**Age at Onset Curves of Retinitis Pigmentosa**

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**Objective:** To calculate age at onset curves of retinitis pigmentosa (RP) to resolve the difficulty in calculating the recurrence risk in a family. Retinitis pigmentosa is a common hereditary retinal disease that leads to blindness. It is a slow-onset disease, and family members of patients sometimes develop RP later.

**Methods:** We studied 370 patients with typical RP. The age at onset was defined as when the patient's RP was diagnosed by an ophthalmologist. After confirmation that the age at onset came from normal distribution, we drew the age at onset curves.

**Results:** The average age when patients were diagnosed with RP was 35.1 years, and the median age was 36.5. The onset ratio straightly increased with age until 65 years, so the onset ratio was relatively low at young ages.

**Conclusions:** The age at onset curves are quite simple and useful tools that facilitate counseling at an RP clinic. Without them, the recurrence risk would be misleading.


RETINITIS PIGMENTOSA (RP) IS a set of inherited retinal disorders that lead to blindness. Usually, patients have no prominent symptoms in childhood; however, because of progressive photoreceptor cell degeneration, their vision is gradually lost during adolescence and adulthood.1

Because no efficient therapies have been developed, genetic counseling is quite important at an RP clinic. One of the issues that patients are interested in is recurrence risk in their family, which is the probability of the development of a specific disease in other family members. At an RP clinic, this risk rate is usually calculated as a segregation rate of the disease genotype.2,3 For example, under the assumption of autosomal recessive inheritance, the probability of a disease genotype in a sibling of the proband is calculated as 25%.

This calculation is completely true for the probability of a disease genotype. However, it does not hold true for the RP phenotype because RP is a late-onset disease. In RP, the genotype is fixed at conception; however, the onset of disease may not manifest until several decades later. So it is possible that the family members display a normal phenotype and develop the RP phenotype at a later stage. Retinitis pigmentosa is not a lethal disease, so the rate of family members displaying the RP phenotype will increase with age. On the contrary, the probability that a healthy member of the family will develop RP will decrease with age. For example, when the age of the patient's sibling is 0 years, the recurrence risk is 25%, the same as the segregation rate. However, the risk rate will decrease with age and the older the sibling, the lower the risk that he or she will develop RP. An important question to ask is how much will the risk decrease with age?

In such late-onset diseases, including Huntington disease,4-6 late-onset cerebellar ataxia,7 and hereditary hemorrhagic telangiectasia,8 age at onset curves are useful in genetic counseling. Onset curves enable us to estimate the chance of an asymptomatic person subsequently developing the disease.9 However, to our knowledge, to date, the curve has not been estimated for RP. In this article, we calculated an age at onset curve for RP in the Japanese population.

**METHODS**

We studied 370 patients with typical RP seen at Tohoku University Medical School and Osaka University Medical School. Patients with typical RP were identified by the characteristic retinal pigmentary change, visual field loss, and abnormalities on electroretinography. The type
of mendelian inheritance was classified based on previous reports. The age at onset was defined as when the patient's RP was diagnosed by an ophthalmologist. We assumed the penetrance of autosomal RP in Japan as 87%. Complete penetrance was assumed in the other types of RP.

RESULTS

BASELINE INFORMATION

In 370 patients with typical RP, 80 (21.6%) were classified as having autosomal dominant RP (ADRP); 80 (21.6%), autosomal recessive RP (ARRP); 194 (52.4%), sporadic RP; and 13 (3.51%), X-linked RP. Of these, 177 (47.8%) were male and 193 (52.2%) were female. We could not determine the heritage trait in 3 patients (0.81%). These spectrums (heritage trait and sex) are not significantly different from those in previous reports of Japanese RP etiology using the /H92732 test.

ALL TYPES OF RP

The average age when patients were diagnosed with RP was 35.1 years, and the median was 36.5 years. The youngest age was 1 year and the oldest age was 89 years. As described earlier, we declared the age at onset as the age of diagnosis. This could possibly cause some errors, which would make the samples not suitable for statistical analysis. We first performed the Kolmogorov-Smirnov test to decide if the samples came from a population with normal distribution. The maximum difference between samples and normal distribution (mean [SD], 35.1 [17.35]) was 0.61, which is smaller than 1.165 (Kolmogorov-Smirnov z). Therefore, the sample distribution was not different from the normal distribution (P = .13).

Figure 1 shows an age at onset curve for all RP. The curve displays a probability that an individual carrying the disease genotype will have developed RP by a given age (onset ratio). The onset ratio increases in a straight fashion until age 65 years.

Autosomal Dominant RP

Figure 2 shows an age at onset curve for patients with ADRP. Curve A shows the probability that an individual carrying the disease allele will have developed RP by a given age. Curve B shows the risk that a healthy child of an affected patient carries the disease allele. The average age when they were diagnosed with RP was 36.9 years old, and the median age was 40 years.

Autosomal Recessive RP

The age at onset curve for ARRP is shown in Figure 3. The average age when they were diagnosed with RP was 36.2 years old, and the median age was 40 years. Autosomal recessive inheritance diseases are mainly caused by a loss of function–type mutation and are sometimes more severe than the autosomal dominant mutations. To confirm this is also the case in RP onset age, we per-

Figure 1. An age at onset curve containing all types of retinitis pigmentosa. The curve shows the probability that an individual carrying the disease genotype will have developed retinitis pigmentosa by a given age.

Figure 2. An age at onset curve of autosomal dominant retinitis pigmentosa. Curve A indicates the probability that an individual carrying the disease allele will have developed retinitis pigmentosa by a given age. Curve B indicates the risk that a healthy child of an affected patient carries the disease allele (the rate of carrier).

Figure 3. An age at onset curve of autosomal recessive retinitis pigmentosa. The curve shows the probability that an individual carrying the disease allele will have developed retinitis pigmentosa by a given age.
formed a standard $t$ test that revealed there was no significant difference in the age at onset between ADRP and ARRP ($P = .40$). However, our ascertainment might contain a bias since individuals in ADRP families (who often have $\geq 1$ affected parent) might be examined by an ophthalmologist more frequently, leading to a diagnosis at an earlier age.

**COMMENT**

Retinitis pigmentosa is not only a late-onset disease, but a disease that slowly progresses. Because of this feature, it is quite difficult to state exactly when onset of RP occurs. Some patients receive a diagnosis under subclinical conditions (without any symptoms), while others will display severe visual field loss. This would account for an error in our study. Because of this difficulty, we defined the age at onset as the time in which the patient was diagnosed with RP. There were other choices, for example, the presence of symptoms, such as night blindness. However, to determine the onset age of such subjective symptoms is much more difficult. Patients sometimes could not say exactly when they began to have night blindness and some patients did not complain about night blindness altogether. In an RP clinic, at the time of diagnosis of RP, the declaration that a patient’s disease may lead to blindness is quite an important event in a patient’s life. Because the age at onset curve will be used in genetic counseling, the point of diagnosis of RP may fit our purpose. Moreover, we collected a relatively large number of samples and the Kolmogorov-Smirnov test revealed that the sample distribution was not significantly different from a normal distribution.

The age at onset curve is an important tool for counseling patients with RP. However, most clinicians are not familiar with the use of this curve. Thus, we will show some examples.

**EXAMPLE 1: ARRP**

Example 1 is an ARRP family as shown in Figure 4A. Usually, the recurrence risk for member II$_2$ is explained as 25% using the segregation rate of carrying a homozygous recessive mutation. However, if you use the age at onset curve, the risk rate decreases drastically with the patient’s age. The probability that member II$_2$ has a disease genotype under the condition that member II$_2$ has not developed RP is calculated as:

$$ P(H|E) = \frac{0.25 \times (1-f(x))}{0.25 \times (1-f(x)) + 0.75 \times 1}, $$

where $H$ is member II$_2$ having not developed RP, $E$ is member II$_2$ carrying the disease genotype, and $f(x)$ is the onset ratio given by the age at onset curve ($x$ is age; $P[E|H] = 1-f(x)$).

If $f(x) = 0$ ($x = 0$; age 0 years), $P(H|E) = 0.25$, the segregation rate. However, with the increase of age, the ratio decreases as shown in Figure 4B. For example, at the age of 50 years, the probability is 0.06. This means that if the sibling has not been diagnosed with RP at the age of 50 years, we can say without any clinical examination that he or she will not develop RP with the probability of 94%.

**EXAMPLE 2: ADRP**

The curve is much more important in a dominant trait, in other words, the diagnoses of carriers of ADRP families (Figure 5A). Using the Bayes theorem for combining probabilities, the probability that member II$_3$ is a carrier under the condition that member II$_3$ does not have onset of RP is:

$$ P(H_3|E) = \frac{P(H_3) \times P(E|H_3)}{P(H_3) \times P(E|H_3) + P(H_1) \times P(E|H_1)} = \frac{0.5 \times (1-f(x)) / (0.5 \times (1-f(x)) + 0.5 \times 1)}{1-f(x) / (2-f(x))}, $$

where $H_0$ is member II$_2$ being a carrier, $H_1$ is member II$_2$ not being a carrier, $E$ is member II$_3$ carrying a disease genotype, and $f(x)$ is the onset ratio given by the age at onset curve.

Figure 4. The recurrence risk reduces with age in autosomal recessive retinitis pigmentosa. A, Typical autosomal recessive retinitis pigmentosa family tree. Member II$_2$ is whose recurrence risk rate should be assessed. B, Recurrence risk rate at varying ages. The rate decreases drastically with age.

Figure 5. The probability of carrying the disease allele in families with autosomal dominant retinitis pigmentosa. A, A typical autosomal dominant retinitis pigmentosa family tree. B, The calculation of the probability that member II$_2$ is a carrier without an age at onset curve. The presence of unaffected member III$_3$ drastically reduces the probability. C, The calculation of the probability that member II$_2$ is a carrier with the age at onset curve. Member III$_3$ reduces the probability by approximately 1%.

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If you use only the segregation rate and penetrance rate (which was reported as 87% in Japanese individuals; \( f(x) = 0.87 \) for any \( x \)), \( P(H_0|E) = 0.115 \). On the other hand, if you use the age at onset curve \( (f(x) = 0.272 \forall x = 30) \), this gives a result of \( P(H_0|E) = 0.421 \). The ratio is more than 3 times the former ratio. The age of 30 years is old enough to reproduce, so the difference could not be ignored. In the autosomal dominant condition, having an unaffected child(ren) reduces the probability of the carrier. In Figure 2 curve A, the presence of an unaffected child, member III_1, reduces the probability that member II_1 is a carrier. If one considers only the non-penetration condition \( (f(x) = 0.87) \), the decrease is drastic. The presence of member III_1 reduced the probability slightly less than 1% (0.09) if member III_1 is 10 years old (Figure 5C). Even if member III_1 is 20 years old, it can reduce the probability by only 2.1% (0.40). Using an age at onset curve, we are also able to estimate the recurrence risk for second-degree relatives such as member III_1. The probability is:

\[
P(H_0|E) = \frac{P(H_0) \times P(E|H_0)}{P(H_0) \times P(E|H_0) + P(H_1) \times P(E|H_1)}
\]

\[
= \frac{0.412/2 \times (1-0.076/2-0.13/2)/(0.412/2 \times (1-0.076/2-0.13/2)+(1-0.412/2) \times 1]}{0.189},
\]

where \( H_0 \) is member III_1 developing RP, \( H_1 \) is member III_1 not developing RP, and \( E \) is member III_1 carrying a disease genotype.

The value is more than twice of that calculated using the conventional way (0.086). The relatively low onset ratio at a younger age explains the problems of sporadic cases. The “sporadic” is defined when the proband is the only patient in his or her family tree. Our study revealed that it does not mean the proband is the only family member who has a disease genotype. Our study presents a relatively high possibility that the families may contain persons who have the disease genotype but do not develop RP at that time. It is a problem in sporadic cases that possess the ADRP gene mutations, because in such cases, the recurrence risk in families is much higher than other circumstances. In fact, the empirical recurrence risk of a sporadic case is reported as 1% to 2% in Japan, which is much higher than that of ARRP families (0.4%-0.8%). A possible way to explain this phenomenon is that the sporadic cases contain some ADRP families. Once the trait of dominance is confirmed, the recurrence risk for the newborns of the patients jumps up from 2% to 48%. In the counseling of sporadic cases, we should state the possibility of ADRP and its high recurrence rate, in addition to the relatively low empirical recurrence risk, especially in a case when the sporadic patient maintains a small family tree.

Recent progress in genetic diagnoses, especially using DNA chip technology, gives us a great chance to determine the genotype of approximately 40% of patients with ADRP and 30% of patients with ARRP. However, in about half of families, disease mutations are not detected and empirical recurrence risk is still important. In such families, some clinical tests, including electrophoretography and fundus photography, gave us final diagnoses of RP without empirical recurrence risk assessments. However, empirical recurrent risk basically gives us a prior probability before any clinical tests are performed. The final probability should be calculated as a combining probability using the Bayes theorem from the prior probability by age at onset curve and the conditional probabilities in series of clinical tests. Without age at onset curves, empirical risk might be misleading.

The age at onset curve is quite simple. However, it displays very important features of RP and contains useful tools for the counseling of patients with RP.

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REFERENCE