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1 **Letter to the Editor**

2 False hypercortisolemia due to abnormal albumin-cortisol binding in a 3 patient with familial dysalbuminemic hyperthyroxinemia

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5 **Running title:** Hypercortisolemia with FDH

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7 **Key words:** hypercortisolemia, hyperthyroxinemia, albumin

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9 **Authors:**

10 Koki Chiba, M.D.[1)], Hiraku Kameda, M.D., Ph.D.[1)], Aika Miya, M.D., Ph.D.[1)], Hiroshi

11 Nomoto, M.D., Ph.D.[1)], Kyu Yong Cho, M.D., Ph.D.[1)], Akinobu Nakamura, M.D., Ph.D.[1)],

12 Shigeki Jin, Ph.D.[2)], Kotaro Matoba, M.D., Ph.D.[2)], Hideaki Miyoshi, M.D., Ph.D.[1,3)],

13 Tatsuya Atsumi, M.D., Ph.D.[1)]

14 [1]Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and

15 Graduate School of Medicine, Hokkaido University, Sapporo, Japan.

16 [2]Department of Forensic Medicine, Graduate School of Medicine, Sapporo, Hokkaido

17 University, Japan.

18 [3]Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine,

Hokkaido University, Sapporo, Japan.

Author for correspondence: Hiraku Kameda, M.D., Ph.D.

Department of Rheumatology, Endocrinology and Nephrology,

Faculty of Medicine and Graduate School of Medicine,

Hokkaido University Graduate School of Medicine

Contact information

Koki Chiba, ko.chiba419@gmail.com, +81-011-706-5915

Hiraku Kameda, hirarak@gmail.com, +81-011-706-5915

Aika Miya, miyaxgag@gmail.com, +81-090-6874-0078

Hiroshi Nomoto, hnomoto@med.hokudai.ac.jp, +81-090-3117-4775

Kyu Yong Cho, ky9494@gmail.com, +81-090-6266-4785

Akinobu Nakamura, akinbo@huhp.hokudai.ac.jp, +81-090-7654-6586

Shigeki Jin, s-jin@hs.hokudai.ac.jp, +81-011-706-5905

Kotaro Matoba, k-matoba@med.hokudai.ac.jp, +81-011-706-5905

Hideaki Miyoshi, hidemiyoshi2003@yahoo.co.jp, +81-011-706-8192

Tatsuya Atsumi, at3tat@med.hokudai.ac.jp, +81-011-706-5913

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38 **Dear Editor,**

39 The report of familial dysalbuminemic hyperthyroxinemia (FDH) due to Pro^{218} (R218P)

40 mutant albumin that caused hypercortisolemia in Swiss family members by Moran et al.

41 (1) was of great interest to us. FDH subjects with R218P have been reported in Swiss

42 and Japanese families (2)(3), and here, we report to our knowledge the first Japanese

43 FDH case of false hypercortisolemia.

44 A 46-year man, previously diagnosed with FDH due to R218P (TSH 2.2 mU/L, FT3 8.2

45 pmol/L, FT4 >103.0 pmol/L) by genetic testing (3), developed hypercortisolemia with

46 normal adrenocorticotropic hormone (ACTH) level (ACTH 14.2 pmol/L, cortisol 957.3

47 nmol/L) during an investigation for Parkinson's syndrome and was referred to our

48 department for further examination. His cortisol level was 195.9 nmol/L at midnight and

49 411.1 nmol/L after a low dose dexamethasone overnight test. ACTH and cortisol

50 responded to CRH load, although basal and peak cortisol levels were high (976.6 and

51 1487.0 nmol/L, respectively). A high dose dexamethasone overnight test showed

52 suppressed ACTH and cortisol levels, and MRI showed no obvious pituitary adenoma.

53 Despite a significantly high cortisol level, no Cushing signs or metabolic abnormalities

54 were observed and urinary free cortisol was within the normal range (30.7 μg/day),

55 suggesting the presence of factors affecting the laboratory testing. We removed albumin
56 from the patient serum using an immunoprecipitation method (Pierce Direct Magnetic
57 IP/Co-IP Kit; Thermo Fisher Scientific, Waltham, MA, USA) and anti-albumin antibody
58 (Proteintech, Rosemont, IL, USA). Cortisol levels were measured by LC-MS/MS
59 performed using a Dionex Ultimate 3000 liquid chromatography system coupled to a TSQ
60 Quantum Access Max triple stage quadrupole mass spectrometer containing a heated-
61 electrospray ionization (HESI-II) probe (Thermo Fisher Scientific).
62 His serum cortisol decreased by 38% after removing albumin despite unremarkable
63 changes in the controls such as ectopic ACTH syndrome, primary hyperparathyroidism
64 and resistance to thyroid hormone beta (Table 1), suggesting the binding rate of cortisol
65 to mutant albumin in the patient was increased, leading to false hypercortisolemia.
66 R218P causes a missense mutation (G to C) of the same nucleotide, which leads to the
67 replacement of normal Arg218 with a proline. This mutation results in the presence of a
68 restriction site for *Ava*II (4). The presence of R218P is characterized by extremely high
69 concentrations of total T4 compared with other FDH types. Regarding cases of R218P,
70 moderate conformational changes are combined with a concomitant distortion of the
71 helix main chain, which promotes the translation of T4 toward the mutated residue. This
72 closer contact results in very strong T4 binding (5).

In our patient, the binding rate of cortisol to mutant albumin might be increased, leading to false hypercortisolemia, and the degree of cortisol reduction after albumin removal was similar to that of the Swiss case. Our case highlights Japanese individuals with FDH due to R218P mutant albumin develop hypercortisolemia, confirming the results of the Swiss case. More detailed molecular studies on cortisol binding to albumin are required.

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Author Contribution statement

Koki Chiba and Hiraku Kameda wrote the manuscript. Shigeki Jin and Kotaro Matoba measured cortisol levels. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

Author Disclosure Statement

The authors have nothing to disclose.

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Table 1. Cortisol levels after pre/post albumin removal.

Case	Pre-cortisol (nmol/L)	Post-cortisol (nmol/L)	% Change
This study	1117.3	692.5	−38.0
Control 1	1131.1	1087.0	−4.0
Control 2	168.3	231.7	38.7
Control 3	63.5	69.0	8.2

Pre-cortisol: amount of cortisol before removing albumin. Post-cortisol: amount of cortisol measured by LC-MS/MS after removing albumin by immunoprecipitation using an anti-albumin antibody. % Change: percentage change in cortisol before and after albumin removal. Control 1: ectopic ACTH syndrome. Control 2: primary hyperparathyroidism. Control 3: resistance to thyroid hormone beta.