

tion and function of ϵ -sarcoglycan in neurons have not been investigated, and the mechanism by which ϵ -sarcoglycan deficiency causes MDS is unknown.

Interestingly, in a patient with early-onset dystonia with myoclonic features, a 18bp deletion in the torsin A gene has been reported.¹⁶ Further studies will be needed to clarify whether mutations of SGCE and torsin A act independently to cause MDS or if they are functionally connected.

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Preserved Visual Function in a Case of Occipitoparietal Microgyria

Pascal Zesiger, PhD,¹ Daniel Kiper, PhD,² Philippe Maeder, MD,³ Thierry Deonna, MD,⁴ and Giorgio M. Innocenti, MD⁵

A 20-year-old man with bilateral parasagittal occipitoparietal polymicrogyria and epilepsy, from whom normal functional magnetic resonance imaging and electroencephalogram responses to visual stimuli were obtained, was found to have no visual perceptual deficits. This suggests that microgyric cortex can perform normal visual functions, despite its gross structural abnormalities.

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Microgyria is a disorder in cortical layering and gyration probably caused by local ischemia before the end of neuronal migration, as suggested by neuropathological and imaging observations in humans^{1,2} and by experimental work in animals.^{3–6}

Electrophysiological and imaging observations in animals⁷ and in man⁸ indicate that the microgyric cortex can be activated by normal stimuli and preserves much of its normal functional characteristics. However, it may become hyperexcitable or epileptic.^{9–11} Therefore, it is unclear what the consequences of microgyria

From the ¹Faculty of Psychology and Educational Sciences, University of Geneva, Geneva; ²Institute of Neuroinformatics, University/ETH Zürich, Zürich; Departments of ³Radiology and ⁴Pediatric Neurology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; and ⁵Division of Neuroanatomy and Brain Development, Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden.

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Address correspondence to Dr Innocenti, Division of Neuroanatomy and Brain Development, Department of Neuroscience, Karolinska Institutet, S 17177 Stockholm, Sweden.
E-mail: giorgio.innocenti@neuro.ki.se

might be in the perceptual or cognitive domains, especially because the cortex surrounding the microgyric focus also can be altered.¹²

We report here the case of a young man in whom normal activation of the visual cortex⁸ including the polymicrogyria was accompanied by preserved vision.

Case Report

The full clinical history of R.d.V., including magnetic resonance imaging, functional magnetic resonance imaging, and electroencephalogram analyses were described previously.⁸ The patient has bilateral polymicrogyria at the occipital pole, upper bank, and deep portion of the calcarine sulcus and in the cuneus (Fig 1). At clinical examination, his visual function showed moderate concentric narrowing of the visual fields (Fig 2). This probably was caused by the treatment with vigabatrin¹³ (Sabril R; 3gm/day) which from 13.5 to 17 years of age replaced carbamazepine that could no longer control epileptic seizures. Visual acuity using optotypes was decreased (30/60 right, 36/60 left), not confirmed with psychophysical tests (see below), and stereoscopic vision was lacking possibly because of early convergent microstrabismus.

Results

Neuropsychological Examination with Standard Tests

The patient was examined at age 18.5 years using an extensive battery of tests (Table).

Results of the Revised Wechsler Intelligence Scale for Adults were globally within norms but with an important difference between the verbal and performance scales because of his slowness and therefore poor results in timed items.

R.d.V.'s visual perception test results were normal. All subtests of the Birmingham Object Recognition Battery yielded normal results. The matching of unfamiliar faces was within norms. He could easily identify Poppelreuter-type overlapping figures. The performance at Hooper's visual organization test was within normal limits. There was no deviation in the line bisection tests. In Bell's visual search test, there was no sign of hemineglect, although the overall performance was weak because of a high rate of omissions.

In contrast, the patient performed poorly in tests involving visual memory, particularly those demanding delayed recall. The copy and immediate memory of Rey's complex figure were adequate although very slow. Immediate and delayed recall of lists of words¹⁴ was within norms. With lists of drawings,¹⁴ however, a peculiar phenomenon was observed. In the immediate recall, the form of the drawing usually was correctly produced but rotated at 90 degrees. Consequently, if the performance is scored without taking orientation into account, it falls within norms; if orientation is taken into consideration, it is below norms. The same observation holds for delayed recall, but the performance was below normal whatever scoring method was used. No such difficulty was observed in an immediate

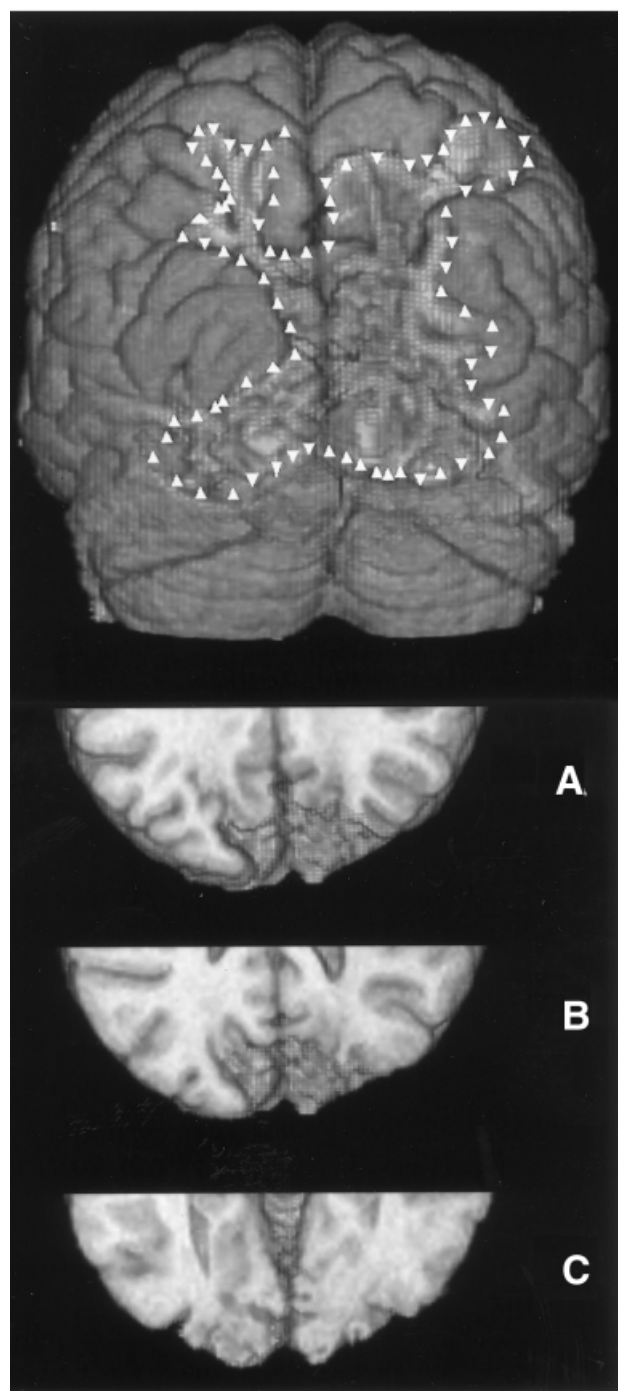


Fig 1. (top) Three-dimensional surface rendering of the occipital poles of the patient. The microgyric region is outlined. (bottom) Sections through occipital poles of the same patient correspond to those marked in Figure 2 (A, B, C).

recognition memory test¹⁵ for written words and designs. The visuospatial span at Corsi's test was at the inferior limit of norms. Finally, a reduced stereoscopic sensitivity was observed, with no coherent response when the angle of stereopsis was smaller than 100 feet at 16 inches.

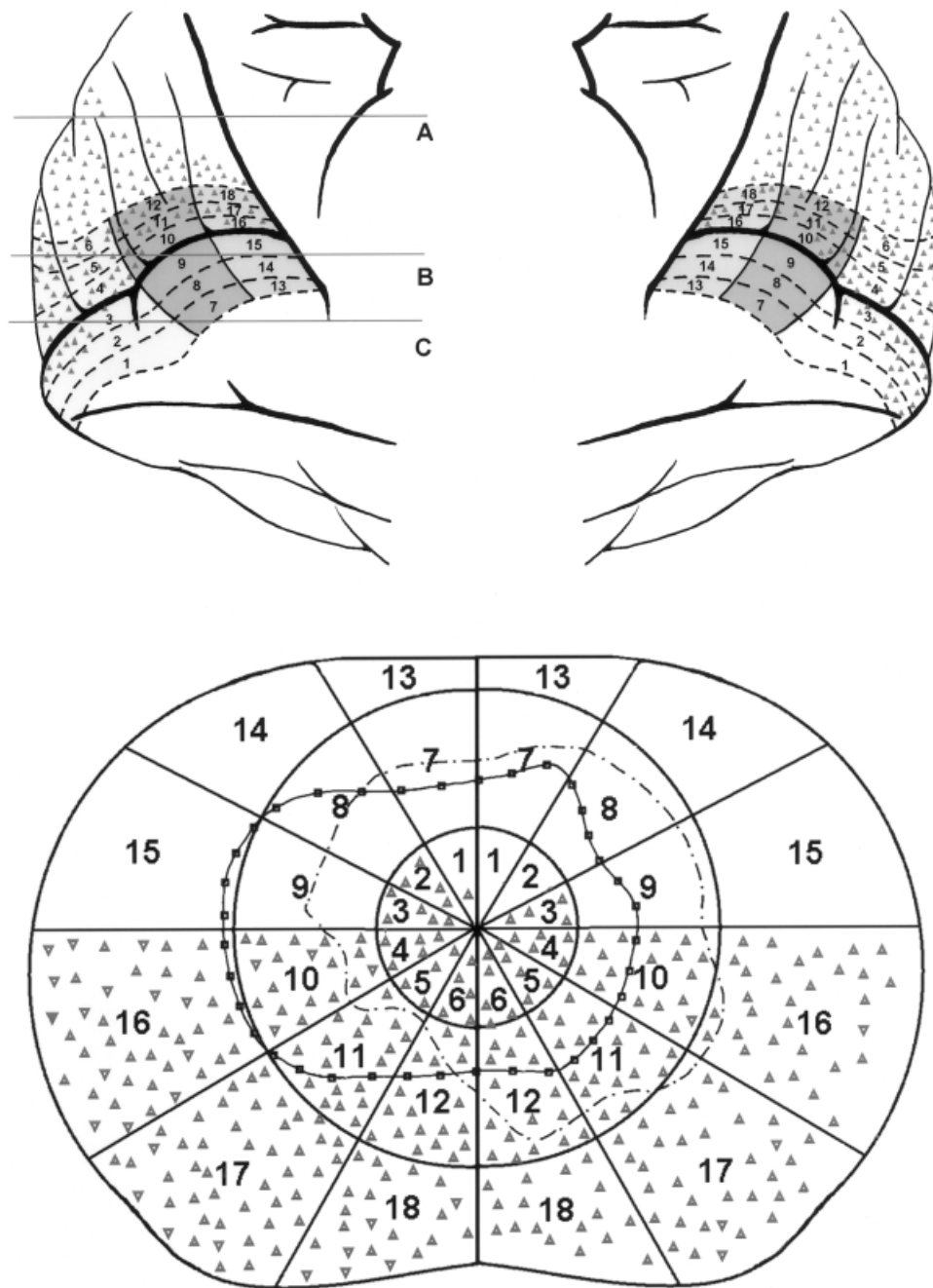


Fig 2. (top panels) Schematic rendering of the region of the calcarine sulcus showing the classic representation of visual field coordinates (redrawn from Grüsser and Landis¹⁸). The microgyric region is marked with small triangles. The planes of sections shown in Fig 1 are indicated (A, B, and C). (bottom) Chart of the visual field showing the region corresponding to the microgyric part of V1 (triangles) as well as the visual field of the patient, as determined by Goldman perimetry (left eye, continuous line with squares; right eye, interrupted line). Notice that most of the central visual field and the entire lower hemifield of the patient correspond to a microgyric portion of cortex. The concentric narrowing of the visual field probably is caused by the prolonged subadministration of vigabatrin¹³ and does not correlate with the visual field coordinates of the microgyric cortex.

Visual Psychophysical Studies

R.d.V. was examined at age 17.5 years with psychophysical tests and ad hoc tests of visual function previously used in children.¹⁶ Data from a normal adult (aged 38 years) with corrections to normal vision were

collected at the time of the experiments, using the same stimuli and viewing conditions.

CONTRAST SENSITIVITY A single static patch of sinusoidal grating was presented on either side of the mon-

Table. Results of R.d.V.'s Neuropsychological Examination

Test	Score	Comment
WAIS-R		
Full-scale IQ	92	Normal
Verbal IQ	108	Normal
Information	9	Normal
Digit span	11	Normal
Vocabulary	9	Normal
Arithmetics	11	Normal
Comprehension	13	Normal
Similarity	12	Normal
Performance IQ	72	Lower limit of norms
Picture completion	7	Normal
Picture arrangement	8	Normal
Block design	6	Slightly subnormal
Object assembly	7	Normal
Code	3	Sub-normal
Birmingham Object Recognition Battery		
Object copy	Good performance	Normal
Length match	25/30	Normal
Size match	29/30	Normal
Orientation match	30/30	Normal
Position match	38/40	Normal
Minimal feature match	25/25	Normal
Foreshortened view	25/25	Normal
Object decision (hard)	26/32	Normal
Single object identification	10/10	Normal
Overlapping object identification	10/10	Normal
Two overlapping letters	17/18	Normal
Three overlapping letters	15/18	Normal
Benton facial recognition test	45/54	Normal
Poppelreuter-type overlapping figures	26/26	Normal
Hooper visual organization test	21/30	Low probability of impairment
Line bisection test	No deviation	Normal
Bell visual search test	29/35	Subnormal (−3.5 SD)
Rey's complex figure		
Copy		
Accuracy	33	Normal
Type	I	Normal
Speed	5 min 33 sec	Subnormal (centile 10)
Immediate memory		
Accuracy	32	Normal (superior)
Visual and verbal memory ¹⁴		
12-word learning	10.5/12	Normal
Delayed recall	8/12	Normal
12-design learning		
With orientation	3.5/12	Subnormal (−3.3 SD)
Without orientation	10/12	Normal
Delayed recall		
With orientation	2/12	Subnormal (−4.2 SD)
Without orientation	6/12	Subnormal (−2.0 SD)
Corsi block tapping test (span)	4	Low normal
Visual and verbal recognition ¹⁵		
Words	21/24	Normal
Figures	15/24	Normal
Recognition memory for faces	15/25	Subnormal (< centile 5)
Stereoscopic vision test (Stereoptical)	6/12	Reduced stereoscopic vision

WAIS-R = Revised Wechsler Intelligence Scale for Adults; SD = standard deviation.

itor. The space-averaged luminance of the patch was equal to that of the background (32 candela [cd]/m²). At the viewing distances that we used (100–200cm),

the screen subtended from 8.5 to 17 degrees and the patches from 2.8 to 1.4 degrees. For the lower spatial frequencies, the patch size was increased to ensure that

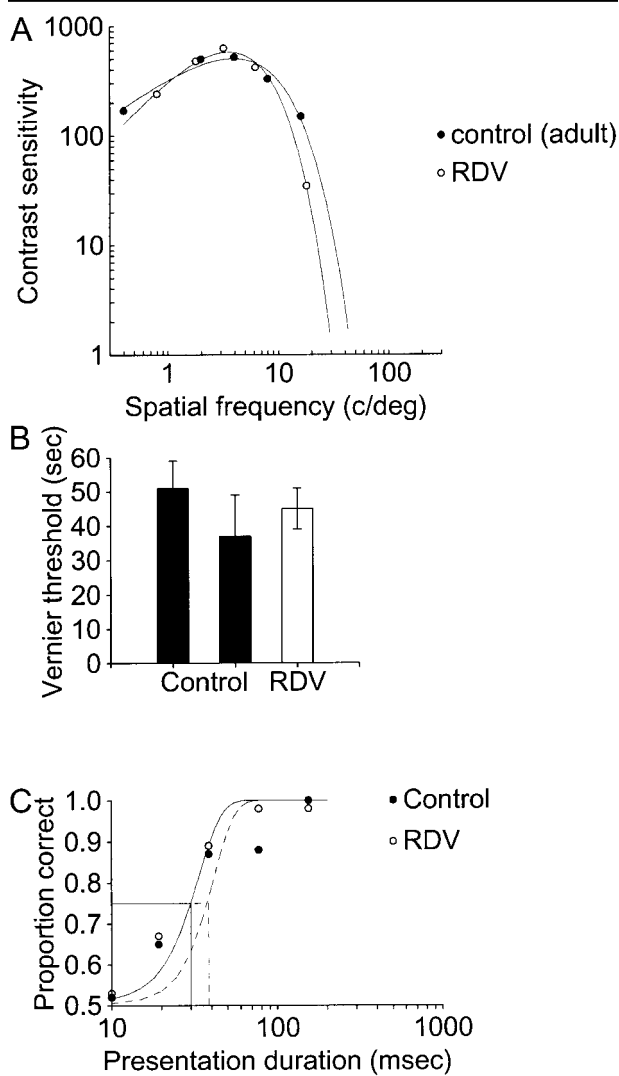


Fig 3. Results of the psychophysical experiments. All stimuli were presented on an Eizo T-560i monitor, driven by an AT Truevision Vista graphics board mounted in a personal computer. The screen refresh rate was 104Hz, interlaced. Testing was performed in a dimly illuminated room. Viewing was binocular. All experiments used a two- or three-alternative forced choice procedures and the method of constant stimuli. Initially, five values of the experimental variable were determined, spanning the subject's performance range from chance to 100% correct. These five stimuli then were presented in pseudorandom order within each of 20 or more blocks. Psychometric functions were fitted to the data by probit analysis,¹⁹ and thresholds were defined as the 75% (for 2AFC), or 66% (3AFC) correct points. Responses (verbal) were recorded in the computer by the experimenter. The subject was told after each trial whether the preceding response had been right or wrong. (A) Binocular contrast sensitivity functions for R.d.V. (open circles) and a normal adult observer (filled circles). We measured contrast detection thresholds for five different spatial frequencies (0.8, 1.8, 3.2, 6.2, and 18 c/degrees). The inverse of the contrast detection threshold (ie, contrast sensitivity) is plotted here as a function of spatial frequency. These points were fitted with a double-exponential function of the form: $k_1 (\omega k_\omega)^\alpha e^{-\beta \omega k_\omega}$, where ω is spatial frequency. The four free parameters affect primarily the steepness of the low- (α) and high-frequency (β) portions of the curves and shifts along the horizontal (k_ω) and vertical (k_s) axes. The intersection of the curves with the abscissa provides an estimate of the subject's grating acuity. It was 31 c/degrees for R.d.V. and 38 c/degrees for the control. (B) Vernier offset thresholds (in seconds of arc) for R.d.V. (open bar) versus that of the control (filled bars). In the control subject, the test was repeated at approximately a 1-year interval. (C) R.d.V.'s (open circles) and control (filled circles) proportions of correct responses as a function of the presentation duration are shown. The curves through the data are integrals of a Gaussian, obtained by Probit analysis (see text). R.d.V.'s threshold (defined as the 75% correct point, solid line intersecting the solid curve) was not significantly different from that of the control subject (dashed line and curve).

at least three cycles of the grating were visible. The subject indicated which side of the screen the patch had been presented on: the left or the right.

Figure 3A shows R.d.V.'s binocular contrast sensitivity curve, compared with that of the normal adult control. At all the spatial frequencies tested, the patient's sensitivity was normal, and so was his extrapolated acuity (seen as the intersection of the contrast sensitivity function with the abscissa; R.d.V.: 31 c/degrees, control: 38 c/degrees). Independent measures of R.d.V.'s monocular contrast sensitivity yielded similar results (not shown).

VERNIER ACUITY Two vertical line segments (luminance, 64cd/m²) were presented on a low-luminance background (2cd/m²). The top, longer segment (5.6 degrees in length; 5.1 minutes in width) remained in a fixed position, whereas the bottom segment (same width; 2.84 degrees in length) could be presented either to the right or to the left of the top one. The

vertical distance between the two segments was 1.2 minutes. The patient indicated the position of the bottom segment relative to the top one (left, right, or aligned), and we measured the minimal offset necessary for reliable, correct responses.

Figure 3B shows the Vernier threshold for R.d.V. compared with that of the normal adult control. R.d.V.'s threshold was 45 (± 6) seconds, which is similar to that of the normal adult (51 ± 8 seconds and 37 ± 12 seconds in two separate assessments) tested in the same conditions.

FIGURE-GROUND SEGREGATION An array of iso-oriented line segments was presented, subtending 22.3 degrees, and containing 16 by 16 equally spaced elements. The line segments subtended 0.9 degrees and had a luminance of 62cd/m². Background luminance

was 2cd/m². Within this array, a subset of segments arranged in a rectangle 4 degrees in width and 10 degrees in height had a different orientation from those in the background. The orientation of the lines was pseudorandomly varied from trial to trial, but the angle between the rectangle's elements and those in the background was kept at 90 degrees. The subject had to say whether the rectangle was presented vertically ("standing") or horizontally ("lying"). We measured the minimal presentation duration necessary for the reliable detection of the rectangle's orientation, which, like the rectangle's position, was pseudorandomly varied from trial to trial. The same task was also performed with rectangles defined by other visual attributes. In the first variation, small rectangles or triangles replaced the line segments, the first used for the background and the second for the figure. In the second variation, the figure was defined by segments that had a subthreshold angle difference with those in the background (10 degrees for a 100-millisecond presentation), and the rectangle moved (horizontally or vertically) across the screen. In the third variation, the line segments in the rectangle had the same orientation as those in the background but differed in luminance. In the last variation, the elements defining the figure were small squares (0.3 degrees side), whose color differed from those in the background.

When the rectangle was defined by line segments differently oriented from those in the background (see Fig 3C), R.d.V. needed presentation times of 30 (± 12) milliseconds to correctly identify the rectangle's orientation, which is slightly better than the normal adult threshold (38 ± 11 milliseconds). Although the absolute value of the thresholds measured in the different variations of the task did vary significantly (not shown), R.d.V.'s performance was indistinguishable from normal in all conditions.

Discussion

This patient's condition is similar to that reported by Guerrini and colleagues¹⁷ in nine patients with bilateral parasagittal occipitoparietal polymicrogyria and epilepsy. Those patients showed no obvious visual impairment, but none of them underwent detailed neuropsychological testing and psychophysical evaluation of vision.

R.d.V.'s lack of stereoscopic vision is probably caused by a loss of binocular neurons in the visual areas, caused by the early microstrabismus. Microgyria "per se" did not eliminate binocular responses in an animal model.⁷ The weak results on the visual memory for faces, visual search task, and long-term memory may represent subtle deficits in these demanding tasks that are not directly related to the microgyric alteration in low-order visual areas.

The mild deficits mentioned above contrasted with

the normal performance of this patient in all tests of visual perception, including the accurately quantified psychophysical investigations. Therefore, it appears that a malformed cortex, which can provide normal responses to functional investigations such as functional magnetic resonance imaging and electroencephalogram,⁸ is also capable of serving visual function.

This study of R.d.V. demonstrates that structural-functional relations can be particularly multifaceted and elusive in the cerebral cortex, at least after early-onset developmental pathologies. This conclusion became even more compelling when we compared R.d.V. with two patients with perinatal destruction of the primary visual areas due to bacterial meningitis^{16,20} and with one patient with congenital temporooccipital epilepsy without any visible lesion of the visual areas (T. Deonna, unpublished data). In all those three cases severe visual deficits were found. Indeed, the patients were severely impaired in several perceptual tasks, particularly in figure/ground discriminations, which were normal in R.d.V.

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Involvement of Lysosomes in the Pathogenesis of CAG Repeat Diseases

Mitsunori Yamada, MD, PhD,¹ Shoji Tsuji, MD, PhD,² and Hitoshi Takahashi, MD, PhD¹

In CAG repeat diseases, affected neurons possess many cytoplasmic granules immunopositive for expanded polyglutamine stretches. Electron microscopic immunohistochemistry showed that the granules corresponded to lysosomes of primitive type. The results suggest that, in addition to the ubiquitin/proteasome pathway, mutant proteins with expanded polyglutamine stretches are involved in the lysosomal pathway for protein degradation and that this processing mechanism may serve as a target for a new therapeutic approach to CAG repeat diseases.

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The expansion of a CAG repeat encoding a polyglutamine tract is a common gene mutation in several hereditary neurodegenerative diseases, including Machado–Joseph disease (MJD) and dentatorubral-pallidoluysian atrophy (DRPLA).^{1,2} The formation of neuronal intranuclear inclusions (NIIs) is a common pathological hallmark^{3–6} and is closely related to a pathogenic mechanism of these disorders.^{5,7} In our previous studies of Huntington's disease,⁸ MJD,⁹ and DRPLA,¹⁰ we observed that affected neurons also possessed many cytoplasmic granules immunopositive for expanded polyglutamine (polyQ) stretches, which were undetectable by ubiquitin immunohistochemistry.⁴ The morphology of these granules differed from that of the intracytoplasmic filamentous inclusions seen in dentate nuclear neurons in DRPLA^{11–13} and were present throughout the central nervous system regions affected by each disease. To elucidate the molecular mechanism responsible for neuronal degeneration in CAG repeat diseases, it is necessary to show the ultrastructural nature of the labeled granules. However, such examination has been hitherto impossible, because formic acid treatment, which is an essential step in immunohistochemical detection of expanded

From the Departments of ¹Pathology and ²Neurology, Brain Research Institute, Niigata University, Niigata, Japan.

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Address correspondence to Dr Yamada, Department of Pathology, Brain Research Institute, Niigata University, 1 Asahimachi, Niigata 951-8585, Japan. E-mail: nori@bri.niigata-u.ac.jp