Panel (Illumina, San Diego, CA, USA; Fig. 1c,d), which ANNOVAR annotates as severely deleterious. On Sanger sequencing this was a de novo mutation. DNA libraries from the peripheral blood and buccal mucosa were enriched for deep sequencing of ACTA1 using Nextera (Illumina). The same mutation was detected in both the peripheral blood sample (read depth 65/304, 21%) and the buccal mucosa (read depth 56/307, 18%). This suggests that blood samples could predict the mosaic ratio of other somatic tissue. In addition, there is a possibility that the skeletal muscle also has mosaicism. Actin is a highly conserved protein throughout evolution. In addition, the locus of this mutation itself is highly conserved from lamprey to human. A case of autosomal dominant NM has been described, with a different mutation at the same site (c.478G>T, p.G160C).\(^4\) It was unknown which mutation was more pathogenic compared with the present patient and that past case.\(^4\) Although the clinical information for that previous case was unknown, it was described as severe NM.\(^4\) Generally, the phenotype of mosaicism is milder than that of full mutations.\(^5\) The present patient was not thought to have severe NM. That might be because the present patient had a mosaicism. NGS should be the first method of choice to detect low-grade mosaicism and determine its correct ratio.\(^5\) The ratio of mosaicism may predict outcome in patients with NM.

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**Disclosure**

The authors declare no conflict of interest.

**Author contributions**

T.Y. and K.K. designed the study; Y.E. and T.N. performed experiments, collected and analyzed data; T.Y. wrote the manuscript; and K.S. and K.K. gave technical support and conceptual advice. All authors read and approved the final manuscript.

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**Occurrence of Kawasaki disease after simultaneous immunization**

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**Key words** antibody, bacille Calmette–Guérin inoculation site, measles vaccination, mucocutaneous lymph node syndrome, simultaneous immunization.

A recent population-based study has shown that vaccinations did not increase the risk of Kawasaki disease (KD).\(^1\) In contrast, various vaccines, including those against rotavirus, hepatitis B, and influenza, have been suggested to be triggers for KD occurrence.\(^2\) We report a pediatric case of KD that occurred after simultaneous immunization with measles/rubella, varicella, and pneumococcal vaccine, suggesting that the vaccination is associated with KD.

A healthy 14-month-old Japanese girl without any past or family histories had a fever the day after concomitant inoculation (day 1 of illness) with initial measles/rubella (MR), initial varicella, and fourth pneumococcal vaccination. On day 2 of illness, rash/redness appeared around the previous bacille Calmette–Guérin (BCG) inoculation site (Fig. 1a). On day 4 of
illness, she had conjunctival congestion, rash on the trunk, oral-mucosal inflammation, and reddening of palms with C-reactive protein (CRP) 4.2 mg/dL and white blood cell count 18 200/\mu L. On day 5 of illness with persistent fever, she was diagnosed with definite KD on meeting five of the six KD criteria. Given that KD symptoms were resolving with decreasing serum CRP (3.2 mg/dL), aspirin was given on its own without i.v. immunoglobulin. Rash/redness around the BCG inoculation site was still evident, which became a crust on day 11 of illness (Fig. 1b). Echocardiography indicated neither coronary artery sequelae nor heart lesions throughout the clinical course. Antibody analysis on day 6 of illness was as follows: rubella (−), Varicella-Zoster virus (VZV) (−), Epstein–Barr virus (−), and measles immunoglobulin (Ig)G (−)/IgM (+). Rubella, VZV, and measles seroconverted on antibody analysis 3 months after immunization. The parents of the patient provided informed consent for the publication of this report.

Kawasaki disease symptoms in this patient appeared after simultaneous inoculation with MR, varicella, and pneumococcal vaccine. We diagnosed KD based on clinical symptoms and considered that vaccinations might be associated with KD occurrence. We suggest two possibilities to explain this clinical manifestation: triggered by one of the vaccinations, possibly measles, or by a reaction to the simultaneous immunization itself.

First, KD may have been triggered by one of the vaccinations, possibly measles. Vaccination sometimes accompanies/ causes “fever” or “infection-like symptoms”; therefore, we must distinguish KD from short-term accompanying events with vaccination. This patient had rash/redness around the BCG inoculation site. It appeared soon after vaccination and gradually became a crust, and these findings are pathognomonic for KD. Rash/redness followed by crust formation at the BCG inoculation site has been observed in 70% of KD patients aged 3–20 months.⁴ The presence of five of the six KD criteria and this change at the BCG inoculation site were strongly suggestive of KD. In addition, we need to consider that this patient developed measles after immunization. Six days after vaccination, her serum measles antibody titer was elevated: measles IgG (−)/IgM (+). This result, however, is consistent with the reaction caused by measles vaccination. Also, the occurrence of fever soon after vaccination may rule out the possibility of modified measles caused by live vaccination, because this always takes several days to cause fever.

An association between measles or measles vaccination and KD occurrence has been previously reported. In a 6-month-old infant, KD occurred 2 weeks after measles. This suggests that measles triggered the KD through immunoreaction against measles infection.⁵ An earlier report described the isolation of measles virus from a pediatric patient with KD a few weeks after measles vaccination.⁶ Taken together, a possible association between vaccinations (especially measles) and KD occurrence is suggested, although it is still possible, however, that the timing of vaccinations just before the onset of Kawasaki disease was coincidental.

Second, vaccinations other than measles, that is, rubella, varicella, and pneumococcal vaccine, may have been associated with KD occurrence in this case. In particular, simultaneous inoculation may also be a cause of KD. Fever just after vaccination is possibly related to concomitant inoculation. Although simultaneous inoculation was shown not to increase side-effects, it may trigger a stronger immunoreaction, causing fever and KD in this case.

Another point may be noteworthy. The present patient had the onset of KD only 1 day after the immunization: this rapidity/temporality is very limited. According to the review by

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Chang and Islam, only four cases were reported in which KD manifested ≤1 day after immunization, or KD symptoms appeared ≤12 h after the second shot of various vaccines. 2 They speculated that this rapidity of symptom occurrence reflects “antigen sensitization” due to previous exposure to antigens, and is an immune-mediated phenomenon. In the present case, however, only pneumococcal vaccination was the fourth shot, with the remaining vaccines (MR and varicella) being given for the first time.

In conclusion, the present single case supports the suggestion that vaccination triggers KD. Information on cases of KD associated with vaccination should be accumulated to clarify the pathophysiology or etiology of KD.

Disclosure
The authors declare no conflict of interests.

Author contributions
D.M., T.M., M.S., and T.Y. identified the significance of this case report. D.M. and M.S. wrote the manuscript. D.T. provided information on virology. All authors read and approved the final manuscript.

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Canakinumab eliminates resistant familial Mediterranean fever in a Japanese girl

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Key words canakinumab, children, colchicine-resistant familial Mediterranean fever.

Familial Mediterranean fever (FMF) is a systemic autoinflammatory disorder characterized by recurring episodes of fever and serosal, synovial, or cutaneous inflammation.1 FMF is caused by recessively inherited mutations in MEFV, which encodes pyrin, and is believed to be caused by activation of the pyrin inflammasome, as opposed to the NLRP3 inflammasome. Mutations in MEFV are associated with excessive inflammation arising from increased interleukin-1β (IL-1β) production.2 Colchicine, the standard treatment for FMF, decreases the frequency of attacks, improves quality of life, and has been considered the only treatment proven to prevent secondary amyloidosis.3 Unfortunately, colchicine is ineffective in 5–10% of patients with FMF, a situation termed “colchicine-resistant FMF” (crFMF).4 Recently, an IL-1 inhibitor, canakinumab, has emerged as an agent that can improve clinical and laboratory abnormalities, and may represent a safe and effective treatment for crFMF.4 A few reports have described successful canakinumab therapy for children with crFMF in non-Japanese populations. Here, we report the case of a Japanese girl with crFMF who was treated successfully with canakinumab. Written informed consent for publication was obtained from the patient and her parents.

Since the age of 3 years, a 7-year-old Japanese girl had recurrent febrile attacks including abdominal pain lasting 2–3 days and elevated serum C-reactive protein (CRP). She had