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# Relationship between high trait anxiety in 22q11.2 deletion syndrome and the difficulties in medical, welfare, and educational services

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## Abstract

**Aim:** The 22q11.2 deletion syndrome (22q11DS) is associated with a high prevalence of mental health comorbidities. However, not enough attention has been paid to the elevated prevalence of high trait anxiety that begins early in life and may be enduring. We sought to identify specific medical, welfare, or educational difficulties associated with high trait anxiety in 22q11DS.

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**Methods:** A questionnaire-based survey was conducted for the parents of 22q11DS individuals ($N = 125$). First, a multiple regression analysis was conducted to confirm the hypothesis that high trait anxiety in individuals with 22q11DS would be associated with parents' psychological distress. This was based on 19 questionnaire options regarding what difficulties the parents currently face about their child's disease, characteristics, and traits. Next, we explored what challenges faced in medical, welfare, and educational services would be associated with the trait anxiety in their child.

**Results:** The multiple regression analysis confirmed that the high trait anxiety was significantly associated with parental psychological distress ($\beta = 0.265$, $p = 0.018$) among the 19 clinical/personal characteristics of 22q11DS. Furthermore, this characteristic was associated with various difficulties faced in the medical care, welfare, and education services, and the parent–child relationship.

**Conclusion:** To our knowledge, this is the first study to clarify quantitatively how the characteristic of high anxiety level in 22q11DS individuals is related to the caregivers' perceived difficulties in medical, welfare, and educational services. These results suggest the necessity of designing service structures informed of the fact that high trait anxiety is an important clinical feature of the syndrome.

**KEYWORDS**
22q11.2 deletion syndrome, anxiety, caregiver, educational, medical, welfare

## INTRODUCTION

The 22q11.2 deletion syndrome (22q11DS) is caused by the microdeletion of chromosome 22 with an incidence rate of 1/6000–1/3000.[1] Many individuals with 22q11DS present congenital physical conditions, such as congenital heart disease, characteristic facial features, and immunological problems. Additionally, they often co-develop neurodevelopmental disorders, such as intellectual and learning disabilities, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD), as well as psychiatric disorders, such as anxiety and psychotic disorders.[2,3]

Complications of schizophrenia and developmental disorders have been highlighted in the literature as psychiatric symptoms associated with 22q11DS. The onset of schizophrenia usually occurs during adolescence, with an estimated lifetime prevalence of approximately 20%–25% in 22q11DS patients.[2,3] On the other hand, ADHD and ASD are usually diagnosed in childhood, with an estimated prevalence of 37.1% and 12.8%, respectively.[4]

Although not documented sufficiently, the prevalence of anxiety disorders in children and adolescents with 22q11DS is reportedly 35.6% and 33.9%, respectively.[4] Among these anxiety disorders, specific phobias (17.0%–21.9%), social phobia or social anxiety (9.8%–10.3%), and generalized anxiety disorder (8.3%–10.5%) are the most common in children and adolescents.[4] Previous studies have shown that individuals with 22q11DS have high levels of trait anxiety throughout their lives.[4–7] Additionally, children with 22q11DS are more likely to experience repetitive or chronic stress, including bullying, than typically developing individuals.[8] Schneider and colleagues[9] reported that people with 22q11DS experienced increased negative affect throughout the day and a greater frequency of events that are perceived as unpleasant as compared to controls.

However, a previous study reported that anxiety disorders in individuals with 22q11DS often go undiagnosed and untreated, as only 19% of those participants were diagnosed with an anxiety disorder, even though 58% presented significant anxiety symptom scores.[10] It has been reported that the mental health conditions identified in children with 22q11DS are inadequately treated.[11,12] Furthermore, high levels of anxiety were associated with impaired adaptive functioning,[5,10] and the baseline anxiety symptom was associated with an increased risk of schizophrenia at the 5-year follow-up in 22q11DS children.[13]

It is not yet clear how these anxieties are linked to difficulties faced by individuals and their caregivers in medical, welfare, and education services. However, clarifying this could help to provide better support to the individuals, and alleviate the anxiety and stress levels along the developmental pathway, leading to better social adjustment, reduced risk of psychosis, and reduced burden of care and distress for the family. Accordingly, this study aimed at testing the hypothesis that the presence of high trait anxiety level is associated with parental distress among various perceived difficulties regarding their children's clinical and personal characteristics. Thus, we examined how high trait anxiety was associated with difficulties faced in receiving medical care, welfare, and education services.

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# METHODS

## Development and implementation of the survey

A detailed description of the methodology of our primarily web-based survey is available in our previous studies.[14,15] Briefly, this anonymous online questionnaire survey recorded the challenges and support needs related to medical care, education, and welfare services faced by those affected by 22q11DS. It was developed based on previous literature and clinical guidance,[2,16–18] and with the assistance of two parents caring for an individual with 22q11DS. The final version of the survey questionnaire was divided into 10 domains, as described in detail in our previous study.[15] In this study, we used the data on parental demographics; patient demographics; lifetime diagnosis of comorbidities in individuals with 22q11DS; parental psychological distress; and various challenges faced in medical care, welfare, education services and in the coordination between them and other areas, including child–parent relationships and transition from child to adult medical care. Respondents were instructed to answer "yes" or "no" to each of the questionnaire items as listed in Table 1.

The Kessler 6 Scale (K6), a six-item screening measure for nonspecific psychological distress during the past 30 days,[19] was used for the quantitative measurement of parental psychological distress. The participants rated the items (e.g., "During the past 30 days, about how often did you feel so depressed that nothing could cheer you up?") on a five-point Likert-type scale ranging from 0 (*none of the time*) to 4 (*all of the time*). The final score is a sum of all the response scores, with a possible range of 0–24, and higher scores indicated more severe psychological distress.

The response period was from March 20 to November 8, 2019. Access to the web questionnaire was set up on our research team web page ("22q-pedia"; https://22q-pedia.net/). The survey was publicized to the patients' families by e-mails and/or letters with the help of the Japanese 22q11DS family association (22 HEART CLUB), the Association for the Protection of Children with Heart Disease, and people involved in the medical care of individuals with 22q11DS. Therefore, the recruited population was not defined, and the collection rate could not be calculated. For participants who found it difficult to answer the web questionnaire, a physical form of the questionnaire was mailed to them upon request. Of the 125 valid responses, four were received in the paper questionnaire form.

## Participants

The demographic and clinical information of the individuals with 22q11DS and their parents who participated in the survey were reported in detail in our previous study.[15] A summary of the demographic information and physical, developmental, and psychiatric comorbidities is provided in Table 2.

This study was approved by the Ethics Committee of the Faculty of Medicine, The University of Tokyo (approval No. 2018015NI). The participants expressed their consent to participate in the study by responding to the questionnaires. As a reward for participation, we

**TABLE 1** List of the 83 questionnaire items representing parental difficulties faced in medical care, welfare, education services, and other areas

| | |
|---|---|
| *Perceived challenges in parent–child relationships (4 items)* | |
| 1-1 | Verbal communication |
| 1-2 | Proximity with parents |
| 1-3 | Difficulty becoming independent |
| 1-4 | Defiance or opposition |
| *Perceived challenges in medical care services (12 items)* | |
| 2-1 | Lack of information regarding 22q11.2 deletion syndrome |
| 2-2 | Lack of knowledge on the part of medical staff (doctors, nurses, etc.) regarding 22q11.2 deletion syndrome |
| 2-3 | Attitude of medical staff |
| 2-4 | Lack of explanation from medical staff |
| 2-5 | Difficulty in decision-making with regards to medical care |
| 2-6 | Informing the child of their 22q11.2 deletion syndrome diagnosis |
| 2-7 | Selecting a hospital for treatment |
| 2-8 | Difficulty of going to multiple medical institutions |
| 2-9 | Unable to receive comprehensive treatment due to multimorbidity |
| 2-10 | Difficulty in selecting a hospital for mild diseases/symptoms |
| 2-11 | Individual with 22q11.2 deletion syndrome unable to undergo a consultation by his/herself |
| 2-12 | No medical institution allows parents to come for consultations if the child with 22q11.2 deletion syndrome is unable to undergo a consultation |
| *Perceived challenges in welfare services (21 items)* | |
| 3-1 | Although three disabilities are overlapping (physical, intellectual, and mental), the system (disability certificate, disability pension, etc.) is divided vertically into physical disabilities, intellectual disabilities, and mental disabilities, and the difficulty of overlapping disorders when filing applications has not been considered |
| 3-2 | Unable to receive intractable disease certification |
| 3-3 | Lack of information regarding development-related support, such as rehabilitation |
| 3-4 | Lack of consultants and contacts regarding development-related support, such as rehabilitation |
| 3-5 | Lack of development-related support |
| 3-6 | Lack of information on welfare services |
| 3-7 | Lack of consultants and contacts regarding welfare services |
| 3-8 | Lack of knowledge on the part of supporters (welfare facility personnel and government personnel) regarding 22q11.2 deletion syndrome |
| 3-9 | No welfare facilities suitable for the characteristics and traits of the individual with 22q11.2 deletion syndrome |
| 3-10 | Unable to go to the welfare facility even if one is available |

(Continues)

**TABLE 1** (Continued)

| | |
|---|---|
| 3-11 | Lack of home care/visiting services |
| 3-12 | No support available when parents are exhausted and need a respite |
| 3-13 | Lack of information about employment |
| 3-14 | Lack of consultants and contacts regarding employment support |
| 3-15 | No job opportunities |
| 3-16 | Unable to remain employed for extended periods |
| 3-17 | Lack of understanding in the workplace |
| 3-18 | Lack of help/support in daily life |
| 3-19 | Lack of residences, such as group homes |
| 3-20 | Concerns about marriage |
| 3-21 | Concerns about pregnancy and childbirth |
| *Perceived challenges in education services (25 items)* | |
| 4-1 | Preschool/kindergarten staff were unhelpful |
| 4-2 | Reluctance to attend kindergarten or preschool |
| 4-3 | Lack of information regarding school selection |
| 4-4 | Lack of consultants or contacts regarding school selection |
| 4-5 | No educational institutions suitable for the individual's characteristics/traits with respect to 22q11.2 deletion syndrome |
| 4-6 | Lack of special classes/schools for special needs education |
| 4-7 | Lack of institutions for higher education for individual with 22q11.2 deletion syndrome |
| 4-8 | Lack of home/visiting educational services |
| 4-9 | Regular class teachers were unhelpful |
| 4-10 | Special class teachers were unhelpful |
| 4-11 | Teachers of the schools for special needs education were unhelpful |
| 4-12 | Cannot keep up with school work |
| 4-13 | Difficulty participating in events, such as field days and school festivals |
| 4-14 | Difficulty making friends |
| 4-15 | Refusal to attend school |
| 4-16 | Being bullied |
| 4-17 | What activities to do after school |
| 4-18 | Participating in extracurricular lessons and activities |
| 4-19 | Communicating with the home room teacher |
| 4-20 | Change of home room teacher |
| 4-21 | Lack of knowledge of the school staff (faculty, etc.) regarding 22q11.2 deletion syndrome |
| 4-22 | Lack of understanding of the school staff (faculty, etc.) of the fact that children with 22q11.2 deletion syndrome may need more individual attention than those with ordinary physical or intellectual disabilities |

**TABLE 1** (Continued)

| | |
|---|---|
| 4-23 | Cannot come to an agreement with the school regarding the educational policy for children with 22q11.2 deletion syndrome |
| 4-24 | You (parent/guardian) or your family's anxiety or resistance to selecting a special class or schools for special needs education |
| 4-25 | Anxiety or resistance that the individual feels on selecting a special class or schools for special needs education |
| *Perceived challenges in coordinated support (6 items)* | |
| 5-1 | Lack of coordination between the clinical field (hospitals, etc.) and welfare services (daycare facilities, etc.) |
| 5-2 | Lack of coordination between the clinical field and education services (schools, etc.) |
| 5-3 | Lack of coordination between welfare and education services |
| 5-4 | Lack of consultants or contacts for comprehensive consultations regarding 22q11.2 deletion syndrome |
| 5-5 | Lack of comprehensive support for multimorbidities or disabilities |
| 5-6 | Existing medical, welfare, and educational support services do not fit the individual's characteristics/traits with respect to the 22q11.2 deletion syndrome, and there is no place for them to go |
| *Perceived challenges in transition from child to adult medical care (15 items)* | |
| 6-1 | Individual has not been informed of their diagnosis |
| 6-2 | Lack of understanding of the disease on the part of the individual with 22q11.2 deletion syndrome |
| 6-3 | Selecting a hospital for adult medical care |
| 6-4 | Difficulties accompanying severe physical disorders |
| 6-5 | Primary care physician is unable to address psychiatric symptoms and psychosocial issues |
| 6-6 | Refused treatment by psychiatric departments due to physical disorders and physical symptoms |
| 6-7 | Refused treatment by non-psychiatric departments due to psychiatric disorders and psychiatric symptoms |
| 6-8 | Stress of the need to consult multiple medical institutions |
| 6-9 | Stress of the need to consult multiple clinical departments even in the same hospital |
| 6-10 | Lack of specialized medical institutions |
| 6-11 | Difficulties with coordinating transfers to a different clinical department (within the same hospital) or to a different hospital |
| 6-12 | Differences in atmosphere and response between pediatric and adult medical care |
| 6-13 | When transitioning to adult medical care, co-payment for medical expenses is required, which is a significant financial burden |
| 6-14 | Lack of adult medical institutions offering comprehensive care |
| 6-15 | No particular difficulties |

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**TABLE 2** Descriptive statistics of the study participants

| Parents | | |
|---|---|---|
| Age (years), mean (SD) | 44.3 | (7.5) |
| Mother, *N* (%) | 114 | (91.2) |
| Father, *N* (%) | 11 | (8.8) |
| Annual household income, *N* (%) | | |
| 0–2.99 million yen | 13 | (10.4) |
| 3–5.99 million yen | 36 | (28.8) |
| 6–8.99 million yen | 42 | (33.6) |
| 9–11.99 million yen | 11 | (8.8) |
| 12–14.99 million yen | 13 | (10.4) |
| 15–17.99 million yen | 1 | (0.8) |
| ≧18 million yen | 6 | (4.8) |
| Unknown | 3 | (2.4) |
| Kessler 6 score, mean (SD) | 5.0 | (4.6) |
| Individuals with 22q11.2 deletion syndrome | | |
| Age (in years), mean (SD) | 11.8[a] | (7.7) |
| Male sex, *N* (%) | 63 | (50.4) |
| Total number of lifetime comorbidities, mean (SD) | 4.4 | (1.8) |
| Lifetime comorbidities, *N* (%) | | |
| Congenital heart disease | 106 | (84.8) |
| Immune system disorders | 38 | (30.4) |
| Endocrine disorders | 48 | (38.4) |
| Gastrointestinal diseases | 36 | (28.8) |
| Otorhinolaryngology/maxillofacial diseases | 94 | (75.2) |
| Orthopedic diseases | 51 | (40.8) |
| Growth/developmental disorders | | |
| Intellectual disability | 80 | (64) |
| Autism spectrum disorder | 12 | (9.6) |
| Attention deficit hyperactivity disorder | 8 | (6.4) |
| Oppositional defiant disorder | 1 | (0.8) |
| Learning disability | 22 | (17.6) |
| Speech delay | 73 | (58.4) |
| Selective mutism | 6 | (4.8) |
| Delayed motor development | 55 | (44) |
| Growth disorder/short stature | 34 | (27.2) |
| Other growth/developmental disorders | 6 | (4.8) |
| Psychiatric/neurological disorders | | |
| Schizophrenia | 8 | (6.4) |
| Major depression | 1 | (0.8) |
| Bipolar disorder | 2 | (1.6) |
| Anxiety disorder (including panic disorder) | 13 | (10.4) |
| Obsessive–compulsive disorder | 4 | (3.2) |
| Epilepsy | 19 | (15.2) |
| Other neuropsychiatric disorders | 7 | (5.6) |
| Other | 24 | (19.2) |

Abbreviation: SD, standard deviation.

[a]0–5 years: $n = 33$; 6–11 years: $n = 35$; 12–18 years: $n = 28$; over 19 years: $n = 29$.

distributed prepaid cards equivalent to 5000 yen (approximately 45 USD) in value to each respondent.

## Data analysis

### Analysis I: Confirmation of the hypothesis of significant association between children's high trait anxiety (among many characteristics) and parental distress

For the question, "In supporting your child who has 22q11DS as a family member, what difficulties do you currently face (in the past year) regarding his/her disease, characteristics, and traits?", respondents were instructed to answer "yes" or "no" to the following 19 options, with an additional item for free writing: (1) cardiovascular diseases; (2) repeated infections; (3) hampered motor functions/skills; (4) short stature; (5) articulation disorder (pronunciation/articulation); (6) speech delay; (7) intellectual disability; (8) arithmetic difficulties; (9) difficulty communicating with others; (10) restricted and/or repetitive behavior; (11) temper tantrums; (12) hyperacusis; (13) high trait anxiety; (14) selective mutism; (15) inability to join groups; (16) socially withdrawn; (17) easily tired; (18) hallucinations/delusions; (19) excitement/violence; (20) other (free writing). To test our hypothesis of whether the characteristic of high trait anxiety (Item #13) was significantly associated with parental distress among these 19 items, we conducted a multiple regression analysis (forced entry method). This analysis was conducted using the aforementioned 19 items along with parental gender, parental age, child's gender, child's age, and household income (a total of 24 items) as independent variables, and the parental K6 score as the dependent variable.

### Analysis II: Exploratory analysis for association between children's trait anxiety and various difficulties faced by parents

Next, we determined which of the 83 questionnaire items of the parental difficulties in medical care, welfare, education services, and others (Table 1) were associated with the parents' perceived child's trait anxiety. For this, an exploratory analysis using $\chi^2$ test was conducted to examine whether there was a difference between the groups that answered "yes" ($N = 33$) and "no" ($N = 92$) to "#13: high

**TABLE 3** Summary of 19 items that were significantly different in the $\chi^2$ test comparing groups with and without high trait anxiety.

| Item # | Item | $\chi^2$ | Uncorrected *p* | FDR corrected *p* |
|---|---|---|---|---|
| 1. Perceived challenges in parent–child relationships | | | | |
| 1-1 | Verbal communication | 7.748 | 0.00538 | 0.0241 |
| 1-2 | Proximity with parents | 10.256 | 0.00136 | 0.0103 |
| 1-3 | Difficulty becoming independent | 8.022 | 0.00462 | 0.0226 |
| 1-4 | Defiance or opposition | 9.904 | 0.00165 | 0.0114 |
| 2. Perceived challenges in medical care services | | | | |
| 2-6 | Informing the child of their 22q11.2 deletion syndrome diagnosis | 14.685 | 0.00013 | 0.0026 |
| 3. Perceived challenges in welfare services | | | | |
| 3-8 | Lack of knowledge on the part of supporters (welfare facility personnel and government personnel) regarding 22q11.2 deletion syndrome | 10.984 | 0.00092 | 0.0098 |
| 3-9 | No welfare facilities suitable for the characteristics and traits of the individual with 22q11.2 deletion syndrome | 21.272 | 0.000004 | 0.0003 |
| 3-13 | Lack of information about employment | 9.3 | 0.00229 | 0.0132 |
| 3-15 | No job opportunities | 16.422 | 0.00005 | 0.0021 |
| 3-18 | Lack of help/support in daily life | 9.22 | 0.00239 | 0.0132 |
| 4. Perceived challenges in education services | | | | |
| 4-19 | Communicating with the home room teacher | 13.698 | 0.00021 | 0.0030 |
| 5. Perceived challenges in coordinated support | | | | |
| 5-5 | Lack of comprehensive support for multimorbidity or disabilities | 8.064 | 0.00452 | 0.0226 |
| 5-6 | Existing medical, welfare, and educational support services do not fit the individual's characteristics/traits, and there is no place for them to go | 10.885 | 0.00097 | 0.0098 |
| 6. Perceived challenges in transition from child to adult medical care | | | | |
| 6-2 | Lack of understanding of the disease on the part of the individual with 22q11.2 deletion syndrome | 13.834 | 0.00020 | 0.0030 |
| 6-3 | Selecting a hospital for adult medical care | 10.646 | 0.00110 | 0.0098 |
| 6-5 | Primary care physician is unable to address psychiatric symptoms and psychosocial issues | 10.514 | 0.00118 | 0.0098 |
| 6-10 | Lack of specialized medical institutions | 9.22 | 0.00239 | 0.0132 |
| 6-13 | When transitioning to adult medical care, co-payment for medical expenses is required, which is a significant financial burden | 7.701 | 0.00552 | 0.0241 |
| 6-14 | Lack of adult medical institutions offering comprehensive care | 15.58 | 0.00008 | 0.0022 |

Abbreviation: FDR, false discovery rate.

trait anxiety" for each of the 83 questionnaire items. The false discovery rate (FDR) was used for multiple statistical comparisons.

### Analysis III: Confirmatory logistic regression analysis accounting for confounding factors

Finally, to determine the relationship between the high trait anxiety and parental difficulties accounting for potential confounding factors, binomial logistic regression analysis (forced entry method) was conducted with each item that yielded statistical significance in *Analysis II* (19 items: Table 3), and parental age, parental gender, child's age, child's gender, and household income were used as independent variables, and "#13: high trait anxiety" was the dependent variable. The FDR was used for multiple statistical comparisons.

All statistical analyses were conducted using IBM SPSS Statistics, Version 27.

## RESULTS

### Analysis I

The results of multiple regression analysis showed that *R* was 0.610 and the $R^2$ was 0.372 ($p = 0.001$). Of the 24 variables, the following five were significantly associated with parental psychological distress (K6 score):

**TABLE 4** Summary of binomial logistic regression analysis on relationship between high trait anxiety and each of the 19 items, parental age, parental gender, child's age, child's gender, and household income

| Item # | Item | OR | 95% CI | Uncorrected *p* | FDR corrected *p* |
|---|---|---|---|---|---|
| 1. Perceived challenges in parent–child relationships | | | | | |
| 1-2 | Proximity with parents | 4.067 | 1.496–11.060 | 0.006 | 0.023 |
| 1-4 | Defiance or opposition | 8.241 | 2.246–30.245 | 0.001 | 0.009 |
| 2. Perceived challenges in medical care services | | | | | |
| 2-6 | Informing the individual of their diagnosis with 22q11.2 deletion syndrome | 4.434 | 1.497–13.127 | 0.007 | 0.023 |
| 3. Perceived challenges in welfare services | | | | | |
| 3-8 | Lack of knowledge on the part of supporters (welfare facility personnel and government personnel) regarding 22q11.2 deletion syndrome | 4.429 | 1.632–12.017 | 0.003 | 0.017 |
| 3-9 | No welfare facilities suitable for the characteristics and traits of the individual with 22q11.2 deletion syndrome | 7.463 | 2.621–21.250 | 0.0002 | 0.003 |
| 3-18 | Lack of help/support in daily life | 6.017 | 1.564–23.144 | 0.009 | 0.024 |
| 4. Perceived challenges in education services | | | | | |
| 4-19 | Communicating with the home room teacher | 14.125 | 3.036–65.727 | 0.001 | 0.007 |

Abbreviations: CI, confidence interval; FDR, false discovery rate; OR, odds ratio.

child's gender ($\beta = -0.215$, $p = 0.018$), hampered motor functions/skills ($\beta = 0.196$, $p = 0.047$), high trait anxiety ($\beta = 0.265$, $p = 0.018$), inability to join groups ($\beta = -0.266$, $p = 0.013$), and excitement/violence ($\beta = 0.252$, $p = 0.013$). These results confirmed that the characteristic of high anxiety of the children was significantly related to the difficulties that the family encountered in supporting them.

## Analysis II

The $\chi^2$ tests for the 83 items indicated that 19 items showed a statistical significance (FDR-corrected $p < 0.05$) (Table 3).

## Analysis III

Finally, the binomial logistic regression analysis indicated that seven items showed statistical significance (FDR-corrected $p < 0.05$) (Table 4).

# DISCUSSION

To our knowledge, this study is the first to clarify quantitatively how high trait anxiety in 22q11DS is related to the parents' perceived difficulties in medical, welfare, and educational services. Among the various characteristics of 22q11DS, we confirmed that high trait anxiety was significantly associated with parental psychological distress. Furthermore, high trait anxiety was associated with various difficulties encountered in medical care, welfare, education services, coordination between these services, and the parent–child relationship.

In terms of difficulties related to medical care services, the problem of disclosing their child's diagnosis of 22q11DS to the child was related to the anxiety characteristics of the children. It is possible that parents are concerned about how the disclosure of the diagnosis would distress their child with high trait anxiety levels. A previous study conducting an online survey revealed that parents who have children with 22q11DS reported that the diagnosis experience was negative and often accompanied by a lack of support and appropriate information.[20] Moreover, in the parent–child relationship, the fact that defiance and proximity with parents were statistically significant in this study may be related to the difficulties associated with the disclosure of 22q11DS diagnosis. Previous studies have reported that parents were concerned about disclosing the diagnosis to the child, and they needed information on when, at what level, and how to disclose this.[21] In Japan, there is a lack of genetic counseling specialists, and this issue needs to be addressed in the future.

In terms of difficulties related to welfare services, it was suggested that there is a relationship between the individual's adjustment to social life and anxiety characteristics, such as a lack of welfare facilities and workplace that match the individual's characteristics and traits, and lack of help and support in daily life. In response to these situations, inadequate knowledge about 22q11DS among the supporting services (welfare service staff, administrative staff, etc.) may make it difficult to provide better support, thus creating a vicious circle between children's anxiety, social maladjustment, and parent's distress due to perceived lack of appropriate support.

In terms of difficulties related to education services, difficulty in communication with the teacher in charge was observed. There is a possibility that teachers do not understand the severity of the child's anxiety as a medical characteristic and impose the stereotype in the education of children with typical development or those with single disability (physical or intellectual) that the social anxiety and fear should be overcome through school life. Cutler-Landsman[22] suggested that the educational staff needs to be informed about the syndrome so they can understand the risk of too much pressure, for which our study may provide empirical evidence.

In terms of difficulties related to the parent–child relationship, defiance and proximity with parents were significant. The mismatch between anxiety as a characteristic and the social environment and structure of medical care, welfare, education, and so forth designed for the majority of children may lead to further avoidance, closer parent–child relationships, and rebellious attitudes within the family.[22] Furthermore, previous research[9] showed that adults with 22q11DS spend significantly more time with those closest to them than healthy controls, which suggests that there is a high burden on the families of individuals with severe trait anxiety.

## Limitations

This study has some methodological limitations. First, there is the issue of the representativeness of the target population. Information for the survey was disseminated through family associations and websites, and individuals presenting different demographic and clinical characteristics responded from all over Japan. However, since the author's group is the only one in Japan that operates a specialized psychiatric outpatient clinic for 22q11DS patients, it is possible that individuals with greater difficulties and needs than those with the standard syndrome characteristics in Japan had participated in the study. Second, the interviews were conducted with family members, and the answers were mainly provided by mothers. Conducting interviews and questionnaire surveys for individuals with 22q11DS on a large scale is difficult due to intellectual limitations and high anxiety and tension in interpersonal situations; however, this should be addressed in future investigations. Third, related to the second limitation, children's anxiety may reflect at least in part a projection of their parents' anxiety, which should be carefully considered when interpreting the results of our findings. Fourth, our study was cross-sectional and the causal relationship in the strict sense was not clear. Finally, we did not assess the parental own diagnosis of 22q11DS, although unlikely being the case for many, and thus could not control the potential effect of the possibility that parents and their child may share the challenges and that parental stress may be elevated due to parents' own challenges.

## CONCLUSION

This study clarified the situations and circumstances in which 22q11DS individuals with severe trait anxiety and their caregivers face difficulties. These results suggest the necessity of reconstructing service structures to more "anxiety-informed" ones, where it is important to provide person-centered places and services that match the characteristics and features of each individual, rather than conforming them to existing uniform services.

### AUTHOR CONTRIBUTIONS

Naomi Nakajima, Miho Tanaka, Akiko Kanehara, Ryo Morishima, Yousuke Kumakura, Noriko Ohkouchi, Junko Hamada, Tomoko Ogawa, Hidetaka Tamune, Mutsumi Nakahara, Kayo Ichihashi, Seiichiro Jinde, Yukiko Kano, Kyoko Tanaka, Yoichiro Hirata, and Kiyoto Kasai conceptualized and designed the study. Akiko Kanehara, Ryo Morishima, Yousuke Kumakura, Junko Hamada, Ichiro Sakamoto, Kyoko Tanaka, Yoichiro Hirata, Hirofumi Ohashi, Tokuko Shinohara, and Kiyoto Kasai acquired the data. Naomi Nakajima, Miho Tanaka, Akiko Kanehara, Ryo Morishima, Shunsuke Mori, and Kiyoto Kasai analyzed the data. Naomi Nakajima and Kiyoto Kasai drafted the manuscript. All authors participated in result interpretation; moreover, they reviewed and approved the final version of the manuscript.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

The availability of the data in this study is not open access due to the provisions of the ethics committee and the extent of the participants' consent. If readers wish to apply for the use of data, they must contact the corresponding author and consult the Ethics Committee, Faculty of Medicine, The University of Tokyo.

## ETHICS APPROVAL STATEMENT

This study was approved by the Ethics Committee of the Faculty of Medicine, The University of Tokyo (approval No. 2018015NI). The participants expressed theirconsent to participate in the study by responding to the questionnaires.

## PATIENT CONSENT STATEMENT

The participants expressed their consent to participate in the study by responding to the questionnaires.

## CLINICAL TRIAL REGISTRATION

N/A

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