting significantly different mutational profiles relative to Western countries. Korean populations often exhibit different mutation rates relative to other countries, with *BRAF* mutation rates higher

Table 5. The Prevalence of *TERT* Promoter Mutations in Well-Differentiated Thyroid Cancers

Study	Country	Year	PTC	FTC
Asian total			57/840 (6.8)	15/141 (10.7)
Song et al. (2015) [92]	Korea	1993–2012	18/432 (4.2)	7/119 (5.9)
Jung et al. (2015) [93]	Korea	-	12/222 (5.4)[a]	-
Liu et al. (2014) [91]	China	-	39/408 (9.6)	8/22 (36.4)
American total			91/764 (11.9)	11/79 (13.9)
Liu et al. (2013) [94]	USA	-	30/257 (11.7)	11/79 (13.9)
Xing et al. (2014) [88]	USA	1990–2012	61/507 (12.0)	-
European total			81/686 (11.8)	37/216 (17.1)
Liu et al. (2014) [89]	Sweden	-	13/51 (25.5)	8/36 (22.2)
Wang et al. (2014) [95]	Sweden	1986–2004	25/332 (7.5)	9/52 (17.3)
Melo et al. (2014) [90]	Portugal, Spain	-	22/182 (12.1)	12/70 (17.1)
Muzza et al. (2015) [96]	Italy	-	21/121 (17.4)	8/58 (13.8)
Gandolfi et al. (2015) [97]	Italy	1979–2013	-	-

Values are expressed as number/total number (%).
TERT, telomerase reverse transcriptase; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer.
[a]These data include both FTC and PTC, and are therefore not included in the total results.

than any other country, whereas *RET*/*PTC* and *PAX8*/*PPARγ* rearrangements, and *TERT* promoter mutations, are generally lower. Awareness of the role and prevalence of each mutation may be important for the design of future studies, and may hold promise as either a diagnostic tool or a therapeutic target.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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