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Abstract

Aim: *FOXL2* encodes a forkhead transcription factor which is selectively expressed in the mesenchyme of developing mouse eyelids and in the adult ovarian follicles.[1)] Recent studies have revealed that a somatic *FOXL2* codon 134 mutation (c.402C>G, p.C134W) is a feature shared by over 94-97% of adult GCT, which suggests that is constitutes an early event in their pathogenesis.[2)3)4)5)6)]

To assess whether *FOXL2* p.C134W mutation may play a role in the development of human ovarian tumors in the Japanese, we investigated the *FOXL2* codon 134 mutation and protein expression of inhibin-α, bone morphogenetic protein 2 (BMP2) and follistatin (FST) in Japanese patients with granulosa cell tumor (GCT) of the ovary and other ovarian tumors.

Methods: The study was performed between 2009 and 2012 in around Nagoya, Japan. Enrolled subjects were women with granulosa cell tumor of the ovary (GCT, n=46; 44 adult-type GCT and 2 juvenile-type GCT), surface epithelial-stromal ovarian cancer (n=63), germ cell tumor (n=3) and others (n=2).We analyzed 114 tumor tissues from ovarian tumors, including 44 adult-type and 2 juvenile-type GCT of the ovary and 68

ovarian tumors by DNA sequencing. Immunohistochemistry was also performed in the adult and juvenile GCT tissues by immunostaining inhibin-α, BMP2 and FST.

Results: We found the *FOXL2* p.C134W mutation in 27 out of 44 (61.4%) adult-type GCT of the ovary, but none in other ovarian tumors. Histologically, all of the adult-type GCT sections were positive for inhibin-α, and the expression of BMP2 and FST was detected in 14 of 44 (31.8%) and 0 of 47 (0%), respectively. No significant differences regarding the diagnosed age, preoperative serum CA125 levels, or BMP2 immunopositivity between the *FOXL2* p.C134W mutation-positive and mutation-negative were found in the adult-type GCT patients.

Conclusion: Our findings suggest that *FOXL2* p.C134W mutation-positive adult-type GCT of the ovary may not be as prevalent in the Japanese as compared to the previous data.

Reference

1. Crisponi L, Deiana M, Loi A, et al. The putative forkhead transcription factor FOXL2 is mutatedin blepharophimosis/ptosis/epicanthus inversus syndrome. Nat Genet 2001; 27: 159-166.
2. Shah SP, Kobel M, Senz J, Morin RD, Clarke BA, Wiegand KC, et al. Mutation of FOXL2 in granulosa-cell tumors of the ovary. N Engl J Med 2009; 360: 2719-2729.
3. Kim MS, Hur SY, Yoo NJ, Lee SH. Mutational analysis of FOXL2 codon 134 in granulose cell tumour of ovary and other human cancers. J Pathol 2010; 221: 147-152.

4. Schrader KA, Gorbatcheva B, Senz J, Heravi-Moussavi A, Melnyk N, Salamanca C, et al. The specificity of the FOXL2 c.402C>G somatic mutation: a survey of solid tumors. PLoS One. 2009; 4: e7988.
5. Benayoun BA, Caburet S, Dipietromaria A, Georges A, D'Haene B, Pandaranayaka PJ, et al. Functional exporation of the adult ovarian granulosa cell tumor-associated somatic FOXL2 mutation p.Cys134Trp (c.402C>G). PLoS One 2010; 5: e8789.
6. Rosario R, Araki H, Print CG, Shelling AN. The transcriptional targets of mutant FOXL2 in granulosa cell tumours. PLoS One 2012; 7: e46270.
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