Unraveling the Mechanism Driving Concurrent Pituitary and Thyroid Dysfunction Induced by Immune Checkpoint Inhibitors: HLA-DR15-related Haplotypes Holds the Answer

Key Points

•While immune checkpoint inhibitors (ICIs) are highly effective against various cancers, hormone-related adverse effects remain a major challenge. To address this, Nagoya University Hospital has been conducting a world-leading prospective study for nearly a decade, analyzing hormonal side effects in all patients treated with ICIs.

•This study is the first to demonstrate that hormonal abnormalities in the pituitary gland and thyroid frequently occur together in the same patient. Furthermore, we uncovered the underlying mechanism: a feature known as the HLA-DR15-associated haplotype plays a key role.

•These findings are expected to enable the identification of patients at higher risk for pituitary and thyroid adverse effects before treatment, paving the way for safer and more personalized cancer immunotherapy.

Summary

Researchers at Nagoya University Hospital, led by Dr. Tomoko Kobayashi (Assistant Professor, first author), Dr. Shintaro Iwama (Lecturer, corresponding author), and Professor Hiroshi Arima (corresponding author) of the Graduate School of Medicine, have discovered that immune-related adverse events (irAEs) affecting the pituitary and thyroid glands occur together in the same patient. Furthermore, they identified that this co-occurrence is associated with a patient's immune character: HLA-DR15-related haplotypes.

In this study, the team analyzed hormone-related adverse events in 1,014 patients who received immune checkpoint inhibitors (ICIs) at Nagoya University Hospital since November 2015. The results showed that patients who developed pituitary irAEs had a significantly higher incidence of thyroid irAEs. Among those with both conditions, the HLA-DRB1*15:01 haplotype was more frequent, while patients with only pituitary irAEs more commonly carried the HLA-DRB1*15:02-related haplotype. These findings were further validated in a collaborative study involving cases from affiliated institutions.

This is the first study to demonstrate that specific irAEs co-occur and to identify HLA types associated with this co-occurrence, providing critical

insights into the mechanisms behind irAE clustering. Pituitary and thyroid irAEs require lifelong hormone replacement therapy and, if left untreated, can be life-threatening. By identifying patients at higher risk for these combined adverse effects before treatment, this research paves the way for safer, personalized cancer immunotherapy.

The findings will be published in Cancer Immunology Research, a journal of the American Association for Cancer Research, on February 4, 2026 (Japan time: February 5, 2026).

Research Background

Immune checkpoint inhibitors (ICIs) are cancer immunotherapy drugs that enhance the body's immune response against tumors, and their use has rapidly expanded in recent years. However, activation of the immune system can also lead to immune-related adverse events (irAEs) when it targets the body's own organs. These irAEs can affect multiple systems, including the lungs, gastrointestinal tract, skin, nerves, and muscles, as well as endocrine organs such as the pituitary, thyroid, adrenal glands, pancreas, and parathyroid glands. Among endocrine irAEs, pituitary and thyroid disorders are the most common, but whether they tend to occur together has remained unclear.

Our research team has been conducting a world-leading prospective study for nearly a decade at Nagoya University Hospital, analyzing endocrine irAEs in all patients treated with ICIs. We previously reported an association between pituitary irAEs and the HLA-DR15 haplotype, while thyroid irAEs have been linked to HLA types such as DPB1*02:01. However, no prior studies have examined whether the co-occurrence of these irAEs is associated with specific HLA haplotypes. This study aimed to clarify whether pituitary and thyroid irAEs frequently co-occur and whether such co-occurrence is linked to particular HLA profiles.

Research Results

We prospectively analyzed 1,014 patients who received ICI therapy at Nagoya University Hospital since November 2015, measuring pituitary and thyroid hormone levels and assessing irAE onset. HLA typing was performed in patients who developed pituitary or thyroid irAEs.

Among these patients, 68 developed pituitary irAEs and 128 developed thyroid irAEs. The incidence of thyroid irAEs was significantly higher in patients with pituitary irAEs compared to those without (30.9% vs. 11.3%, $p < 0.001$), and this trend remained consistent across cancer types and ICI regimens.

HLA analysis revealed that DRB1*15:01, DRB1*15:02, and related haplotypes

encoding HLA-DR15 were significantly more frequent in patients with pituitary irAEs compared to the general population. Among thyroid irAE patients, DRB1∗15:01-related haplotypes were also significantly enriched. Furthermore, in pituitary irAE patients, those with co-occurring thyroid irAEs showed a higher prevalence of DRB1∗15:01-related haplotypes (e.g., DRB1∗15:01-DQB1∗06:02-DPB1∗02:01), whereas those with pituitary irAEs alone more frequently carried DRB1∗15:02-related haplotypes (e.g., DRB1∗15:02-DQB1∗06:01-DPB1∗09:01). These findings indicate that the associated HLA haplotypes differ depending on whether thyroid irAEs co-occur.

The results were validated in an independent cohort of 92 pituitary irAE patients from collaborative institutions affiliated with Nagoya University Hospital.

Research Summary and Future Perspective

This study is the first to demonstrate that pituitary and thyroid irAEs significantly co-occur and to identify specific HLA haplotypes associated with this co-occurrence, providing critical insights into the mechanisms underlying irAE clustering. Both pituitary and thyroid irAEs require lifelong hormone replacement therapy and, if left untreated, can be life-threatening. Therefore, predicting their onset is of paramount clinical importance.

Our findings pave the way for personalized cancer immunotherapy: by identifying patients at high risk for combined endocrine irAEs before treatment, clinicians can tailor therapy to minimize risk and ensure safer, individualized care.

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Authors: Tomoko Kobayashi[1], Shintaro Iwama[1], Eri Sugiyama[2,3], Shohei Koyama[2,4], Tetsushi Izuchi[1], Koji Suzuki[1], Takanori Murase[1], Masahiko Ando[5], Hidefumi Inaba[6], Hiroki Izumi[3], Koichi Goto[3], Tomoko Handa[1], Takeshi Onoue[1], Takashi Miyata[1], Mariko Sugiyama[1], Daisuke Hagiwara[1], Hidetaka Suga[1], Ryoichi Banno[7], Yoshiki Akatsuka[8], Hiroyoshi Nishikawa[8, 9, 10], Hiroshi Arima[1], and the Nagoya University related Hospitals group

1 Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, Japan.

2 Department of Immuno-genomic Medicine, Research Institute, National

Cancer Center, Tokyo, /Chiba, Japan.
3 Department of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan
4 Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, Japan.
5 Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan.
6 Department of Physiology, Wakayama Medical University, Wakayama, Japan
7 Research Center of Health, Physical Fitness and Sports, Nagoya University, Nagoya, Japan.
8 Department of Immunology, Nagoya University Graduate School of Medicine, Nagoya, Japan
9 Division of Cancer Immune Multicellular System Regulation, Center for Cancer Immunotherapy and Immunobiology (CCII), Graduate School of Medicine, Kyoto University, Kyoto, Japan.
10 Division of Cancer Immunology, Research Institute/Exploratory Oncology Research and Clinical Trial Center (EPOC), National Cancer Center Japan, Tokyo/Chiba, Japan.

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