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研究成果の刊行に関する一覧表レイアウト（色素異常班）

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Epidemiological study and considerations of primary focal hyperhidrosis in Japan: From questionnaire analysis

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ABSTRACT

Primary hyperhidrosis is a disorder of excessive, bilateral and relatively symmetrical sweating occurring in the palms, soles and axillae regions without obvious etiology. There have been some reports of the epidemiology of primary hyperhidrosis abroad so far, but there has never been any research performed in Japan. We performed a questionnaire survey for people aged 5–64 years who agreed with the purpose of this study at 20 companies or schools, and received 5807 valid responses. From this survey, each prevalence could broken down into 5.33% for primary palm hyperhidrosis, 2.79% for primary plantar hyperhidrosis, 5.75% for primary axillae hyperhidrosis and 4.7% for primary head hyperhidrosis. Patients with severe symptoms were estimated to be approximately 616 000 for primary palmar hyperhidrosis and 2 239 000 for primary axillae hyperhidrosis in Japan. These findings reveal that many patients feel a decreased quality of life because of symptoms of hyperhidrosis every day. However, only 6.2% of the patients had visited medical institutions. Moreover, few patients take appropriate treatment even after visiting the hospital.

Key words: Hyperhidrosis Diseases Severity Scale, Japan, prevalence, primary hyperhidrosis, quality of life, visual analog scale.

INTRODUCTION

Primary focal hyperhidrosis is a disease characterized by bilateral excessive sweating in some parts of the body, such as the palms, soles, axillae, head and face. Sweating occurs from eccrine sweat glands, and excitation of cholinergic sympathetic nerves among autonomic nerves is involved in such sweating. As for the mode of sweating, while thermal sweating which is promoted by elevation of the sensory temperature according to the season and humidity is involved, the characteristic involvement of emotional sweating that reflects factors such as tension and concentration is also noted. It was previously reported that health-related quality of life is equivalent to or worse than that in patients with psoriasis, atopic dermatitis or urticaria.[1] Guidelines for the diagnosis and treatment of hyperhidrosis have been reported by joint facilities in the USA, UK, Germany and Sweden,[2] and also issued in Canada.[3] In Japan, similar guidelines were also developed in 2009.[4] The Japanese guidelines recommend stepwise treatment according to the severity of symptoms, beginning with: (i) topical treatment with aluminum chloride for all areas of any severity; (ii) iontophoresis with tap water for the palmoplantar area of any severity; (iii) botulinum toxin treatment for severe symptom of axillae and palms; and (iv) endoscopic thoracic sympathectomy (ETS) for severe symptoms of the axillae and palms. According to need, medication with anticholinergic drugs or Asian medicines or axillary liposuction is also carried out. However, in Japan, only a limited number of medical facilities are implementing these treatments comprehensively. Under the present circumstances, affected individuals collect information via the Internet and tend to visit cosmetic surgery clinics or esthetic salons without careful consideration.

The aims of the present study were to investigate the prevalence and the severity of primary focal hyperhidrosis (affecting the palms, soles, axillae or head) in Japan, and to review the details of the treatments given to affected individuals.

METHODS

Subjects

We developed a questionnaire requesting that respondents select an answer from among several options provided for each question or enter appropriate numbers. This questionnaire was sent to staff members and students in a total of 20 business enterprises and school facilities located in various parts of Japan, ranging from Hokkaido to Okinawa. The questionnaire was distributed to and recovered from the subjects who gave consent, between 22 December 2009 and

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30 January 2010, to participate in this study. After collecting the questionnaire forms, data were analyzed without allowing identification of the respondents.

Contents of the questionnaire

Respondents who specified sex and age and answered "yes" to the question as to whether sweating caused problems in their daily activities of living proceeded with further questions. Questions included a history of medical consultation, site of the symptoms of hyperhidrosis, family history, the severity and seasons of sweating, treatment regimens and types of hygiene products, complications and past history.

Exclusion criteria

1. Responses in which age data were lacking or unclear were excluded.
2. Responses from individuals aged 0–4 years or 65 years or older, not given or unclear were excluded.
3. Responses from individuals who might have had conditions possibly causing secondary hyperhidrosis were excluded from the analysis of primary focal hyperhidrosis.

Instruments

Hyperhidrosis Disease Severity Scale. The severity of sweating was classified by the Hyperhidrosis Diseases Severity Scale (HDSS)[5] into four grades according to the degree of sweating-derived difficulties in daily living (Table 1). Participants chose the items that most closely represented their subjective symptoms and the frequency of sweating. Participants who chose score 3 or score 4 were considered to have severe hyperhidrosis, and those who chose score 1 or score 2 were considered to have mild or moderate hyperhidrosis.

Hyperhidrosis severity of quantitative observation. Intolerance to sweating does not necessarily correlate with the amount of actual sweating. It is often noticed in daily clinical practice that some individuals can tolerate profuse sweating while others have difficulties in daily living even if sweating is not particularly profuse. In this regard, in this study, subjects were required to assess the amount of their sweating by themselves. The amount of sweating in the palms and soles was classified into three grades according to the following criteria: "slightly visible", "sweat can be seen as water drops" and "sweat drips and falls." The amount of axillary sweating was classified into three grades according to the following criteria: "sweat staining of clothes is not a concern", "sweat can be managed with armpit pads" and "sweat cannot be managed with armpit pads and requires spare clothes". These classes were expressed as mild, moderate or severe (Table 2).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Statistical analysis used two-tailed tests, with a significance level of 5% and expressed as $P < 0.05$, respectively. All differences were regarded as statistically significant at $P < 0.05$.

Ethical considerations

This study was approved by the ethics board of Tokyo Medical and Dental University School of Medicine (receipt no. 681, 22 December 2009). This study was carried out after explaining the purpose of the study to each participant. The cost required for implementation of the study was covered by a 2009 Grant-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare (Project for Research of Intractable Diseases). There were no conflicts of interest associated with this study.

RESULTS

Of the 8250 questionnaire forms sent, 6040 were recovered (recovery rate, 73.2%). Excluding responses meeting exclusion criteria, responses from 5807 individuals (3181 males and 2626 females) with a mean age of 40.2 years (40.6 years in males and 39.2 years in females) were analyzed. Respondents were grouped by 5-year intervals beginning from age 5 to age 64 (Table 3). Because the survey was mostly targeted at students, young individuals between 10 and 20 years of age were predominant among respondents, not reflecting the actual age composition of the Japanese population. Corrections were performed to obtain a provisional estimate of affected individuals.

Exclusion criteria

Participants with secondary hyperhidrosis were excluded from among those who reported that they had hyperhidrosis. Underlying diseases in those with secondary hyperhidrosis, in descending order of frequency, were climacteric disorder (0.31%), thyroid dysfunction (0.21%), hypoglycemia (0.07%),

Table 1. Hyperhidrosis Disease Severity Scale

	How would you rate the severity of your hyperhidrosis?
1	My sweating is never noticeable and never interferes with my daily activities
2	My sweating is tolerable but sometimes interferes with my daily activities
3	My sweating is barely tolerable and frequently interferes with my daily activities
4	My sweating is intolerable and always interferes with my daily activities

Table 2. Hyperhidrosis severity of quantitative observation

Palmoplantar	
Mild	Sweat is slightly visible
Moderate	Sweat can be seen as water drops
Severe	Sweat drips and falls
Axillary	
Mild	Sweat staining of clothing is not worrisome
Moderate	Sweat can treated with armpit pads
Severe	Sweat cannot be treated with armpit pads and requires spare clothing

Table 3. Prevalence and mean age of hyperhidrosis in Japan from questionnaire result

	No. of individuals	Mean age (years)	No. of hyperhidrosis patients and prevalence rate (%)	No. of primary focal hyperhidrosis patients and prevalence rate (%)
All	5807	40.2	810 (13.95)	741 (12.76)
Male	3181	40.6	530 (16.66)	490 (15.4)
Female	2626	39.2	280 (10.66)	251 (9.56)

Age group (years)	No. of individuals (M/F)	No. of hyperhidrosis patients and prevalence rate (%)	No. of primary focal hyperhidrosis patients and prevalence rate (%)
5-9	211 (98/113)	9 (4.27)	9 (4.27)
10-14	1822 (915/907)	119 (6.53)	113 (6.20)
15-19	622 (357/265)	81 (13.02)	77 (12.38)
20-24	263 (129/134)	33 (12.55)	30 (11.41)
25-29	314 (170/144)	82 (26.12)	81 (25.80)
30-34	493 (263/230)	99 (20.08)	95 (19.27)
35-39	642 (370/272)	119 (18.54)	108 (16.82)
40-44	527 (302/225)	100 (18.98)	85 (16.13)
45-49	381 (255/126)	80 (21.00)	71 (18.64)
50-54	241 (166/75)	53 (21.99)	47 (19.50)
55-59	144 (85/59)	13 (9.03)	10 (6.94)
60-64	147 (71/76)	22 (14.97)	15 (10.20)

Primary focal hyperhidrosis patients: persons with hyperhidrosis of palmoplantar or armpits or head without obvious secondary diseases. Hyperhidrosis patients: secondary hyperhidrosis included.

Basedow's disease (0.05%), cerebral infarction (0.03%), acromegaly (0.03%), Parkinson's disease (0.03%) and spinal cord injury (0.02%). None of the respondents had pheochromocytoma or carcinoid tumor. The prevalence rates of diseases that could underlie hyperhidrosis were very low (data not shown).

Backgrounds of respondents with primary focal hyperhidrosis (focusing on prevalence, age, site, sex difference, seasonal symptoms)

The questionnaire survey revealed that participants with primary focal hyperhidrosis involving a certain site (palms, soles, axillae, head) accounted for 12.76% of the total, with the proportion of males being significantly greater (15.4% males vs 9.56% females; $P < 0.05$; Table 3). Among males, 11.43% stated that their fathers had some type of hyperhidrosis, whereas 6.94% reported that their mothers had hyperhidrosis ($P < 0.05$); thus, there were marginally significant sex differences in their parents. The prevalence of primary focal hyperhidrosis by patient age exceeded 10% in an age range of 15–64 years. In particular, the prevalence was approximately 20% in individuals 25–34 years of age, reflecting a substantial proportion of individuals who were aware of their profuse sweating causing a problem in daily living (Table 3).

Next, when the prevalence was analyzed according to the site of sweating, the prevalence of palmar hyperhidrosis was 5.33% (6.35% males and 4.11% females), and the age at onset was 13.8 years (15 years in males and 11.6 years in females; Table 4). The prevalence of plantar hyperhidrosis and age at onset were 2.79% (3.49% in males and 1.94% in females) and 15.9 years (16.6 years in males and 14.4 years in females; Table 4), respectively. The prevalence and age at onset were 5.75% (6.60% in males and 4.72% in females) and 19.5 years (19.8 years in males and 19 years in females) for axillary hyperhidrosis (Table 4), 4.70% (6.95% in males and 1.98% in females) and 21.2 years (21.1 years in males and 21.8 years in females) for head hyperhidrosis (Table 4), and 2.96% (3.93% in males and 1.79% in females) and 21.7 years (21.3 years in males and 22.8 years in females) for hyperhidrosis of other sites (Table 4), respectively. The prevalence tended to be higher in males than females at all sites affected by this disease. Among these diseases, only head and other sites of

Table 4. Prevalence and mean onset age of primary focal hyperhidrosis in Japan

Region of perspiration	No. of individuals	Prevalence rate (%)	Mean onset age (year) (SE)
Palmar	310	5.33	13.8
Male	202	6.35	15 (7.7)
Female	108	4.11	11.6 (7)
Plantar	162	2.79	15.9
Male	111	3.49	16.6 (8.2)
Female	51	1.94	14.4 (7.6)
Axillary	334	5.75	19.5
Male	210	6.60	19.8 (8)
Female	124	4.72	19 (10.4)
Head	273	4.7	21.2
Male	221	6.95	21.1 (10.3)
Female	52	1.98	21.8 (12.7)
Others	172	2.96	21.7
Male	125	3.93	21.3 (10.8)
Female	47	1.79	22.8 (15.1)

SE, standard deviation.

hyperhidrosis in males were significantly more frequent at $P < 0.05$. Age at onset tended to be lower in females with palmar, plantar or axillary hyperhidrosis, whereas age at onset tended to be lower in males with hyperhidrosis of the head or other sites of the body (Table 4). As for seasonal differences in sweating symptoms, patients who had difficulties due to hyperhidrosis were most frequent in summer, accounting for 53%, while 37% of patients had difficulties throughout the year, regardless of the season (data not shown).

Thus, the number of Japanese people with primary focal hyperhidrosis in the age range of 5–64 years is estimated to be approximately 4.931 million for palmar hyperhidrosis, 2.581 million for plantar hyperhidrosis, 5.319 million for axillary hyperhidrosis and 4.348 million for head hyperhidrosis. These estimates were obtained by calculation employing an age-related gradient, based on the population of 92.506 million individuals aged 5–64 years obtained from the estimated population as of 1 October 2008, published on the webpage of the Bureau of Statistics, Ministry of Internal Affairs and Communications.

Clinics, treatments and hygiene products for individuals with hyperhidrosis

The consultation rate of individuals with primary focal hyperhidrosis at medical facilities was 6.3% (5.0% for males and 9.0% for females). It became apparent that males were less likely to seek medical consultation ($P < 0.05$). Patients visited various clinics, with visits to dermatology specialists being most frequent (69%), followed by those of cosmetic surgery (6%), internal medicine (6%), psychosomatic medicine (4%), psychiatry (2%), surgery (2%) and anesthesiology (2%; data not shown).

As for the treatment of primary focal hyperhidrosis, individuals who received no treatment accounted for the greatest proportion (37%) in both males and females. Patients who received topical treatment, such as aluminum chloride solution, accounted for 5.8%, and the corresponding rate was 1.9% for oral medication, 0.4% for Asian medicines, 0.13% for botulinum toxin preparations, 0.13% for psychological therapy and 0.13% for nerve block. The overall percentage of individuals who received some treatment was low, at less than 10%. None of the survey respondents underwent iontophoresis or thoracic sympathetic blockade (data not shown).

Among those with primary focal hyperhidrosis surveyed, nearly half were using commercially available hygiene products, accounting for 47.8% (44.5% for males and 55.4% for females were significantly more frequent at $P < 0.05$). Among these products, the use of deodorants lacking an antiperspirant action was most frequent (34.1%), followed by pads or other items designed to make sweating less noticeable (6.6%). The use of products that have an antiperspirant action was very rare, accounting for only 1.1% of the total (data not shown).

Severity of focal hyperhidrosis (HDSS, VAS)

First, the severity of hyperhidrosis was evaluated using the HDSS, which describes the degree of worrisomeness due to sweating (Table 1). HDSS1 was reported by 5.6% of respondents, whereas the corresponding rate was 47.6% for HDSS2, 34.6% for HDSS3 and 12.2% for HDSS4. Thus, approximately half (46.8%) of the respondents had severe symptoms expressed as score 3 or 4 (Fig. 1). There was no difference in the result between males and females (data not shown). Analysis of the results of HDSS by age group revealed that primary focal hyperhidrosis was severe, expressed as HDSS3 or higher, in more than 40% of respondents across a wide age range covering young adulthood to late middle age (the early 20s to the early 50s; data not shown).

When the severity of the disease was evaluated from the results of self-assessment of the amount of sweating separately for palmar and plantar hyperhidrosis and axillary hyperhidrosis (Table 2), severe cases accounted for 12.5% for palmar and plantar hyperhidrosis and 42.1% for axillary hyperhidrosis (Fig. 2).

In addition, when the degree of difficulty in daily living was evaluated by 10 grades using VAS scores, the score was 4.7 ± 2.5 for males and 4.4 ± 2.3 for females. In relation to the age group, the VAS score was 4 or higher for those in young adulthood to middle age (age 20–49 years; data not shown). The number of respondents experiencing strong worrisomeness in daily living, judged to be a severe condition according to the HDSS, is estimated to be 2.308 million for

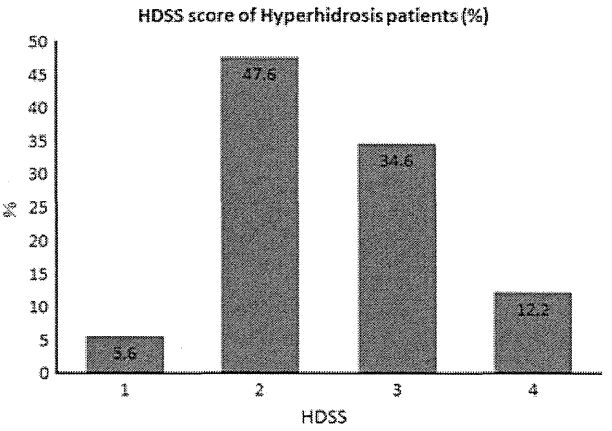

Figure 1. Hyperhidrosis Diseases Severity Scale (HDSS) score of hyperhidrosis patients.

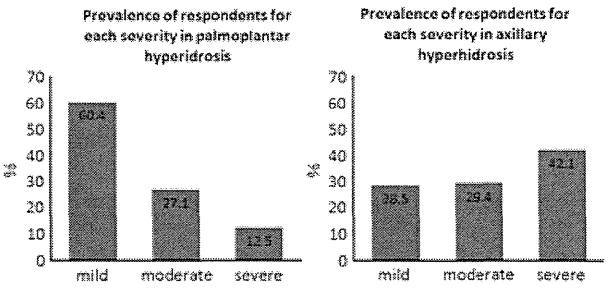

Figure 2. Severity of palmoplantar hyperhidrosis patients (left) and severity of axillary hyperhidrosis patients (right).

palmar hyperhidrosis, 1.635 million for plantar hyperhidrosis and 2.489 million for axillary hyperhidrosis. Among these individuals, those with the most severe excessive sweating are estimated to number 0.616 million for palmar hyperhidrosis, 0.323 million for plantar hyperhidrosis and 2.239 million for axillary hyperhidrosis.

DISCUSSION

The epidemiological profile of primary focal hyperhidrosis has occasionally been reported, and a published work search revealed the prevalence of palmar hyperhidrosis to be 0.6–1% in Israel,[6] 4.36% in China,[7] and the prevalence of axillary hyperhidrosis to be 2.8% in the USA,[8] showing a range of values among reports. In this study, we determined the prevalence rates of primary focal hyperhidrosis in relation to the site involved, namely, palms, soles and axillae, and found that these rates tended to be higher than in previous reports. These prevalence rates are higher than those reported by Strutton *et al.*,[8] who investigated all age groups in the USA. This different rate may be due to the different age range of respondents, diagnostic criteria, different investigating method and geographic disparity. It was suggested that the prevalence of hyperhidrosis is higher among teenage and young adults in South-East Asia.[7] Our survey supports this point of view because it was mostly targeted at students. Consistent with this prevalence rate, the prevalence of primary hyperhidrosis among medical students in Brazil tested by questionnaire 5.5%.[9] A previous epidemiological study carried out in Hawaii found a higher prevalence of palmar and plantar hyperhidrosis among Americans of Japanese origin,[10] suggesting the involvement of race-related differences in genetic background. The results of our present study appear to support the involvement of genetic differences among races. On the other hand, the predominance of individuals 10–20 years of age among the respondents to this questionnaire survey might have been a contributory factor. Because this questionnaire survey covered a large area of Japan including various localities from Hokkaido to Okinawa, we believe that there was no regional bias. In addition, no analysis of regional differences was carried out because the individual data were made unidentifiable for privacy protection prior to the analysis.

However, it was found that only 6.21% of patients visited clinics, presumably reflecting poor awareness of the disease and the psychological state characteristic of patients with this disease, namely, that they are embarrassed or want to conceal the disease. In addition, some medical facilities that dealt with these individuals did not provide treatment. Therefore, respondents who received no treatment accounted for the largest proportion, showing that treatment according to hyperhidrosis guidelines was not implemented sufficiently.

Approximately half of the respondents who did not receive proper treatment, even though they sought medical consultation, used deodorants and pads for axillary sweating or other hygiene products, indicating persistently very low levels of the quality of these individuals' lives. In addition, the fact that this study identified no respondents who had tried iontophoresis or ETS, treatments whose efficacy has been recognized in the guidelines for the treatment of primary focal hyperhidrosis,[4] highlights the current situation in Japan. The provision of proper treatments is far from adequate. The severity of hyperhidrosis measured by HDSS and quantitative observation were almost the same in the patients with axillary hyperhidrosis. In comparison with these data, the severity of palmoplantar hyperhidrosis measured by HDSS was much higher than that measured by quantitative observation, because excessive palmar but not axillary sweating can cause disturbances in social contact, in writing, in manual activities to control and manipulate objects, often rendering these individuals unable to work. On the other hand, excessive axillary sweating does not only disturb these activities but also can be easily treated by axially sweat pad.

Education of patients to raise their awareness of this disease may facilitate more affected individuals seeking medical consultation. For medical facilities, it is important to formulate a system that provides patients with proper treatment chosen from among an extensive range of options based on the spread of guidelines for the diagnosis and treatment of primary focal hyperhidrosis.

CONFLICT OF INTEREST: None declared.

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nature genetics

Mutations in *ADAR1* cause Aicardi-Goutières syndrome associated with a type I interferon signature

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Adenosine deaminases acting on RNA (ADARs) catalyze the hydrolytic deamination of adenosine to inosine in double-stranded RNA (dsRNA) and thereby potentially alter the information content and structure of cellular RNAs. Notably, although the overwhelming majority of such editing events occur in transcripts derived from Alu repeat elements, the biological function of non-coding RNA editing remains uncertain. Here, we show that mutations in *ADAR1* (also known as *ADAR*) cause the autoimmune disorder Aicardi-Goutières syndrome (AGS). As in *Adar1*-null mice, the human disease state is associated with upregulation of interferon-stimulated genes, indicating a possible role for ADAR1 as a suppressor of type I interferon signaling. Considering recent insights derived from the study of other AGS-related proteins, we speculate that ADAR1 may limit the cytoplasmic accumulation of the dsRNA generated from genomic repetitive elements.

Aicardi-Goutières syndrome (MIM 225750) is a genetically determined inflammatory disorder particularly affecting the brain and skin. In its most characteristic form, AGS is a clinical mimic of *in utero*–acquired infection[1] and, like congenital infection, is associated with increased production of the antiviral cytokine interferon α (IFN-α)[2]. AGS can result from mutations in any one of the genes encoding the DNA exonuclease TREX1 (AGS1)[3], the three non-allelic components of the RNase H2 endonuclease complex (RNASEH2B, AGS2; RNASEH2C, AGS3; and RNASEH2A, AGS4)[4] and the deoxynucleoside triphosphate triphosphohydrolase SAMHD1 (AGS5)[5,6]. Although AGS is most typically inherited as an autosomal recessive trait[7], rare examples of disease due to *de novo* dominant mutations in *TREX1* have been reported[8–10].

Studies of the function of TREX1 have delineated a cell-intrinsic mechanism for the initiation of an autoimmune response by interferon (IFN)-stimulatory nucleic acid[11,12], begging the question of the source of nucleic acid inducing the type I IFN–mediated immune disturbance in AGS. In this regard, it has been shown that TREX1 can metabolize reverse-transcribed DNA and that single-stranded DNA derived from endogenous retroelements accumulates in TREX1-deficient cells[11]. On a related note, TREX1 (ref. 13), SAMHD1 (refs. 14–16) and RNase H2 (ref. 17) have been implicated in the metabolism of the (exogenous) retrovirus HIV-1. Perhaps most notably, a recent study showed rescue of the lethal inflammatory TREX1-null mouse phenotype by a combination of reverse transcriptase inhibitors (antiretroviral therapy as used to treat HIV-1)[18], suggesting that the accumulation of cytosolic DNA in TREX1-null cells can be ameliorated by inhibiting endogenous retroelement cycling.

To define other genes relevant to the AGS phenotype, we undertook whole-exome sequencing in four individuals with a clinical diagnosis of AGS, all of whom screened negative for mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C* and *SAMHD1*. Using in-solution hybridization followed by massively parallel sequencing, we derived over 2 Gb of mapped sequence for each subject, such that an average of 56-fold coverage was achieved across the exome for all the samples (**Supplementary Table 1**). We performed an analysis of the called nonsynonymous, splice-site, substitution and coding insertion and/or deletion exome variants under a model of a rare autosomal recessive disorder. Visual inspection of the generated data identified two affected individuals, AGS81_P1 and AGS219,

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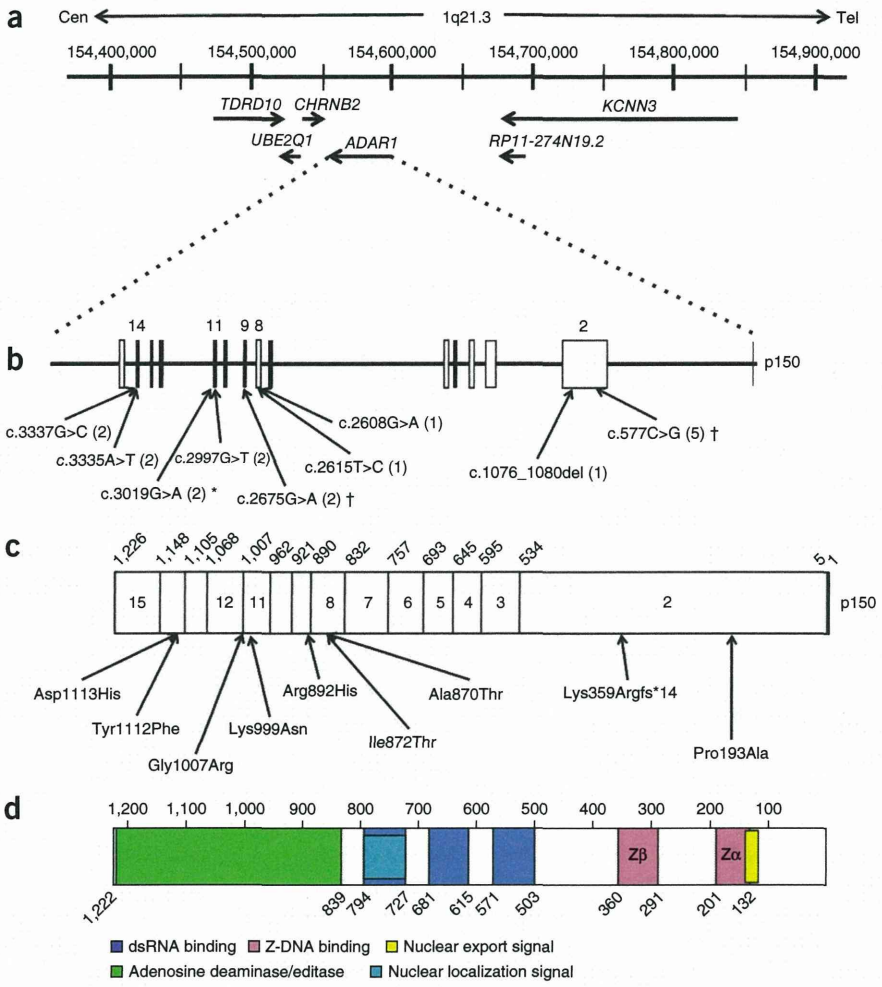

Figure 1 Schematic of the human *ADAR1* gene. (**a**) *ADAR1* spans 26,191 bp of genomic sequence on chromosome 1q21.3 (154,554,533–154,580,724). Neighboring genes are also shown. Cen, centromeric; tel, telomeric. (**b**) Position of identified mutations within the genomic sequence of the *ADAR1* long isoform (p150). The number of alleles with each mutation is shown in parentheses. *, the mutation encoding p.Gly1007Arg identified as a single heterozygous *de novo* change in two families; †, the same mutation identified in identical twins (therefore counted once). Numbers given above the gene indicate the relevant exons (only exons with mutations are numbered). The shorter isoform (p110) of *ADAR1* starts at c.886 of the p150 isoform. (**c**) Position of identified variants within the ADAR1 p150 1,226-amino-acid protein. Numbers above the protein are the amino-acid count at the exon boundaries. The shorter isoform starts at amino acid 296 of p150, giving rise to a 931-amino-acid protein. (**d**) Schematic of the position of protein domains and their amino-acid boundaries in the p150 isoform of ADAR1. Note that the p110 isoform does not include the Zα DNA/RNA-binding domain and nuclear export signal.

who each had two nonsynonymous coding alterations in *ADAR1*, a gene we had already highlighted as a candidate for AGS in view of its known role as a suppressor of type I IFN signaling[19,20]. Sanger sequencing confirmed the variants in these individuals, as well as in two further affected siblings from family AGS81. In light of these data, we proceeded to sequence *ADAR1* in other individuals lacking mutations in *TREX1*, *RNASEH2B*, *RNASEH2C*, *RNASEH2A* and *SAMHD1* (*AGS1–AGS5*, respectively) from our AGS cohort.

In total, 12 affected individuals from 8 families harbored biallelic *ADAR1* variants (**Fig. 1**, **Table 1** and **Supplementary Table 2**), which were considered likely pathogenic on the basis of species conservation (**Supplementary Figs. 1** and **2**) and the output of pathogenicity prediction packages (**Supplementary Table 3**). In these families, all parents tested were heterozygous for one putative mutation. Two further unrelated affected individuals, AGS150 and AGS474, harbored a single mutation encoding p.Gly1007Arg that was not present in either parent. Genotyping of microsatellite markers was consistent with stated paternity, indicating that this variant had arisen *de novo* in both cases (**Supplementary Table 4**). Of the nine distinct *ADAR1* mutations we identified, the c.577C>G (p.Pro193Ala) transversion was seen in the compound heterozygous state in five families of European ancestry. This same variant was observed in 41 subjects (32 of 4,350 European-Americans and 9 of 2,203 African-Americans) annotated on the Exome Variant Server database, whereas none of the other *ADAR1* variants present in our AGS cohort were found in more than 12,000 control alleles.

Table 1 Ancestry, pedigree structure, consanguinity status and sequence alterations in *ADAR1* mutation–positive families in an AGS cohort

Family	Ancestry	Individuals tested	Consanguinity	Nucleotide alteration	Exon	Amino-acid alteration
AGS81	Norwegian	3A, M, F	–	c.[577C>G]+[2675G>A]	2, 9	p.[Pro193Ala]+[Arg892His]
AGS93	Italian	1A, M, F	–	c.[577C>G]+[2608G>A]	2, 8	p.[Pro193Ala]+[Ala870Thr]
AGS107	Pakistani	2A, M, F	+	c.3337G>C (hom)	14	p.Asp1113His
AGS150	Brazilian	1A, M, F	–	c.3019G>A (het, *de novo*)	11	p.Gly1007Arg
AGS219	Pakistani	1A	+	c.3335A>T (hom)	14	p.Tyr1112Phe
AGS228	Indian	1A, M, F	–	c.2997G>T (hom)	11	p.Lys999Asn
AGS251	White British	1A, M	–	c.[577C>G]+[2615T>C]	2, 8	p.[Pro193Ala]+[Ile872Thr]
AGS327	Italian	1A	–	c.[577C>G]+[1076_1080del]	2, 2	p.[Pro193Ala]+[Lys359Argfs*14]
AGS430	Spanish	2A[a], M, F	–	c.[577C>G]+[2675G>A]	2, 9	p.[Pro193Ala]+[Arg892His]
AGS474	European-American	1A, M, F	–	c.3019G>A (het, *de novo*)	11	p.Gly1007Arg

A, affected individual; M, mother; F, father; het, heterozygous; hom, homozygous.
[a]Identical twins.

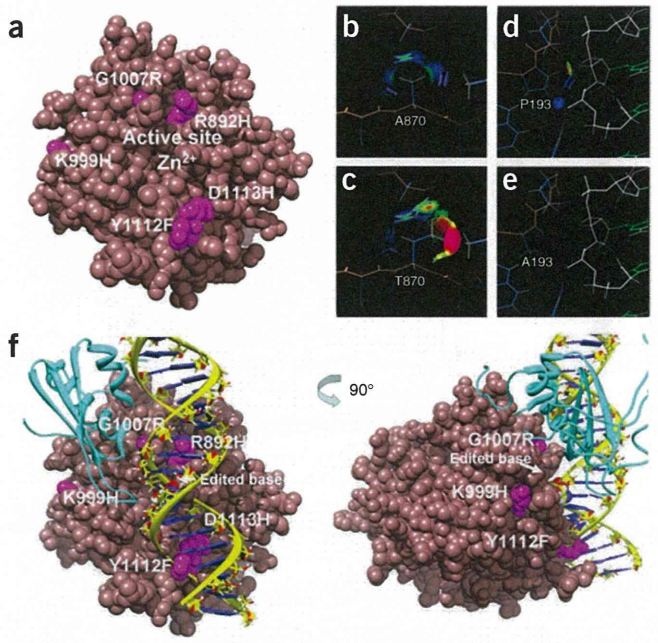

Figure 2 Structural context of ADAR1 protein substitutions. (**a**) The surface of the ADAR domain (dark pink) with surface substitutions highlighted in bright pink. The active site contains a zinc ion (black) in the center. Arg892His, Lys999Asn, Gly1007Arg, Tyr1112Phe and Asp1113His are all on the same side of the domain as the active site, and all have the potential to alter charge and/or hydrogen bonding characteristics of the surface in the region that is likely to be responsible for RNA binding. (**b**,**c**) Models of wild-type (**b**) and mutant (**c**) residues at position 870 in the ADAR domain. Interactions between the residue and the surrounding protein structure are indicated by all-atom contact dots (blue). Green dots represent energetically favorable van der Waals interactions, whereas red and pink spikes indicate unfavorable van der Waals overlaps. The Ile872Thr substitution introduces an unsatisfied hydrogen bond donor/acceptor group, which is destabilizing but not easily depicted. (**d**,**e**) Interactions of the proline residue at position 193 (Pro193) in the Z-DNA–binding domain (**d**). Contact dots (blue, green, yellow) indicate favorable interactions between Pro193 and the DNA backbone (white). These interactions are absent in the mutant form (**e**). (**f**) Modeling of the deaminase domain of ADAR2 suggests contact with dsRBD2 close to Gly1007, highlighting the possibility for an arginine residue to make functionally important polyvalent interactions.

ADARs catalyze the hydrolytic deamination of adenosine to inosine in dsRNA[21]. Four ADARs have been described in mammals (ADAR1, ADAR2, ADAR3 and TENR), although only ADAR1 and ADAR2 are known to have catalytic activity. ADAR1 is encoded by a single-copy gene that maps to human chromosome 1q21. Two main isoforms of ADAR1 are present in mammalian cells: a truncated ADAR1 protein (p110; nucleotide, NM_001025107.2; protein, NP_001020278.1) is constitutively expressed, whereas a full-length form of ADAR1 (p150; nucleotide, NM_001111.4; protein, NP_001102.2) is IFN inducible[22]. Both isoforms have been shown to shuttle between the nucleus and the cytoplasm. ADAR1 is a modular protein with a C-terminal deaminase catalytic domain, three centrally located dsRNA-binding domains (dsRBDs) and one or two N-terminal Z-DNA–binding domains; compared with p110, the p150 isoform of human ADAR1 possesses an additional 295 N-terminal amino acids containing a nuclear export signal and an extra Z-DNA/Z-RNA–binding domain (designated Zα) (**Fig. 1**)[23].

Of the eight amino-acid substitutions identified in our AGS cohort, seven involve residues situated in the catalytic domain of ADAR1 (**Fig. 2**). Five of these seven catalytic domain residues (Arg892, Lys999, Gly1007, Tyr1112 and Asp1113) lie along the surface of the protein that interacts with dsRNA (**Fig. 2a**), and the two others (Ala870 and Ile872) lie internal to the domain structure and are predicted to destabilize the protein (**Fig. 2b**,**c**). In contrast, Pro193 is positioned within the Z-DNA/Z-RNA–binding domain. In the wild-type protein, Pro193 makes direct contact with the nucleic acid, and substitution of this residue with alanine removes important atomic interactions between the protein and DNA/RNA (**Fig. 2d**,**e**).

More than 130 different *ADAR1* mutations (**Supplementary Table 5**) have already been documented in individuals with dyschromatosis symmetrica hereditaria 1 (DSH), an autosomal dominant disorder characterized by the childhood onset of hypo- and hyperpigmented macules on the face and dorsal aspects of the extremities[24,25]. The frequent observation of stop and frameshift *ADAR1* variants in individuals with DSH indicates haploinsufficiency as the likely molecular pathology. However, *ADAR1* missense variants, spread throughout the gene, are also commonly seen in association with the DSH phenotype. All except one of the *ADAR1* mutations recorded in our AGS cohort were missense variants, and protein blotting of lymphoblastoid cells from affected individuals showed normal levels of both the constitutive and IFN-inducible isoforms of ADAR1 (**Fig. 3**). We predict that the proteins containing the amino-acid alterations seen in individuals with AGS act as hypomorphs and that, as in the *Adar1*-null mouse, complete loss of ADAR1 protein activity is embryonic lethal[19].

Of the nine discrete *ADAR1* mutations observed in our AGS cases, only the allele encoding p.Gly1007Arg has been reported previously[26,27]. Uniquely, this mutation was described in two individuals with DSH also demonstrating neurodegeneration with dystonia and intracranial calcification (**Supplementary Table 6**). Using a known ADAR1 editing substrate, miR376-a2, we found that, of six ADAR1 p110 mutants (Ala870Thr, Ile872Thr, Arg892His, Lys999Asn, Gly1007Arg and Asp1113His) expressed following transfection of plasmid constructs into HEK293 cells, only the Gly1007Arg variant showed a significant effect on editing, with levels of editing equivalent to those seen with inactive protein (**Fig. 4a**). Modeling to position the deaminase domain active site at the target adenosine along the dsRNA substrate (**Fig. 2f**) predicts that the deaminase domain also contacts dsRBD2 close to Gly1007. The proximity of Gly1007 to the RNA backbone, and the possibility for an arginine residue to make polyvalent interactions there, suggests a mechanism whereby Arg1007 might confer a dominant-negative effect: by binding more tightly to RNA, the mutant protein could act as a competitive inhibitor of wild-type protein, while being itself catalytically inactive. In keeping with this model, a plasmid expressing Gly1007Arg ADAR1 showed

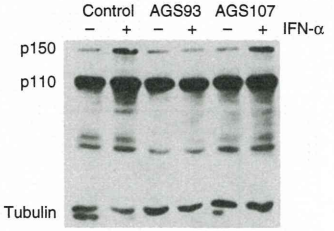

Figure 3 Protein blot of lymphoblastoid cell lines (LCLs). Protein blot analysis of ADAR1 expression in Epstein-Barr virus (EBV)-transformed LCLs from one unrelated control and two affected individuals (AGS93, AGS107). Whole-cell lysates were derived from 1×10^7 cells per sample, and 10 μg of total protein was loaded per lane. To test antibody specificity and confirm IFN induction of the p150 isoform of ADAR1, unstimulated cells were compared to IFN-stimulated cells. The antibody to ADAR1 recognizes both the p110 and p150 isoforms. Immunoblotting of tubulin (50–55 kDa) was used as a loading control.

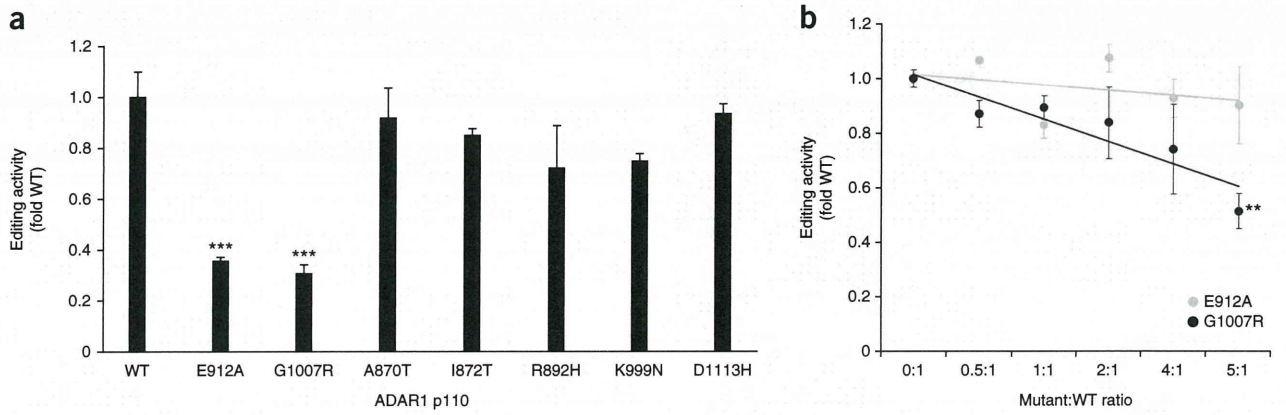

Figure 4 Site-specific and competition editing assays. (**a**) HEK293 cells were co-transfected with 500 ng of a plasmid expressing miR376-a2 and 500 ng of a plasmid expressing wild-type (WT) ADAR1 or ADAR1 mutants. Background editing in HEK293 cells with 500 ng of substrate plasmid is approximately 20%. As previously observed, only one monomer in an ADAR1 dimer is required to be enzymatically active, such that addition of inactive protein initially increases editing[40]. Editing activity is expressed as a proportion of WT ADAR1 editing activity, which is 1 (*y* axis). Error bars, s.e.m. ***$P = 0.0005$. (**b**) Competition between ADAR1 and inactive ADAR1 mutants. HEK293 cells were co-transfected with 200 ng of a plasmid expressing miR376-a2 and 200 ng of a plasmid expressing ADAR1 p110 in the presence of increasing amounts of a plasmid expressing a catalytically inactive form of ADAR1 (Glu912Ala)[28] or Gly1007Arg. Error bars, s.e.m. **$P = 0.0026$.

stronger inhibition of wild-type ADAR1 than equivalent amounts of a plasmid expressing catalytically inactive ADAR1 (**Fig. 4b**). Although these observations might explain the seemingly unique nature of the Gly1007Arg variant, how the other mutations that were tested in our system cause an aberrant phenotype remains unclear at this time. Possible explanations might relate, for example, to non-editing functions of ADAR1 (ref. 28) or to editing substrate[29] or cell type specificity[19].

The recurrent p.Pro193Ala alteration lies in the Zα DNA/RNA-binding domain, thus implicating the IFN-inducible p150 isoform of ADAR1 in the AGS phenotype. Mice lacking ADAR1 die by around embryonic day 12.5 owing to defective hematopoiesis and widespread apoptosis, which are associated with global upregulation of IFN-stimulated genes (ISGs), indicating that ADAR1 acts as a suppressor of type I IFN signaling[19]. In light of these observations, using whole blood from 8 *ADAR1* mutation–positive individuals, we performed quantitative RT-PCR to analyze the mRNA levels of 15 ISGs. Compared to nine controls, all tested individuals with mutations in *ADAR1*, including AGS150 and AGS474 harboring a *de novo* heterozygous allele encoding p.Gly1007Arg, showed a consistent pattern of ISG upregulation (**Supplementary Fig. 3**). We then undertook an analysis of a subset of the 6 most highly expressed ISGs in 10 *ADAR1* mutation–positive AGS cases, 6 sets of parents with heterozygous mutations in *ADAR1* and 18 *ADAR1* mutation–positive individuals with DSH (**Fig. 5** and **Supplementary Table 7**). For the six ISGs assayed, expression was variably higher in AGS heterozygous parents and DSH cases versus controls, whereas individuals with a clinical diagnosis of AGS (due either to biallelic mutations in *ADAR1* or a heterozygous mutation resulting in a p.Gly1007Arg amino-acid substitution) had even higher levels of expression.

The skin lesions typical of DSH have not been described in AGS (they are distinct from AGS-related chilblains)[30], and none of the *ADAR1* mutation–positive AGS cases included in our study had

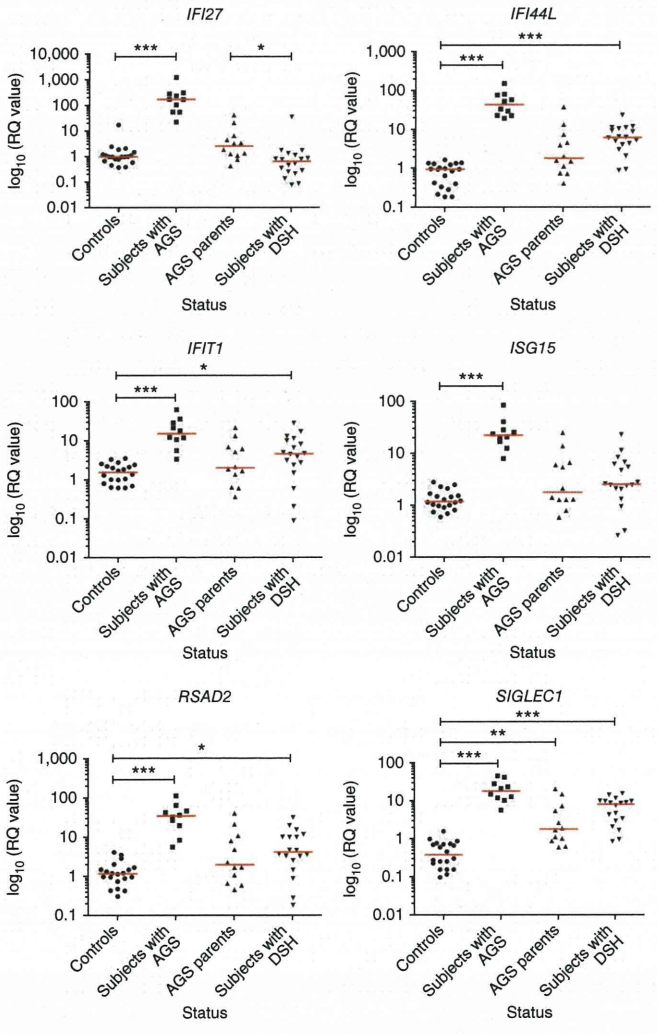

Figure 5 Quantitative RT-PCR of a panel of six ISGs in whole blood measured in individuals with AGS, their parents and individuals with DSH. Scatter plots showing $\log_{10}$-transformed RQ values for a panel of 6 ISGs measured in whole blood from 10 AGS cases with mutations in *ADAR1*, 6 sets of parents heterozygous for mutations in *ADAR1*, 18 individuals with *ADAR1* mutation–positive DSH and 20 healthy controls. All genes were significantly upregulated in AGS cases ($P < 0.001$) compared to controls. RQ is equal to $2^{-\Delta\Delta C_T}$, with $-\Delta\Delta C_T \pm$ s.d., that is the normalized fold change relative to a calibrator. ***$P \leq 0.001$; **$P \leq 0.01$; *$P < 0.05$.