厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

黄斑ジストロフィに関する研究

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研究要旨
今回我々は、網膜色素変性で進められている患者レジストリシステムを利用して黄斑ジストロフィの患者レジストリを開始した。また、昨年度の調査で解析した日本における黄斑ジストロフィの患者数調査の結果を英文論文にまとめて国際紙に発表した。さらに、代表的な黄斑ジストロフィであるABCA4に病的バリアントを有するスタルガルト病においては、多施設共同研究で63人の患者の遺伝型と臨床像を解析し、遺伝子型がtruncation/ truncationの患者ではより重症な臨床像を示すことが確認された。また難病のホームページをわかりやすく改変し、患者とその家族の利便性を向上させた。

A．研究目的

(1) 網膜色素変性で進められている患者レジストリシステムを利用して、黄斑ジストロフィにおいても患者レジストリを開始し、このレジストリを用いて日本における黄斑ジストロフィの臨床調査および将来の治療研究に役立てること。

(2) 昨年度の調査で解析した日本における黄斑ジストロフィの患者数調査の結果を英文論文にまとめて国際紙に発表すること。

(3) 黄斑ジストロフィの患者レジストリを用いて、小児期から青年期に発症する代表的な黄斑ジストロフィであるスタルガルト病の日本における遺伝子型と表現型の関連を明らかにすること。

(4)難病のホームページ（指定難病 301）を更新し、患者およびその家族に疾患の情報をわかりやすく伝えること。

B．研究方法

(1) これまで我々の研究班においては、網膜色素変性グループ（G2）では難病プラットフォームシステムを使用した患者レジストリ作成が進行していた。今回我々は G2 班と連携し、同じシステムを用いて黄斑ジストロフィの患者レジストリを構築できないかを検討した。

(2) 昨年度の調査で解析した日本における黄斑ジストロフィの患者数推定調査の結果を統計の専門家に相談して確認したのちに英文論文にまとめ、Jpn J Ophthal 誌に投稿した。

(3) 黄斑ジストロフィの専門家による 13

の施設からABCA4遺伝子の両アリルに病的バリアントを有する患者を解析した。遺伝学的検査には全エクソーム配列解析が用いられた。合致した患者に対してマルチモーダル網膜画像を含む包括的な眼科検査を行った。

(4) 難病のホームページの内容を見直し、患者やその家族にとって分かりやすい言葉を用いて修正し、新たな情報を加えて改訂した。

（倫理面への配慮）

今回の研究に関しては患者の個人情報は全て匿名化し、倫理面に十分配慮して行った。

C．研究結果

(1) 網膜色素変性グループ（G2）が使用している難病プラットフォームシステムを用いて黄斑ジストロフィの患者もレジストリが構築できることを確認した。現時点では既に50名以上の黄斑ジストロフィの登録が終わっている。

(2) 新たに診断された患者の年間推定数は以下の通りである： ベスト病が55.3例、スタルガルト病が36.7例、オカルト黄斑ジストロフィが35.8例、錐体（-杆体）ジストロフィーが160.6例、X連鎖性網膜分離症が31.0例、中心性輪紋状脈絡膜ジストロフィが29.8例、その他のタイプの黄斑ジストロフィが174.1例であった。主要施設で診断され、追跡調査を受けている黄斑ジストロフィー患者の総数は6651人と推定された。

(3) 63人の患者が研究された。(添付資料#) missense/missense 19例、missense/ truncation 23例、truncation/ truncationが21例であった。合計62の病的バリアントが同定され、29の新規バリアントが含まれた。6人の患者は、foveal sparingまたはfoveal structureの温存を特徴とする軽度の表現型を有しており、そのうち4人はmissense/missense、2人はmissense/truncationの遺伝子型であった。p.Arg212His変異体は、軽度の表現型を有する患者において最も頻度が高かった（4/12）。truncation/ truncationの患者では、数年以内に網膜変性が急速に進行した。

(4) 難病ホームページの中でも特に「患者への説明」に大幅な修正を行い、患者の利便性を向上させた。

D．考察

(1) 黄斑ジストロフィにおいても本年度より患者レジストリが本格的に開始された。これは日本における黄斑ジストロフィ患者の調査や臨床試験に役立つと考えられた。(2)日本における黄斑ジストロフィの推定患者数が国際誌に報告され、これにより患者数の国際比較が可能になった。(3)本邦におけるスタルガルト病の遺伝子型と表現型の関係が明らかとなった。(4) 難病ホームページの修正により、患者および家族が疾患の情報を得る際の利便性が向上した。今後も修正および加筆を加えていきたい。

E. 結論

黄斑ジストロフィの患者レジストリが開始された。これにより日本における黄斑ジ

ストロフィの遺伝子型や表現型の研究が進み、将来の臨床試験に役立てることができると考えられた。

Ｆ．健康危険情報 ： なし

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H. 知的財産権の出願・登録状況

1. 特許取得　なし
2. 実用新案登録　なし
3.その他　なし

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CLINICAL INVESTIGATION

Nationwide epidemiologic survey on incidence of macular dystrophy in Japan

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Abstract

Purpose The aim of this study was to estimate the number of patients in Japan who had visited an ophthalmologist for macular dystrophy of various types, including Best vitelliform macular dystrophy (BVMD), Stargardt disease, occult macular dystrophy (OMD), cone (-rod) dystrophy, X-linked retinoschisis (XLRS), and central areolar choroid dystrophy (CACD).

Study design Nationwide epidemiologic survey

Methods Questionnaires were distributed to 965 major facilities, including all the university hospitals in Japan. The aim of the questionnaire was to determine the number of patients with each type of macular dystrophy who had visited an outpatient clinic during the past 5 years (January 2015 to December 2019).

Results Over 70% of the patients were diagnosed and followed up at university hospitals. The estimated annual number of newly diagnosed cases was as follows: 55.3 for BVMD, 36.7 for Stargardt disease, 35.8 for OMD, 160.6 for cone (-rod) dystrophy, 31.0 for XLRS, 29.8 for CACD, and 174.1 for other types of macular dystrophy. The total number of patients with macular dystrophy diagnosed and followed at major institutions was estimated to be 6651.

Conclusion This was the first nationwide survey of macular dystrophy in Japan and provided an approximate number of affected patients. The diagnosis of macular dystrophy is primarily carried out at facilities with affiliated specialists, such as university hospitals. By examining the incidence of multiple diseases simultaneously, we were able to compare the incidence of each type of macular dystrophy.

Keywords Best vitelliform macular dystrophy · Macular dystrophy · Occult macular dystrophy · Prevalence · Stargardt disease

Introduction

With the development of various treatment options, including gene therapy, inherited retinal diseases have attracted increased attention. In Japan, retinal diseases account for a relatively high percentage of the visually impaired population [1]. Among these, retinitis pigmentosa and macular dystrophy are designated as intractable diseases by the Japanese Ministry of Health, Labour, and Welfare. Retinitis pigmentosa is the most common inherited retinal disease, with an incidence of 1 in 3000 to 5000 people [2–5]. However, the incidence and prevalence of macular dystrophy is not yet fully understood, not only in Japan but also in other countries, owing to its rarity and the difficulty in its diagnosis. In Japan, guidelines for the diagnosis of macular dystrophy were established in 2015 by the Research Committee on the Epidemiology of Intractable Diseases of Retinochoroidal and Optic Nerve Atrophy, in collaboration with the Japanese

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Ophthalmological Society, which was authorized by the Ministry of Health, Labour, and Welfare (https://www.nanbyou.or.jp/entry/4798). According to these guidelines, macular dystrophy is classified into 7 types of diseases as follows: Best vitelliform macular dystrophy (BVMD), Stargardt disease, occult macular dystrophy (OMD), cone (-rod) dystrophy, X-linked retinoschisis (XLRS), central areolar choroid dystrophy (CACD), and other types of macular dystrophies. Other types of macular dystrophy are defined as degeneration of the macula that does not correspond to the diagnostic criteria defined by the 6 other types of macular dystrophy and exhibit a normal or nearly normal full-field electroretinogram (ERG). Other types of macular dystrophy include autosomal dominant familial drusen (Doyne honeycomb retinal dystrophy/Malattia Leventinese), North Carolina macular dystrophy, Sorsby fundus dystrophy, and atypical macular dystrophy.

This was the first nationwide epidemiologic survey of patients diagnosed with macular dystrophy in Japan. The study aimed to estimate the number of patients with each type of macular dystrophy in Japan. Our data will facilitate the improvement of welfare services and research on future clinical trials of patients with macular dystrophy.

Patients and methods

The institutional review board of Mie university ruled that approval was not required for the study owing to the study design involving questionnaires. The study protocol adhered to the tenets of the Declaration of Helsinki. In April 2020, questionnaires were mailed directly to the heads of 965 major facilities in Japan, which were certified as the strata of "selected departments" by the Japanese Ophthalmological Society according to previous similar epidemiologic surveys of intractable disease [6]. This included all the university hospitals in Japan. The purpose of the questionnaire was to determine the number of patients with macular dystrophy who had visited outpatient clinics over the past 5 years (January 2015 to December 2019). The questions assessed the number of new and long-standing patients (patients diagnosed before December 2014 and continuously followed thereafter). The former was used to determine the approximate annual incidence, and the latter was used to determine the number of patients who were diagnosed with and followed up for macular dystrophy in Japan. The heads of the facilities were requested to respond to the questionnaire.

Each facility received diagnostic criteria for the 7 types of macular dystrophy defined by the Research Committee on the Epidemiology of Intractable Diseases of Retinochoroidal and Optic Nerve Atrophy (https://www.nanbyou.or.jp/entry/4798). The facilities were asked to provide the patient numbers based on electronic medical records and disease name searches. Genetic testing was not included in the diagnostic criteria because it is not covered by health insurance in Japan. Among the 965 facilities, 646 responded to the questionnaire (response rate: 66.5%).

Aggregated data were used for all 3 analyses. First, we examined the proportion of patients attending university hospitals and their branches, which were thought to be affiliated with specialists. In this study, the collective term "university hospitals" refers to the university hospital itself and its associated branches.

In the second analysis, the number of patients with each type of macular dystrophy in Japan was assessed. We estimated the annual number of newly diagnosed cases of each type of macular dystrophy in Japan by dividing the sum of the number of patients reported by collection facilities by the response rates (0.66) and further divided this result by the span of 5 years. Additionally, we calculated the total number of patients followed up at major institutions in Japan over a 5-year period. This involved summing the newly diagnosed cases over 5 years and the number of long-standing patients diagnosed before December 2014 who received continuous follow-up thereafter. The resultant total was then divided by the response rates (0.66). We aimed to determine the characteristics of the incidence of each macular dystrophy disease in the Japanese population with reference to previous literature from other countries.

The third analysis examined the uneven distribution of patients with macular dystrophy according to region. The country was divided into 6 regions: Hokkaido, Tohoku, Kanto (including Yamanashi Prefecture), Chubu (including the Tokai, Hokuriku, and Shinetsu regions), Kinki, Chugoku/Shikoku, and Kyushu/Okinawa. The number of reported patients per region was calculated, and the number of patients per 10,000 people was estimated. On the basis of data from the Statistics Bureau of the Ministry of Internal Affairs and Communications in 2019 (https://www.stat.go.jp/), the population of each region was assumed to be 14 million for the Hokkaido/Tohoku region, 42.8 million for the Kanto region, 20.6 million for the Chubu region, 22.5 million for the Kinki region, 11.3 million for the Chugoku/Shikoku region, and 14.4 million for the Kyushu/Okinawa region.

Excel software (Microsoft Corporation, Redmond, WA, U.S) was used for the analysis and tabulation. The population was calculated on the basis of 2019 data published by the Statistics Bureau of the Ministry of Internal Affairs and Communications, assuming a total Japanese population of 126 million.

Results

Percentage of patients attending university hospitals

Overall, 646 facilities responded to the survey, of which 90 were university hospitals. University hospitals accounted for 14% of the responding facilities, but more than 70% of the reported patients, both new and long-standing patients, visited university hospitals (Table 1).

Table 2 shows the estimated number of newly diagnosed patients per year based on the number of new patients over a 5-year period for each type of macular dystrophy. The number of newly diagnosed patients was 55.3 for BVMD, 36.7 for Stargardt disease, 35.8 for OMD, 160.6 for cone (-rod) dystrophy, 31.0 for XLRS, 29.8 for CACD, and 174.1 for other types of macular dystrophy. In all, 520.3 patients were newly diagnosed with macular dystrophy each year.

The total number of patients diagnosed before December 2014 and followed up thereafter, plus the number of patients newly diagnosed during the 5-year period, was considered as the estimated number of patients who visited an ophthalmologist at any of the major hospitals during the 5-year period (Table 2). The total number of patients was 6651. By dividing the total population (126 million) by the number of patients being followed up and newly diagnosed with each type of macular dystrophy, it is possible to estimate the number of people in Japan attending the major facilities for each disease. This value was found to be approximately 1 in 180,000 for BVMD, 1 in 250,000 for Stargardt disease, 1 in 290,000 for OMD, 1 in 60,000 for cone (rod) dystrophy, 1 in 250,000 for XLRS, 1 in 330,000 for CACD, and 1 in 60,000 for other types of macular dystrophy.

The highest number of patients who visited the major facilities over 5 years were those with cone (-rod) dystrophy, followed by those with other types of macular dystrophy. The remaining diseases, including Stargardt disease, OMD, and CACD had similar numbers of cases, and the number of cases with BVMD was 1.6 to 1.8 times higher than the number of these diseases.

Table 3 shows the numbers of new and long-standing patients and their sum in each region. These are the actual numbers from 646 institutions that were not divided by the response rate (66.5%). The numbers of patients per 100,000 people who visited the selected institutions over a 5-year period are also shown in the Table 3. The number of patients was higher in densely populated areas such as the Kanto and Kinki regions, and the number of patients per population was also high in the Chugoku and Shikoku regions. In contrast, the number of patients per population tended to be low in the Tohoku/Hokkaido and Kyushu regions, which are depopulated and have low population densities. The number of patients per population in the Hokkaido/Tohoku region was approximately half of that in the Kinki region, which had the highest number of patients per population.

Table 1 Percentage of macular dystrophy patients attending university hospitals

	Newly diagnosed cases in 5 years	Long-standing cases in 5 years
(A) Responded 646 facilities	1730	2693
(B) 90 university hospitals	1237	1991
(B)/(A)	0.715	0.739

Discussion

This was the first nationwide survey on the incidence of macular dystrophy in Japan. Given that macular dystrophy is expected to be diagnosed at facilities with affiliated specialists, the estimated number of newly diagnosed patients

Table 2 Estimated number of new and long-standing patients with each type of macular dystrophy

	Newly diagnosed patients/year	Long-standing patients in 5 years	Sum of newly diagnosed and long-standing patients in 5 years
BVMD	55.3	421.1	697.7
Stargardt	33.7	335.3	503.8
OMD	35.8	254.1	433.1
Cone (-rod) dystrophy	160.6	1272.2	2088.7
XLRS	31.0	356.4	511.3
CACD	29.8	231.6	380.5
Other	174.1	1178.9	2049.6
Total	520.3	4049.6	6651.1

BVMD best vitelliform macular dystrophy, *OMD* occult macular dystrophy, *XLRS* X-linked retinoschisis, *CACD* central areolar choroid dystrophy

Table 3 Regional differences in the number of macular dystrophy cases

Region	(A) Population (million)	(B) Newly diagnosed macular dystrophy patients in 5 years	(C) Long-standing macular dystrophy patients in 5 years	(B)+(C)	Number of patients per 10,000 people (B)+(C) (A)×10
Hokkaido/Tohoku	14.0	122	212	334	2.39
Kanto	42.8	571	1068	1639	3.83
Chubu	20.6	264	355	619	3.00
Kinki	22.5	406	590	996	4.43
Chugoku/Shikoku	11.3	174	265	439	3.88
Kyushu/Okinawa	14.4	193	203	396	2.75

is thought to be close to the actual number. In this study, it was found that many patients attended university hospitals with high expertise and that fewer patients were diagnosed and followed up in rural areas, where depopulation is increasing. By simultaneously examining multiple diseases, we were able to determine the most common type of macular dystrophy in Japan. It was estimated that approximately 520 patients in Japan are diagnosed with macular dystrophy annually.

Number of patients at university hospitals

In Japan, patients with rare diseases are referred by local clinics to highly specialized medical institutions, including university hospitals. In this survey, we found that in Japan, macular dystrophy is often diagnosed and followed up at university hospitals, which are usually affiliated with retina specialists. One possible reason for this trend could be that the diagnosis of macular dystrophy requires special equipment, such as ERG and fundus autofluorescence, which can only be performed at more specialized facilities. In addition, with recent advances in research, such as genetic analysis, patients may prefer to visit university hospitals for inherited retinal diseases. However, because there is no effective treatment for macular dystrophy after diagnosis, many patients may visit local ophthalmology clinics instead of specialized facilities or stop ophthalmology follow-up altogether. Therefore, the actual number of patients in Japan is expected to be much higher than the number of new and long-standing patients combined.

Characteristics of each disease

BVMD

According to studies conducted in other countries, the prevalence of BVMD varied among reports. In the United States, it was estimated to be about 1 in 20,000 people according to data from a specific region [7], and in Denmark, it was estimated to be at least 1.5 in 100,000 people [8]. In the present study, the number of patients with BVMD attending ophthalmology hospitals in Japan was about 700, which was calculated as 1 in 180,000 people. We could not directly compare the current data with those of previous reports because many patients may not have visited hospitals owing to having stable symptoms. However, our data seemed to be closer to those of previous reports from Denmark (1.5/100,000).

Stargardt disease

Stargardt disease is one of the most common causes of inherited childhood and adult visual impairment in Europe and the United States [9]. However, it has long been believed that Stargardt disease is not as common in Japan as in Western countries. In Europe and the United States, Stargardt disease is estimated to occur in one in every 8000 to 10,000 individuals. This estimated number was expected because Stargardt disease is more common than retinoblastoma and less common than retinitis pigmentosa and this is not reported in epidemiologic studies [10]. A recent national survey in the United Kingdom reported 0.127 cases per 100,000 people per year (81 cases per year/60 million population) [10]. This survey was a national survey conducted by reporting of cases of diagnosed Stargardt disease throughout the United Kingdom, and the survey methodology was similar to that of our study. Applying our results to this study, the incidence of Stargardt disease was 0.0267 cases per 100,000 people per year, indicating that the incidence in Japan was approximately one-fifth of that in the United Kingdom. This demonstrated a possible difference in the prevalence of Stargardt disease among diverse ethnicities.

OMD

OMD was first reported by the ophthalmologist Yozo Miyake, in Japan [11, 12]. Therefore, clinical and genetic research on OMD, including the discovery of the causative gene, *RP1L1*, and abnormal OCT findings in the outer retina, have mainly been conducted in Japan [13–15]. The condition with mutations in *RP1L1* is specifically called

RP1L1-related macular dystrophy, or Miyake disease [16, 17]. Although it is a difficult disease to diagnose, it is highly recognized in Japan, and we suspected that more OMD patients are diagnosed in Japan than in other countries. This study revealed that OMD occurred as frequently as Stargardt disease and CACD in Japan.

Cone (-rod) dystrophy

In this study, cone (rod) dystrophy had the highest incidence of newly diagnosed patients per year among patients with macular dystrophies. On the basis of the number of patients, including both new and long-standing patients, the estimated number of patients with cone (rod) dystrophy in the population was approximately 1 in 60,000. In previous reports, the frequency of cone dystrophy was reported to be 1 in 30,000 to 40,000 people [18], whereas that of cone-rod dystrophy has also been reported to be 1 in 30,000 to 40,000 people [19, 20]. These data were not derived from epidemiologic data but were estimated from the incidence of causative genes. The prevalence in our survey (about 1 in 60,000) is likely to be even higher than that estimated from previous data, when considering the dropout of followed-up patients or patients followed up at clinics that were not selected for this survey. Cone (-rod) dystrophy was defined as macular dystrophies with or without fundus abnormalities and those with reduced response to photopic ERGs (and scotopic ERGs for cone-rod dystrophy). This study might have included various types of inherited retinal degeneration because it was difficult for nonspecialists of ERG to diagnose, which might have led to an overestimation of the number of patients.

XLRS

XLRS has the unique features of OCT (retinoschisis) and ERG (negative waveform); therefore, its diagnosis is considered confirmatory. However, the prevalence of XLRS has not been determined previously. In our study, about 510 patients with XLRS, including new and long-standing patients, attended the institutions participating in this survey, indicating 1 per 250,000 of the population. Considering the dropout rate of a non-negligible number of patients during follow-up, the actual number of patients with XLRS may be much higher.

CACD

Few epidemiologic reports on CACD have been published; however, the number of newly diagnosed patients in the present study was comparable to the annual incidence of Stargardt disease, OMD, and XLRS. Usually, CACD is diagnosed at an older age than is Stargardt disease or XLRS, and the actual number of patients with CACD is expected to be smaller than those with these diseases.

Other types of macular dystrophy

Cases diagnosed with other types of macular dystrophies were higher in both the newly diagnosed and the long-standing cases in this survey. The diagnosis of macular dystrophy is sometimes difficult in daily practice because of the similarity between hereditary and acquired macular degeneration. Therefore, the overestimation of this type of macular dystrophy should be considered. However, it is necessary to establish a disease definition that enables accurate classification of other types of macular dystrophy more accurately in the future.

Regional segregation

Japan is an almost monoethnic country with a relatively uniform genetic background, small land area, and high degree of interregional mobility. Therefore, the regional differences in the incidence of inherited retinal diseases are assumed to be small. In this study, we suspected that the variation in the number of patients among regions was largely due to social factors. The disparity in medical care between rural and urban areas is an urgent problem in Japan. In rural areas, a shortage of doctors and lack of hospitals force many patients to visit distant hospitals. The low number of patients per population in the Hokkaido-Tohoku and Kyushu regions may indicate difficulty in visiting specialized hospitals or university hospitals in these regions. The fact that there was a 2-fold difference between rural and urban areas might indicate that the number of patients in rural areas was underestimated.

Limitations

In adhering to the guidelines provided by a research group under the Ministry of Health, Labour, and Welfare in Japan (https://www.jichi.ac.jp/dph/nanbyou/manual_2017.pdf) , our survey encountered certain limitations. The recommended approach entails the distribution of the questionnaire not only to large hospitals like university hospitals, but also to smaller clinics. It is also recommended that after the results of the first questionnaire have been compiled, a second questionnaire should be sent to obtain detailed clinical and genetic information for individual patients. However, in this study, we did not send the questionnaire to smaller clinics because we assumed it would be challenging to make an accurate diagnosis in such clinics. Further we did not conduct a secondary survey because the first questionnaire included multiple

diseases, and it was difficult to obtain clinical findings from a large number of patients through a second questionnaire. These deviations from the guidelines may have reduced the accuracy of the data.

In Japan, genetic testing has not been introduced into routine medical practice, and the diagnosis of diseases such as BVMD, Stargardt disease, and XLRS is still based on the clinical findings, even though the causative genes of these diseases have been determined. Therefore, the diagnosis depends on the judgment of each physician, and the accuracy of the diagnosis of the disease is not always ensured. Therefore, it is possible that the number of patients with each disease was either overestimated or underestimated owing to the misdiagnosis of atypical clinical findings. Distinguishing between BVMD and acquired vitelliform lesions is particularly difficult. In addition, the diagnosis of OMD is also difficult, and the possibility exists of misdiagnosing nonhereditary diseases or cone dystrophy without fundus abnormalities as OMD. Some cases of CACD have a characteristic fundus, but also have reduced cone and scotopic full-field ERGs, which may overlap with the diagnosis of cone-rod dystrophy. In addition, patients diagnosed with CACD, cone-rod dystrophy, or other types of macular dystrophy, especially those aged 50 years or older, may have dry age-related macular degeneration or macular atrophy due to high myopia.

Another limitation of this study was that the analysis was based on a survey of 965 selected facilities, and the number of cases diagnosed and followed up at other clinics was underestimated; however, the number was probably not very high. The number of duplicate cases involving the same patient from multiple centers was also unknown.

To our knowledge, this was the first epidemiologic investigation on macular dystrophy in Japan. Over 70% of the patients were diagnosed and followed up at university hospitals. The number of annually diagnosed cases of BVMD was approximately 55, and that of Stargardt disease, OMD, XLRS, and CACD was each approximately 30. In contrast, the number of patients with cone (-rod) dystrophy and other types of macular dystrophy was higher. There were some regional variations in the number of patients: in rural areas, fewer patients were diagnosed or followed up at hospitals than in urban areas.

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Declarations

Conflict of interest S. Ueno, None; T. Hayashi, None; K. Tsunoda, None; T. Aoki, None; M. Kondo, None.

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Genetic and Clinical Features of *ABCA4*-Associated Retinopathy in a Japanese Nationwide Cohort

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• PURPOSE: To clarify the genetic and clinical features of Japanese patients with *ABCA4*-associated retinopathy.
• DESIGN: Retrospective, multicenter cohort study.
• METHODS: Patients with retinal degeneration and biallelic *ABCA4* variants were recruited from 13 different hospitals. Whole exome sequencing analysis was used for genetic testing. Comprehensive ophthalmic examinations were performed on matched patients. The primary outcome measure was identifying multimodal retinal imaging findings associated with disease progression.
• RESULTS: This study included 63 patients: 19 with missense/missense, 23 with missense/truncation, and 21 with truncation/truncation genotypes. In total, 62 variants were identified, including 29 novel variants. Six patients had a mild phenotype characterized by foveal-sparing or preserved foveal structure, including 4 with missense/missense and 2 with missense/truncation genotypes. The p.Arg212His variant was the most frequent in patients with mild phenotypes (4/12 alleles). Clinical findings showed a disease duration-dependent worsening of the phenotypic stage. Patients with the truncation/truncation genotype exhibited rapid retinal degeneration within a few years and definite fundus autofluorescence imaging patterns, including hyper autofluorescence at the macula and few or no flecks.
• CONCLUSIONS: Our results indicate that missense/missense or missense/truncation genotypes, including the p.Arg212His variant, are associated with a relatively mild phenotype. In contrast, the truncation/truncation genotype causes rapid and severe retinal degeneration in Japanese patients with *ABCA4*-associated retinopathy. These data are vital in predicting patient prognosis, guiding genetic counseling, and stratifying patients for future clinical trials. (Am J Ophthalmol 2024;264: 36–43.

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IN 1997, STARGARDT DISEASE (STGD1, MIM: 248200) WAS first reported to be caused by biallelic variants of the ATP-binding cassette transporter, alpha 4 subunit (*ABCA4*) gene.[1] These variants are associated with several retinal conditions, including bull's-eye maculopathy,[2] macular atrophy,[3] fundus flavimaculatus,[4] cone-rod dystrophy, and retinitis pigmentosa.[5-7] *ABCA4*-associated retinopathy is a commonly inherited retinal disorder, affecting approximately 1 in 8000 to 10,000 people.[8,9] A recent national survey in the United Kingdom reported a yearly incidence of 0.127 per 100,000 population,[10] which is 5 times higher than that observed in a study from the Nationwide Epidemiological Survey of Macular Dystrophy in Japan.[11] Previous large cohort studies have identified genotype-phenotype correlations in patients with *ABCA4*-associated retinopathy, showing that disease severity correlates with variant severity and worsens over time.[12,13]

Notably, several therapies, including oral treatments[14] and gene therapies using adeno-associated viruses,[15] other large vectors,[16,17] and antisense oligonucleotides,[18]

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have recently been explored. However, *ABCA4*-associated retinopathy is rare among the Japanese, accounting for 1.7% of inherited retinal disorder cases (20 of 1210 pedigrees).[19] With imminent clinical trials, it is crucial to thoroughly investigate this retinopathy's genetic and clinical characteristics in Japanese patients to precisely evaluate treatment efficacy and timing of interventions. This study represents the first nationwide Japanese cohort focused on *ABCA4*-associated retinopathy, aiming to elucidate the genetic and clinical profiles of patients with this condition, particularly concerning disease progression and genotype.

METHODS

• **ETHICS STATEMENT:** The Institutional Review Boards of The Jikei University School of Medicine (approval number 24-231 6997), Nihon University School of Medicine (approval number 20211105), Kindai University Faculty of Medicine (approval number 22-132 and R05-071), Kyushu University (approval number 536-08), The University of Tokyo (approval number 2018191G), Hamamatsu University School of Medicine (approval number 14-040), Teikyo University (approval number 10-007-5), Kobe City Eye Hospital (approval number E19002), Nagoya University Graduate School of Medicine (approval Number: 2020-0598), University of Miyazaki (approval number G-0118), Mie University Graduate School of Medicine (approval number MIE-2429), and the National Hospital Organization Tokyo Medical Center (approval number R18-029) approved this study. The study protocol followed the Declaration of Helsinki, and all participants provided written informed consent.

• **INCLUSION CRITERIA:** We studied 3324 patients with inherited retinal disorders who underwent genetic analysis. The inclusion criteria for patients were retinal degeneration conditions, such as macular dystrophy, cone-rod dystrophy, and retinitis pigmentosa phenotypes. Eligible patients exhibited either homozygous or compound heterozygous variants in the *ABCA4* gene as confirmed by genetic analysis across the consortium of 13 participating hospitals. The phenotypes were determined using findings from multimodal retinal imaging, visual field testing, and full-field electroretinography.

• **MOLECULAR GENETIC ANALYSIS:** Genetic testing was performed using whole exome sequencing analysis based on previously described methods.[20-23] The pathogenicity of the *ABCA4* variants was evaluated using the Human Gene Mutation Database Professional (HGMD, http://www.hgmd.cf.ac.uk/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), Genome Aggregation Database (gnomAD, https://gnomad.broadinstitute.org/), and the Japanese Multi Omics Reference Panel (jMorp; https://jmorp.megabank.tohoku.ac.jp/). Patients with biallelic *ABCA4* variants were classified into 3 groups according to their genotypes (missense/missense, missense/truncation, and truncation/truncation) based on a modified method from a previous study.[24] Consequently, canonical and non-canonical splice site, frameshift, and stop-gain variants were defined as truncation variants.

• **CLINICAL EXAMINATIONS:** Comprehensive ophthalmic examinations, including medical review (age at onset and chief complaint), decimal best-corrected visual acuity (BCVA), fundus photograph, and short-wavelength fundus autofluorescence imaging (FAF) were performed using Spectralis HRA (Heidelberg Engineering, Heidelberg, Germany), and/or Optos 200Tx/California, ultrawidefield retinal imaging system (Optos, Dunfermline, UK), optical coherence tomography (OCT; Carl Zeiss Meditec AG, Dublin, CA, USA), and Goldmann perimetry (Haag Streit, Bern, Switzerland).

Phenotypic stage analysis

We analyzed the correlations between the phenotypic stage, disease duration, and BCVA across 3 genotypes. Based on the findings of well-established studies,[4,13,25] the ophthalmologists K.M. and T.H. conducted independent evaluations of the phenotypic stages, utilizing fundus imaging and specific criteria outlined below:

Stage I: Macular lesions limited to the macula, exhibiting irregular pigmentary alterations, a bull's-eye maculopathy, or a distinctive "beaten-bronze" appearance.

Stage II: Macular lesions with characteristic yellowish flecks that emanate from the macula and extend beyond the vascular arcades and optic disc.

Stage III: Diffuse atrophy of the macular choriocapillaris with associated resorption of flecks within the macular area.

Stage IV: Extensive atrophy of the choriocapillaris accompanied by pigment deposition in the central posterior pole or further.

Representative images of each stage are shown in Figure 1.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp, Armonk, NY, USA), R and R-studio (version 3.6.3; http://www.R-project.org/). Bonferroni's multiple comparison test was used to determine the significant differences in the age at onset and patients with each genotype. Decimal BCVA was converted to a logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. Furthermore, the BCVA of counting fingers, hand motions, and light perceptions were converted to 2.0, 2.4, and 2.7 logMAR units, respectively.[26] Kaplan–Meier survival curves with the log-rank test were used to compare survival experiences (logMAR BCVA) among the

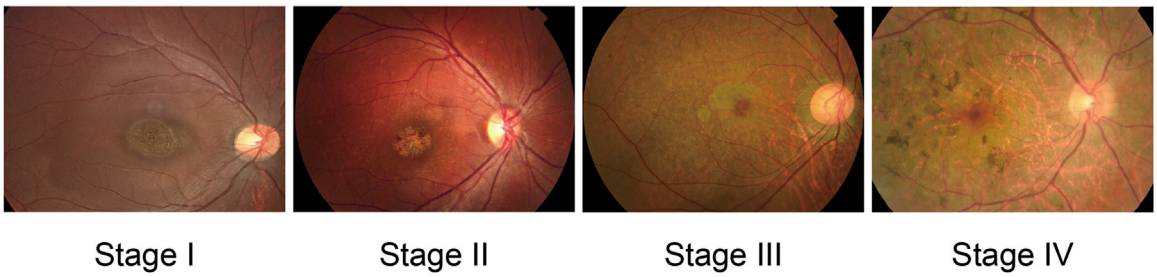

FIGURE 1. Representative imaging of each stage in patients with *ABCA4*-associated retinopathy.
Stage I: Macular lesions limited to the macula, exhibiting irregular pigmentary alterations, a bull's-eye maculopathy, or a distinctive "beaten-bronze" appearance. Stage II: Macular lesions with characteristic yellowish flecks that emanate from the macula and extend beyond the vascular arcades and optic disc. Stage III: Diffuse atrophy of the macular choriocapillaris with associated resorption of flecks within the macular area. Stage IV: Extensive atrophy of the choriocapillaris accompanied by pigment deposition in the central posterior pole or further.

3 genotypes. A significance threshold of $P < .05$ was established, and for cases where this was achieved among the 3 genotypes, a Bonferroni correction was applied to pinpoint which genotype pairs exhibited significant differences, using an adjusted significance level of $P < .017$.

RESULTS

• **MOLECULAR GENETIC FINDINGS:** In total, 63 patients who met the inclusion criteria were recruited, and 62 variants were identified, including 29 novel ones (Supplemental Tables 1 and 2). Of these variants, 42 were missense (67.7%), 9 were stop-gain (14.5%), 6 were frameshift (9.7%), and 5 were canonical/noncanonical splice-site variants (8.1%). The patients were categorized into 3 genotype groups: 19 (30.2%), 23 (36.5%), and 21 (33.3%) with missense/missense, missense/truncation, and truncation/truncation genotypes, respectively.

• **CLINICAL FINDINGS:** Supplemental Table 1 presents the clinical findings in the 63 patients with biallelic *ABCA4* variants, including the age at onset, symptoms, disease duration (from onset to examination), BCVA (first and last examinations), and the phenotypic stage (first and last examinations).

Age at onset

Patients with truncation/truncation genotypes had a younger age at onset (7.29 ± 2.37 years; range, 3-11 years) than did those with missense/missense genotypes (26.44 ± 19.46 years; range, 6-68 years; $P = .000$) and missense/truncation (17.81 ± 11.75 years; range, 6-40 years; $P = .030$) genotypes. However, the patients with missense/missense and missense/truncation genotypes ($P = .234$) showed no differences in the age at onset (Figure 2).

Survival curves of visual acuity

Kaplan–Meier survival curves were initially plotted using a cutoff of 1.0 logMAR unit (equivalent to 0.1 a decimal visual acuity) to estimate the changes in BCVA during the disease course in all 63 patients. The survival curves indicated that BCVA required a median duration of 42 years to reach a 1.0 logMAR unit. Subsequently, comparing the BCVA progression among the 3 genotypes (missense/missense, missense/truncation, and truncation/truncation) showed that the median age for BCVA to reach a 1.0 logMAR unit was the late 60s, approximately 50 years, and approximately 30 years in patients with the missense/missense, missense/truncation, and truncation/truncation genotypes, respectively (Figure 3). The genotype comparison results were as follows: a significant difference was observed between the missense/missense and truncation/truncation genotypes ($P = .003$), as well as between the missense/truncation and truncation/truncation genotypes ($P = .003$). However, no significant difference was noted when comparing the missense/missense genotype with the missense/truncation genotype ($P = .900$) (Figure 3).

Phenotypic stage

Supplemental Figure 1 illustrates the correlations among the phenotypic stage, disease duration, and logMAR BCVA for the 3 genotypes. Among 15 patients with the missense/missense genotype, all but 5 patients (JU0266, JU2182, JU2189, JU2211, and Teikyo1024) exhibited an early stage (stage I or II) within the first 20 years of disease onset. Patients exhibited varying correlations between phenotypic stage and disease duration, and between phenotypic stage and logMAR BCVA. In 18 patients with the missense/truncation genotype, there was a tendency for the phenotypic stage to progressively worsen over time; however, some (JU0717, JU2154, and Kinki141-107) remained at an early stage (stage I or II) despite having had the disease for >20 years. This pattern was also observed in the correlation between the phenotypic stage and logMAR BCVA.

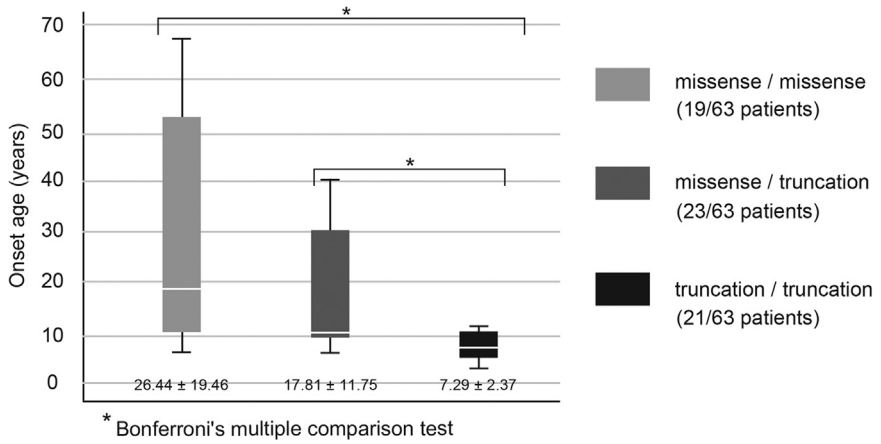

FIGURE 2. Age at onset across genotypes. Patients with the truncation/truncation genotype have a significantly younger age at onset (7.29 ± 2.37 years; range, 3-11 years) compared with those with missense/missense (23.60 ± 16.45 years; range, 6-50 years) and missense/truncation (16.90 ± 11.27 years; range, 6-40 years) genotypes, with *P*-values of <0.001 and 0.020, respectively. However, the missense/missense and missense/truncation genotypes show no significant differences in age at onset (*P* = .234).

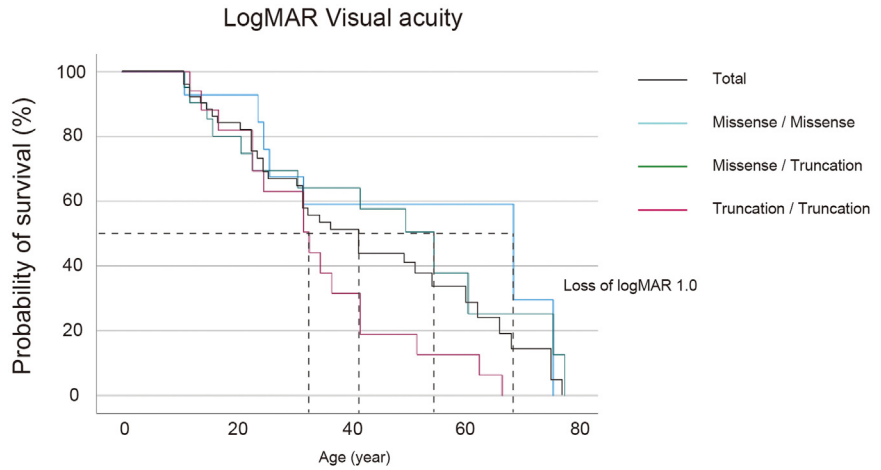

FIGURE 3. Survival curves and clinical course of visual acuity. Kaplan–Meier survival curves are plotted using a cut-off of 1.0 logMAR unit, equivalent to 0.1 a decimal visual acuity. In all 63 patients, the survival curves indicate that the median duration required for best-corrected visual acuity (BCVA) to decline to a 1.0 logMAR unit in half of the patients is 42 years. When comparing progression among the 3 genotypes, we find that the median age in patients when BCVA reaches a 1.0 logMAR unit is the late 60s, approximately 50 years, and approximately 30 years for the missense/missense, missense/truncation, and truncation/truncation genotypes, respectively. Log-rank test with Bonferroni correction is applied for the comparisons. The genotype comparison results show significant differences between missense/missense and truncation/truncation (*P* = .003) and between missense/truncation and truncation/truncation (*P* = .003) but not between missense/missense and missense/truncation (*P* = .900).

In 15 patients with the truncation/truncation genotype, a clear time-dependent progression of the phenotypic stage was observed. Furthermore, logMAR BCVA also deteriorated with the worsening of the phenotypic stage.

Multimodal retinal imaging

Supplemental Figure 2 shows the detailed multimodal retinal images of representative patients across the 3 genotypes.

Missense/missense genotype

In patients with missense/missense genotypes, fundus photography findings generally showed a gradually worsened phenotypic stage over time. However, this trend was not observed in patients with foveal sparing or a preserved foveal structure (JU2151, JU2182, and JU2211). Flecks were observed in all early stage patients (KA304, KA241, KA115, and JU2151) but were absent in those at the end-stage (Teikyo1024, JU0266, JU2182, JU2189, and JU2211). FAF imaging revealed hypo-AF in the macular region, indicating macular degeneration or atrophy with a combination of hypo-AF and hyper-AF. This was consistent with flecks in the surrounding area in early-stage patients. In contrast, end-stage patients showed hypo-AF extending beyond the arcade vessels. The OCT

findings demonstrated foveal-sparing or preserved foveal structure in some patients, specifically those identified as JU2151 (p.Arg212His and p.His1865Tyr), JU2182 (p.Asp586Glu and p.Gly2041Asp), JU2189 (p.Arg212His and p.Arg212His), and JU2211 (p.Arg212His and p.Asn269Ser). Conversely, a different group of patients showed a disruption of the outer retinal layers at the fovea, including KA304 (p.Arg511Cys and p.Val675Ile), KA241 (p.Gly1623Ser and p.Arg1862Cys), and KA115 (p.Thr1019Met and p.Cys1488Tyr). Over the 8-year follow-up, the 68-year-old patient (JU2189) exhibited progressive damage to the outer retinal layers at the fovea.

Missense/truncation genotype

Fundus photography findings indicated that the phenotypic stage consistently worsened with increasing disease duration in patients with the missense/truncated genotype. Notably, all patients but one (KA074) had flecks throughout the disease course. The FAF findings revealed hypo-AF in the macular area, consistent with macular degeneration or atrophy, with or without additional hypo-AF and hyper-AF around the area, corresponding to flecks in all patients. OCT findings revealed foveal sparing in 2 patients (JU0657 and JU2208) and a disruption of the outer retinal layers at the fovea in other patients (N528, JU0099, JU0666, and KA074). However, 1 patient (JU0657) exhibited this disruption in the outer retinal layers at the fovea over time.

Truncation/truncation genotype

Fundus photography initially showed discoloration or a normal appearance in patients with the truncation/truncation genotype; however, all patients had rapidly increased retinal degeneration from the arcade vessels to the peripheral retina as the disease progressed. Only a few or no flecks were observed throughout the disease course. During the first examination, FAF findings revealed a normal appearance or hypo-AF in the macular region, with hyper-AF around the area (beyond the arcade vessels). Over time, all patients but one (JU1315) exhibited an expansion of hypo-AF beyond the arcades of vessels. In patient JU1315, hypo-AF was localized to the macular region, a finding that aligns with the expected macular degeneration or atrophy, accompanied by areas of both hypo-AF and hyper-AF nearby. The OCT findings revealed that during the disease course, there was a disruption in the outer retinal layers at the fovea in all patients studied.

DISCUSSION

This study characterized the genetic and clinical features in 63 Japanese patients with biallelic *ABCA4* variants.

In total, 62 distinct *ABCA4* variants were identified, including 41 missense (67.2%), 9 stop-gain (14.8%), 6 frameshifts (9.8%), and 5 splice site variants (8.2%). These findings are consistent with those of previous studies.[12,13] A previously proposed genotype-phenotype correlation, with phenotypic severity dependent on variant severity, was observed in our cohort, particularly regarding age at onset (Figure 2) and visual acuity (Figure 3). Regarding the mild phenotype characterized by foveal sparing or preserved foveal structure, a large Spanish cohort of 506 patients with STGD1 reported only 8 cases of foveal sparing[12] predominantly with genotypes comprising 6 missense/missense and 2 missense/truncation genotypes. Our study observed a mild phenotype in 6 out of 63 patients, with 4 (JU2151, JU2182, JU2189, and JU2211) and 2 (JU0657 and JU2208) with the missense/missense and missense/truncation genotypes, respectively. Previous research suggests that milder phenotypes are strongly associated with the hypomorphic variants (p.Gly1961Glu and p.Arg2030Gln),[27-30] and these vary across ethnic groups.[25] Notably, the p.Arg212His variant was the most frequently observed (4 of 12 alleles) in our patients with a mild phenotype (JU0657, JU2151, JU2182, JU2189, JU2208, and JU2211), suggesting it as a possible hypomorphic variant in Japanese patients with *ABCA4*-associated retinopathy. The p.Arg212His variant has also been detected in previously reported cases of STGD1[31–33]; however, detailed clinical features have not been described. In contrast, a previous study has shown that the alternative variant (p.Arg212Cys) in a homozygous state is associated with a mild phenotype with retention of some ABCA4 protein function.[30] This supports our findings indicating that the p.Arg212His variant is also associated with a mild phenotype.

Previous large cohort studies have elucidated the clinical features and disease progression in patients with biallelic *ABCA4* variants.[12,13] Wang et al. described the disease progression in 42 patients with long-term follow-up, suggesting that the phenotypic stage progressed in a time-dependent manner.[13] Consistent with these findings, our study observed a similar time-dependent progression of the phenotypic stage (retinal degeneration) (Supplemental Figure 1). However, no correlation was found between the phenotypic stage and disease duration in patients with a mild phenotype. This suggests that the actual disease duration may be longer than perceived because of subtle symptoms. Our research also investigated clinical variations based on genotype. A previous study found distinct clinical features in patients with rapid-onset chorioretinopathy (ROC), linked to more deleterious variants, such as truncating variant, differing from other *ABCA4*-associated retinopathy variants.[34] This study observed that deterioration of the macula began with an intense/hyper-AF and homogeneous signal on FAF, followed by a coalescing pattern of ROC within the subsequent decade.[34] Similarly, disease progression is characterized by an expansion of areas with decreased AF of the macula.[35,36] Particularly in cases where the disease onset occurs in childhood, the rate of progression tends to be more rapid than that in adult-onset.[37] In

our cohort, hyper-AF was also observed in patients with the truncation/truncation genotype, subsequently, areas of decreased AF appeared and expanded (Supplemental Figure 2). Consequently, the previous and current studies indicate that hyper-AF at the macular is a characteristic finding in early-stage patients with the truncation/truncation genotype.

Furthermore, the early-stage disease differences in the presence of flecks based on the genotype were also investigated. The term "fundus flavimaculatus" is often used to describe the phenotype of retinal flecks without atrophy. Flecks are thought to correlate with disease severity. They originate from degenerating photoreceptor cells, impaired by the functional failure of the retinal pigment epithelium (RPE),[38,39] and correlate with disease severity.[40] Our findings revealed that flecks were prevalent in patients with missense/missense and missense/truncation genotypes but are less common in those with truncation/truncation genotypes (Supplemental Figure 2). Longitudinal studies of flecks observed on OCT may help understand the differences in flecks observed using FAF imaging.[38,39] Flecks initially appear as hyperreflective bands from the RPE to the outer nuclear layer (ONL), followed by the thinning of the ONL on OCT. Subsequently, as the fleck deposition dissipates, OCT reveals the disruption of the outer retinal layers, including the ellipsoid zone (EZ). These results indicate that the rapid disease progression leads to little or no fleck deposition, resulting in the sudden appearance of atrophic retinal areas. The presence of few or no flecks in the early stages of the disease may also characterize patients with the truncation/truncation genotype. The differences in fleck presentation in the early stages of the disease could predict the degree of progression and genotype.

Additionally, recent studies have investigated the progression of *ABCA4*-associated retinopathy with respect to retinal imaging, microperimetry, and electroretinogram (ERG) findings. Both cross-sectional and longitudinal assessments have reported changes in retinal sensitivity measured by microperimetry and alterations in the EZ observed through OCT in childhood-onset STGD1.[41,42] Assessment using microperimetry has shown that the rate of progression in children is significantly greater than that in adults.[41] Moreover, OCT studies have revealed that quantifying the area of EZ loss offers greater sensitivity than measurements of EZ loss width for evaluating progression.[42] One study has outlined the potential of using ERG evaluation and FAF imaging results to predict disease progression,[43] with patients categorized into 3 ERG groups based on retinal function[29] and 3 FAF groups according to the extent of hypo-AF and retinal background appearance.[44] This study has found a strong correlation between ERG and FAF results. It is suggested that patients assessed in early childhood who possess at least 1 truncation variant and exhibit poor initial BCVA or both, are likely to show a more extensive retinal involvement or progress to a more severe phenotype over time than what baseline FAF imaging might indicate.[43] This enables the possibility of informing patients by comparing FAF with the current gold standard of ERG, thereby aiding in prognostication. They may help determine the appropriate timing for therapeutic intervention and assess the effectiveness of treatment in ongoing gene therapy.

This study has some limitations, including the small cohort size and the absence of whole-genome sequencing data, which may have overlooked additional deep intronic variants.[25] Furthermore, the limitations encompass the lack of microperimetry assessment, grouping of ERG and ultrawidefield FAF evaluation, and assessment of EZ loss. Further research using a larger patient cohort, comprehensive genomic data, and imaging and functional evaluation of the retina is necessary to substantiate our findings.

In conclusion, our study suggests that the missense/missense or missense/truncation genotypes, including the p.Arg212His variant, are associated with a milder phenotype of *ABCA4*-associated retinopathy. However, the truncation/truncation genotype is associated with a more rapid and severe retinal degeneration in Japanese patients with *ABCA4*-associated retinopathy. These findings are crucial for predicting patient prognosis, providing genetic counseling, and stratifying patients for future clinical trials.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Kei Mizobuchi: Writing – original draft, Formal analysis, Conceptualization. **Takaaki Hayashi:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Koji Tanaka:** Data curation. **Kazuki Kuniyoshi:** Data curation. **Yusuke Murakami:** Data curation. **Natsuko Nakamura:** Data curation. **Kaoruko Torii:** Data curation. **Atsushi Mizota:** Data curation. **Daiki Sakai:** Data curation. **Akiko Maeda:** Data curation. **Taro Kominami:** Data curation. **Shinji Ueno:** Data curation. **Shunji Kusaka:** Data curation. **Koji M Nishiguchi:** Writing – review & editing, Data curation. **Yasuhiro Ikeda:** Writing – review & editing, Data curation. **Mineo Kondo:** Writing – review & editing, Data curation. **Kazushige Tsunoda:** Writing – review & editing, Data curation. **Yoshihiro Hotta:** Writing – review & editing, Data curation. **Tadashi Nakano:** Writing – review & editing.

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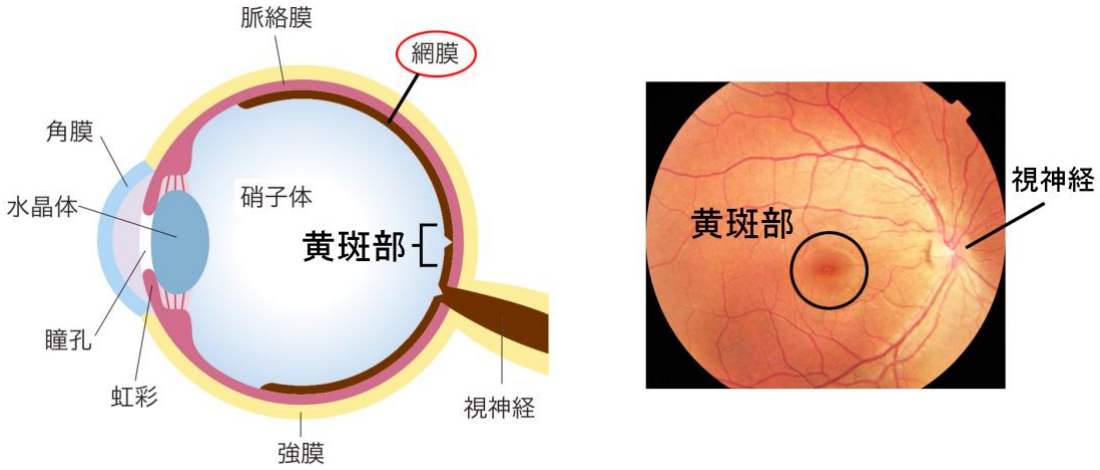
一般利用者向け（患者・家族等）「病気の解説」

①　黄斑ジストロフィとは

眼球の奥には光を感知する薄い膜状の神経があり、網膜（もうまく）と呼ばれています。さらに網膜の中心には黄斑（おうはん）と呼ばれる場所があり、良好な視力を得るために特に重要な役割をしています（下図）。黄斑部は非常に精密で繊細な構造をしているために、多くの疾患が生じやすい部位でもあります。



（図）　眼球の水平断面図（左）と、正常者の眼底写真（右）。
黄斑ジストロフィでは黄斑部が障害されて、その色調や構造に変化が生じる。

黄斑ジストロフィとは、遺伝学的な原因によって網膜の黄斑部がゆっくりと障害され、両眼の視力低下や視野異常を生じる病気の総称です。関係する遺伝子の種類や、病気の性質などによって、卵黄状黄斑ジストロフィ（ベスト病）、スタルガルト病、錐体-杆体ジストロフィ、X 連鎖性若年網膜分離症、オカルト黄斑ジストロフィ（三宅病）、中心性輪紋状網脈絡膜萎縮など、いくつかの代表疾患に分類されています。しかし実際には、上記の分類に入らない黄斑ジストロフィ（分類不能の黄斑ジストロフィ）も多く見られます。このような分類不能の黄斑ジストロフィでも、代表疾患と同様に厚生労働省の難病指定を受けることができます。ただし本疾患の難病指定は、良好な方の目の矯正視力（眼鏡等で矯正した最大の視力）が 0.3 未満に低下している場合に限られます。

② この病気の患者さんはどのくらいいるのですか

厚生労働省の「網膜脈絡膜・視神経萎縮症に関する調査研究班」が全国の主要な医療機関に対して行った調査によると、2020 年の時点では 4423 名の方が黄

斑ジストロフィの診断を受けていました。ただし、調査に含まれていない患者さんも多数いると考えられるため、実際の黄斑ジストロフィの患者数はこれよりも多いことが予想されます。

③ この病気はどのような人に多いのですか

本疾患は全身的な病気とは無関係に生じることが多いため、一般的に発症しやすい体質等の傾向はありません。ただし家族や親戚に黄斑ジストロフィの患者さんがいらっしゃる家系では、発症する確率が高くなることがあります。また、X 連鎖性若年網膜分離症のように男性にしか発症しない疾患もあります。

④ この病気の原因はわかっているのですか

黄斑ジストロフィは、網膜の構造や機能の維持に必要な遺伝子に異常があることで、黄斑部の機能や構造が障害されることによって発症します。多数の遺伝子が黄斑ジストロフィの発症に関与していることが分かっていますが、特に、卵黄状黄斑ジストロフィ（ベスト病）、スタルガルト病、X 連鎖性若年網膜分離症、オカルト黄斑ジストロフィ（三宅病）などでは、それぞれの疾患に関与する代表的な遺伝子が特定されています。

⑤ この病気は遺伝するのですか

黄斑ジストロフィの遺伝形式には、常染色体顕性（優性）遺伝、常染色体潜性（劣性）遺伝、X 連鎖性潜性（劣性）遺伝があり、必ずしも子供に遺伝するとは限りません。また、非常に稀な疾患ですが、これらとは別にミトコンドリア遺伝子異常による黄斑ジストロフィも存在します。

黄斑ジストロフィのうち、卵黄状黄斑ジストロフィ（ベスト病）、オカルト黄斑ジストロフィなどのように常染色体顕性（優性）遺伝の疾患では子供に遺伝する可能性があります。一方、スタルガルト病のように常染色体潜性（劣性）遺伝の疾患では、通常は子供に遺伝することはありません。また X 連鎖性若年網膜分離症の場合は子供には発症しませんが、その子供が女性の場合は、孫の男性に発症する可能性があると言う、やや複雑なパターンが見られます。

なお、令和 5 年に一部の網膜疾患に対する遺伝子検査を保険診療で行えることが決まりましたが、現時点で黄斑ジストロフィは対象疾患に含まれておりません。

⑥ この病気ではどのような症状がおきますか

黄斑ジストロフィには性質の異なる幾つかの疾患が含まれるため、疾患のタイプによって、また個人によっても症状は異なります。

一般的には、視力を保つために重要な黄斑部が障害されるため、視力低下（眼鏡をかけても視力が出ない)、中心視野異常（視野の中心部がぼやける）等の症状が両眼にゆっくりと出現します。また、色覚異常や羞明（しゅうめい＝まぶしく感じること）等の症状も多く見られます。さらに、錐体-杆体ジストロフィやスタルガルト病のうち重症のタイプでは、視野障害（見えにくい場所）が視界の中心から周辺部まで広がることがあります。

⑦ この病気にはどのような治療法がありますか

黄斑ジストロフィはもともと身体に備わった性質、すなわち遺伝子の異常による疾患であり、現在のところ根本的に治療する方法はなく、病院から処方される治療薬もありません。

一般的には、強い太陽光による障害を避けるために屋外ではサングラス（遮光眼鏡）を掛けることが推奨されています。また、治療効果は明らかではありませんが、黄斑部の保護を目的とするサプリメント（ルテイン、ゼアキサンチン等）の内服は世界的にも推奨されています。

なお、網膜の遺伝病のなかには、すでに遺伝子治療や薬物治療等の臨床治験が開始されている疾患もあります。今後の研究の進展により、この病気を根本的に治す治療法が実用化される可能性もあります。

⑧ この病気はどういう経過をたどるのですか

前述の⑥のように、黄斑ジストロフィの経過は疾患のタイプによって、また個人によって大きく異なります。一般的には、視力低下、視野異常等の症状は発症後ゆっくりと進行していきますが、小児期に発症する症例では比較的進行が早く、成人後に発症する症例では進行が遅い傾向があります。また、一般的に発症時期が若年であるほど症状は重く、遅いほど最終的な障害は軽度であることが多いと考えられています。なかには、十分に読み書きができる程度の視力が中年以降まで保たれている患者さんもいらっしゃいます。

⑨この病気は日常生活でどのような注意が必要ですか

網膜はもともと光（とくに紫外線）に弱い組織ですので、長時間日差しの強いところに出る場合は、サングラス、つばの広い帽子などで目を守ることをお勧めします。

また、低下した視力を有効に活用するためには、眼鏡を正確に合わせるだけでなく、遮光眼鏡、ルーペ、タブレット型 PC、拡大読書器などの補助具が必要になることもあります。眼科外来で自分の視力や視野を確認するとともに、学業や就労、職場での不自由さを軽減するために、大学病院などに併設されているロー

ビジョン外来や、各都道府県の視覚障害者支援施設等でそれぞれの障害レベルに合った支援を受けるようにします。

⑩ 各疾患の説明

1)　卵黄状黄斑ジストロフィ(ベスト病)

常染色体優性（顕性）遺伝の黄斑ジストロフィであり、*BEST1* 遺伝子の異常を原因とします。

若年時に発症し、黄斑部にリポフスチンと呼ばれる有害な黄色物質が蓄積することで黄斑部の機能が低下します。本疾患の名前は、この黄色物質が「卵黄」の様に見えることに由来しています。ただし、若年時には視力が低下する可能性は低く、成人以降から中年期になってから視力低下を訴えたり、検診で眼底異常を指摘されたりして眼科を受診することが多いです。進行すると中心部の見え方がゆっくりと悪化していきますが、周辺部の見え方は最後まで良好のまま保たれます。

なお、成人期以降の眼底では本疾患に特徴的な卵黄様物質は消失しており、本疾患を一般の眼科で診断することは困難となります。このため加齢黄斑変性や、中心性漿液性脈絡網膜症など、他の疾患と誤って診断されることが多い疾患でもあります。

なお、本疾患は常染色体顕性（優性）遺伝のため、子供に遺伝する可能性があります。ただし、本疾患と同じく *BEST1* 遺伝子の異常を原因とするものの、常染色体潜性（顕性）遺伝の形式をとる黄斑ジストロフィもあり、このタイプは「常染色体潜性（劣性）ベストロフィン症」と呼ばれています。自覚症状や検査所見に大きな違いは見られませんが、眼底にみられる黄色物質の範囲がやや拡大しているのが特徴です。

現在のところ本疾患に有効な治療法はありませんが、症状が進行した患者さんには、まれに黄斑部に出血（黄斑新生血管）が生じることがあり、その際には対症療法としての治療が必要となります。

2)　スタルガルト病

黄斑部における網膜萎縮（視細胞が消失すること）と、その周囲に見られる黄色斑を特徴とする黄斑ジストロフィです。*ABCA4* 遺伝子の異常を原因とする常染色体潜性（劣性）遺伝の疾患で、発見者の名前から命名されています。

主に若年発症例と晩期発症例に分けられ、若年発症例では 10 歳前後で両眼の視力低下を自覚します。小児期の進行は比較的速く、数年のうちに黄斑部萎縮が進行し、視力が低下していくことが多いです。一方で、発症年齢が 20 歳以上の晩期発症例においては黄斑部のさらに中心部（中心窩）が長期的に温存されるこ

とが多く、比較的長期にわたって視力が維持される傾向があります。また、網膜の障害が黄斑部付近に留まるタイプから、周辺部に拡大して広範囲の視野異常を来すタイプまで、多彩な疾患経過を示すことが知られています。

本疾患に対しては、これまでに再生医療、薬物内服治療、遺伝子治療などの臨床治験が海外を中心に数多く行われておりますが、現在のところ実用化はされていません。今後の治療の実現が期待されています。

なお、本疾患は網膜におけるビタミン A の代謝異常が原因であり、有害な代謝産物が異常蓄積することで網膜が傷害されることが分かっています。このため、サプリメントを服用するさいには、ビタミン A が含まれていない製品を選ぶ必要があります。

3)　オカルト黄斑ジストロフィ（三宅病）

眼底所見が正常であり、その他の画像検査（フルオレセイン蛍光眼底造影および眼底自発蛍光）においても明らかな異常が見つからない、常染色体顕性（優性）遺伝の黄斑ジストロフィです。網膜の障害が正常な眼底所見によって隠されていることから、オカルト（occult＝ 目に見えない）黄斑ジストロフィと命名されています。また発見者の名前から、三宅病とも呼ばれています。本疾患の原因が *RP1L1* 遺伝子の異常であることは、2010 年に日本の研究チームによって初めて明らかにされました。

眼底所見だけでなく、網膜の電気反応（全視野 ERG）が正常であるであるため診断は難しく、弱視、緑内障、視神経疾患、心因性など、他の疾患として経過観察をされている患者さんが多い疾患です。ただし、網膜の断面を撮影する OCT（光干渉断層計）を用いると、本疾患に特徴的な黄斑部の異常を見つけることができます。

特徴的な症状は両目の視力低下と羞明（まぶしさ）です。自覚症状の出現時期は 10 才頃から 60 才以上までと非常に幅があり、両眼の視力が極めてゆっくりと低下するのが特徴です。視力低下の程度には大きな個人差がありますが、他の黄斑ジストロフィに比べると視力低下の割には不自由を訴える程度は軽い傾向があります。日本人多数例における三宅病の長期経過を調査すると、発症から約 15 年間は徐々に視力が低下するものの、それ以降は視力がほとんど変化していないことが分かっています。また、ほとんどの患者さんでは進行期でも 0.1 以上の矯正視力が維持されること、また、中心部以外の周辺部視野は良好に保たれることが確認されており、他の黄斑ジストロフィに比べて障害の程度が軽い疾患であることが分かっています。

現在のところ本疾患に有効な治療法はありません。

4）錐体ジストロフィ，あるいは錐体-杆体ジストロフィ

網膜で最初に光を受け取る細胞を視細胞（しさいぼう）と言います。視細胞には、主に明るい場所で細かい物を見るのに役立つ錐体（すいたい）細胞と、主に暗い場所で周辺の物を見るのに役立つ杆体（かんたい）細胞の 2 種類があります。錐体ジストロフィとは、前者の錐体細胞の機能が徐々に障害されることにより、視力低下、羞明（まぶしさ）、色覚異常などが進行する疾患です。また、進行に伴い錐体機能に続いて杆体機能が障害されることも多く、そのような病態は錐体-杆体ジストロフィと呼ばれています。

錐体ジストロフィおよび錐体-杆体ジストロフィは、黄斑ジストロフィのなかで最も患者数の多い代表疾患です。本疾患の診断には、光に対する網膜の反応を測定する網膜電図（ERG）が必須です。ERG では、錐体機能が杆体機能に比べて特に低下していることを確認します。

遺伝形式は常染色体顕性（優性）遺伝、常染色体潜性（劣性）遺伝、X 連鎖性潜性（劣性）遺伝と様々で、原因となる遺伝子も３０種類以上が報告されています。

一般的な症状としては、学童期から 20 歳頃までに視力低下、眩しさ、色覚異常、中心部の見えにくさなどを訴え、症状は徐々に進行して行きます。特に屋外で感じる眩しさは、本疾患に特徴的な症状です。ただし、原因となる遺伝子も多岐に渡るため、視力低下や視野異常の程度は患者さんによって大きな差があります。また、患者さんによっては中心窩（黄斑部の中心）が長期的に保たれ、30 代以降に初めて症状が出現して眼科を受診する方も珍しくありません。さらに、眼底所見が正常に近いタイプの錐体ジストロフィも比較的多く、この場合には診断がやや難しくなります。

本疾患の原因となる一部の遺伝子については、遺伝子治療を始めとした治療研究が進んでおり、臨床治験も行われています。将来的には、一部の疾患に対する治療が実現される可能性があります。

5）X 連鎖性若年網膜分離症(先天網膜分離症)

ヒトの網膜は網膜神経線維層、神経節細胞層、視細胞層、網膜色素上皮層など多くの層から構成されています。X 連鎖性若年網膜分離症とは、特に黄斑部において網膜の各層が分離してしまい、徐々に視力が低下する疾患です。また、一部の患者さんでは周辺部の網膜でも分離が生じることがあります。本疾患は X 連鎖性潜性（劣性）遺伝の疾患であり、男性のみに発症します。原因遺伝子として、網膜の細胞接着に重要な *RS1* 遺伝子が知られています。

一般的な症状は、主に学童期に自覚する視力低下、羞明です。初期には視力低下が軽度で成人後に初めて受診する症例もあります。多くの患者さんでは、周辺

部の視野は長期的に良好に保たれます。一方、約 1/3 程度の患者さんでは周辺部の網膜でも分離が観察されます。周辺部の網膜分離は、ときに網膜剥離、硝子体出血などを伴うことがあり、手術治療が必要な場合もあります。

若年期の黄斑部分離は、網膜の断面を撮影する OCT（光干渉断層計）によって明瞭に観察することができますが、中年期に近づくと特徴的な所見が消失するため、萎縮型加齢黄斑変性等、他の疾患と間違われることがあります。

本疾患に対しては海外において遺伝子治療の臨床治験が行われていますが、現在のところ治療は実用化されていません。

6）中心性輪紋状脈絡膜ジストロフィ

黄斑部を含む円形の領域で網膜の萎縮が観察されるタイプの黄斑ジストロフィです。黄斑部以外の網膜の色調は良好に見えますが、病変が黄斑部以外に広がっていることもあります。主に眼底所見を元にした分類であるため、前述の「錐体-杆体ジストロフィ」と重複して分類される患者さんも多いです。また、同様の眼底所見は萎縮型加齢黄斑変性の進行期でも見られることがあるため、診断のためには発症からの経過や家族歴を慎重に確認する必要があります。発症原因としては、*GUCY2D* 遺伝子、*PRPH2* 遺伝子を始めとして、主に錐体-杆体ジストロフィに関連する様々な遺伝子が関与していると考えられています。

7）その他の黄斑ジストロフィ

上述の、1）から 6）に分類されない黄斑ジストロフィが対象となります。

具体的には、全視野網膜電図（ERG）において杆体反応、錐体反応がともに正常で、黄斑部の網膜機能のみが傷害されていること。そして、卵黄状黄斑ジストロフィ、スタルガルト病、錐体（錐体-杆体）ジストロフィ、X 連鎖性若年網膜分離症、オカルト黄斑ジストロフィ、中心性輪紋状脈絡膜ジストロフィのいずれにも該当しないことが条件となります。実際の患者数としては、黄斑ジストロフィのなかでは錐体-杆体ジストロフィと並んで最も多く見られるタイプです。

発症に関与する原因遺伝子は多く知られており、遺伝形式も常染色体顕性（優性）遺伝、常染色体潜性（劣性）遺伝、X 連鎖性潜性（劣性）遺伝と様々です。視野障害が中心部に限定されるという特徴がありますが、その他の自覚症状、自然経過、原因遺伝子、治療研究等については、錐体-杆体ジストロフィの項で記載した内容とほぼ同じになります。

⑪この病気に関する資料・リンク

黄斑ジストロフィの診断ガイドライン
https://www.nichigan.or.jp/member/journal/guideline/detail.html?itemid=313&dispmid=909