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Genetic mapping of the dominant albino locus in rainbow trout (*Oncorhynchus mykiss*)

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Abstract Albinism in animals is generally a recessive trait, but in Japan a dominant oculocutaneous albino (OCA) mutant strain has been isolated in rainbow trout (*Oncorhyncus mykiss*). After confirming that this trait is not due to a tyrosinase gene mutation that causes OCA1 (tyrosinase-negative OCA), we combined the amplified fragment length polymorphism (AFLP) technique with bulked segregant analysis (BSA) to map the gene involved in dominant oculocutaneous albinism. Four AFLP markers tightly linked to the dominant albino locus were identified. One of these markers was codominant and we have it converted into a GGAGT-repeat microsatellite marker, OmyD-AlbnTUF. Using this pentanucleotide-repeat DNA marker, the dominant albino locus has been mapped on linkage group G of a reference linkage map of rainbow trout. The markers identified here will facilitate cloning of the dominant albino gene in rainbow trout and contribute to a better understanding of tyrosinase-negative OCA in animals.

Keywords Dominant albino locus · Rainbow trout · Tyrosinase locus · AFLP marker · Microsatellite marker

Introduction

Oculocutaneous albinism (OCA) is the most commonly inherited disorder of generalized hypopigmentation. As the techniques of molecular biology have developed, our knowledge of pigmentation at the molecular level has rapidly increased. Over the past several years, King et al. (1995) have classified human albinism in terms of the genes responsible for the condition. OCA1 is caused by mutations in the tyrosinase gene (TYR), and includes the non-pigmenting type OCA1A, and the pigmenting types OCA1B (yellow OCA), OCA1MP (minimal pigment OCA) and OCA1TS (temperature-sensitive OCA). OCA2 refers to phenotypes caused by mutations at the P gene locus. Brown OCA (BOCA) and Rufous OCA (ROCA) were recently classified as OCA3, and are caused by mutations in the gene for tyrosinase-related protein-1 (TRP-1) (Boissy et al. 1996; Manga et al. 1997).

Autosomal dominant OCA has been described in several families (Bergsma and Kaiser-Kupfer 1974; Fitzpatrick et al. 1974; Frenk and Calame 1977), but remains unclassified. The characterization of this form was incomplete and most cases did not fit the criteria for albinism (King et al. 1995). Final characterization of dominant OCA awaits the careful evaluation of families with clear autosomal dominant expression of OCA (King et al. 1996). As in humans, autosomal dominant OCA is also very rare in other animal species.

In Japan, a spontaneous mutant strain of rainbow trout (*Oncorhynchus mykiss*) is known which shows autosomal dominant albinism that differs from the more common recessive forms of the condition. The original mutant appeared in 1956 (Tatekawa 1974), and its offspring have been bred in various places in Japan. The dominant albino has red-colored eyes and pale orange skin, in contrast to the red-eyed but white-skinned recessive albino.

Bulked segregant analysis (BSA), as described by Michelmore et al. (1991), combined with the amplified fragment length polymorphism (AFLP) technique (BSA/AFLP approach) has proven to be very powerful approach for identifying markers tightly linked to, or cosegregating with, genes underlying monogenic traits (Postlethwait and Talbot 1997; Xu et al. 1999).

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In the present study, as a first step towards the positional cloning of the gene responsible for autosomal dominant OCA, we applied the BSA/AFLP approach and identified a microsatellite marker, derived from an AFLP marker, that is tightly linked to the dominant albino locus on a reference linkage map of rainbow trout (Sakamoto et al. 2000).

Materials and methods

Rainbow trout family

Normally pigmented (wild type) and dominant albino strains were reared at the Fuji Trout Hatchery, Shizuoka Prefecture Fisheries Experimental Station, in Japan. In 1995, an albino male (genotype AA for dominant albino) was crossed with a normal female (aa) to produce a hybrid family, Alb×Nor-95. All of the progeny were albino (Aa). A cross between a hybrid female (Aa) and a normal male (aa, unrelated to the hybrid family) was carried out in 1997 to obtain a family, Alb×Nor-97, that segregated 1:1 for albino (Aa) and normal (aa) individuals (numbers of progeny scored: 1179:1108).

Tyrosinase intragenic microsatellite marker

The tyrosinase gene in rainbow trout has a CT repeat sequence between the third and fourth exons (Iwai and Yoshizaki, unpublished data). As this CT-repeat is polymorphic, a pair of primers was designed to flank the repeats, and used to screen this microsatellite marker (OmyTyr3-4TUF) to determine whether the gene is linked to the dominant albinism.

Microsatellite analysis

A total of 49 microsatellite markers was tested in 25-μl reaction volumes containing 5 pmol of unlabeled primer and 0.17 pmol of primer end-labeled with [γ-^{33}P]ATP using T4 polynucleotide kinase, plus each dNTP at 0.175 mM, 20 mM TRIS-HCl (pH 8.4), 50 mM KCl, 1.5 mM $MgCl_2$, 0.1 mg/ml BSA, 0.25 U *Taq* DNA polymerase and 30 ng of template DNA. A specific annealing temperature was used for each microsatellite marker. The PCR program consisted of initial denaturation at 95°C for 2 min, followed by 35 cycles of 1 min at the annealing temperature, 1 min at 72°C and 30 s at 95°C, with a final extension step for 3 min at 72°C.

The amplification products were mixed with 20 μl of loading buffer (95% formamide, 10 mM EDTA, 0.05% bromophenol blue and xylene cyanol), denatured for 10 min at 95°C and quickly cooled on ice. Two microliters of each sample was loaded onto a denaturing 6% polyacrylamide gel (acrylamide:bisacrylamide = 19:1). After electrophoresis, gels were dried on a standard gel drier for 80 min and exposed to phospho-imaging plates overnight. The imaging plates were scanned with a Bio-image Analyzer (BAS 1000, Fuji Photo Films, Japan).

AFLP analysis

Genomic DNA was extracted from 1 g of fin or muscle tissue obtained from the albino and normal progeny and their parents by the method of Bardakci and Skibinski (1994). AFLP analysis was performed using AFLP Analysis System I (GIBCO/BRL) to implement the technique of Vos et al. (1995) with some modifications. A total of 250 ng of genomic DNA was used in the initial digestion step. PCR amplification was performed in a volume of 26.1 μl, containing 2.5 μl of the diluted restriction-ligation mixture, 20 μl of pre-amp primer mix, 1.5 mM $MgCl_2$, 0.1 mg/ml bovine serum albumin and 0.5 U of *Taq* DNA polymerase (GIBCO/BRL) in PCR buffer (200 mM TRIS-HCl pH 8.4, 50 mM KCl). The PCR program consisted of initial denaturation at 95°C for 2 min, followed by 20 cycles of 30 s at 90°C, 1 min at 56°C and 1 min at 72°C. The amplification mixture was diluted 50-fold in TE buffer. The selective amplification was performed in a volume of 10 μl, containing 2.5 μl of the diluted pre-amplified DNA, 2.5 ng of selective *Eco*RI + 3 primer labeled by phosphorylating the 5′ end with [γ-^{33}P]ATP and T4 polynucleotide kinase, 15 ng of selective *Mse*I + 3 primer (included dNTPs), 1.5 mM $MgCl_2$, 0.1 μg/ml bovine serum albumin and 0.25 U of *Taq* DNA polymerase in PCR buffer. The PCR program was started with a single cycle of 30 s at 94°C, 30 s at 65°C and 1min at 72°C; followed by 12 cycles of 30 s at 94°C, 30 s at 64.3°C and 1 min at 72°C; and then 10 cycles of 30 s at 94°C, 30 s at 56°C, and 1 min at 72°C. Electrophoresis of PCR products and band imaging were performed in the same way as for microsatellite analysis.

AFLP marker analysis

AFLP markers linked to the dominant albino locus were identified by bovine serum albumin according to Michelmore et al. (1991). The bulks were made by pooling equal amounts of DNA from 15 albino and 15 normal individuals. Sixty-four primer combinations were employed, yielding candidate markers from bovine serum albumin which were subsequently used on each individual DNA sample (n = 92; 46 albino; 46 normal) in order to confirm the linkage between the AFLP markers and the dominant albino locus.

Linkage analysis

The LOD scores (log_{10} of odds) and linkage map distances were calculated using the Macintosh version of Map Manager QT (Manly and Olson 1999).

Sequencing of AFLP markers

AFLP markers tightly linked to the dominant albino locus, detected in the linkage analysis, were sequenced. The bands of interest were cut out of the polyacrylamide gel, transferred to a microtube, overlaid with 100 μl of distilled water and incubated for 20 min at room temperature. Subsequently, the supernatant was discarded, 60 μl of water added and the gel band was incubated for 15 min at 65°C and left overnight at room temperature. Debris in the solution was removed by centifugation and the supernatant was transferred to a fresh tube. A 5-μl aliquot was re-amplified using the appropriate, unlabeled, selective primer combination. The amplification product was loaded on a 2% low-melting-point agarose gel in TBE buffer. The DNA band was excised from the agarose gel, melted at 68°C and later ligated to the T-vector (*Eco*RV-digested pBluescript with dTTP added to the 3' end; Toyobo) using Ligation Kit version I (TaKaRa) according to the recommendations of the manufacturer. Competent DH5α cells were transformed with the ligation mixtures and recombinant clones were identified by blue/white selection.

Sequence analysis of cloned fragments was carried out using the ABI PRISM Big Dye Terminator Cycle Sequencing Ready Reaction Kit and the ABI PRISM 310 Gene Analyzer (Perkin Elmer).

Results

Analysis of the possible association between dominant albinism and the tyrosinase locus

OmyTyr3-4TUF, a polymorphic marker derived from the tyrosinase gene, showed no association with the dominant albino phenotype (data not shown). This marker has been mapped to linkage group N on a reference linkage map of rainbow trout (Sakamoto et al.

2000) suggesting that the tyrosinase gene is localized on this chromosome.

Identification of AFLP markers linked to dominant albinism in rainbow trout

A total of 64 primer combinations was used to test the parents and bulks, from which 11 candidate markers were obtained. Bands were present in the albino parent but absent in the normal parent, corresponding to their presence and absence in the albino bulk and normal bulk, respectively (Fig. 1). These markers were screened again in 92 individual samples and three primers were found to generate polymorphic bands predominantly-from the albino population. Primers ACG/CTG (*Eco*RI + ACG/*Mse*I + CTG) and AGC/CAT (*Eco*R-I + AGC/ *Mse*I + CAT) revealed one AFLP marker each, with sizes of 428 and 150 bp, respectively. Primer AGC/CAC (*Eco*RI + AGC/*Mse*I + CAC) revealed two AFLP markers with sizes of 184 and 126 bp. The degree of linkage between these markers and the dominant albino allele was determined. For AGC/CAC-126, no recombinant was detected and for ACG/CTG-428, AGC/CAC-184 and AGC/CAT-150, one, two and four recombinants were detected, respectively. Linkage relationships between these four markers are shown in Table 1.

Generation of a microsatellite marker from one of the AFLP markers

AFLP marker AGC/CTG-428 consisted of two closely spaced DNA bands in the profile (Fig. 1B). The marker AGC/CTG-428 was linked in coupling phase to the dominant albino (presence of the fragment was linked to the albino phenotype and its absence to normal pigmentation) and the upper band AGC/CTG-438 was linked in repulsion phase to the dominant albino trait (presence

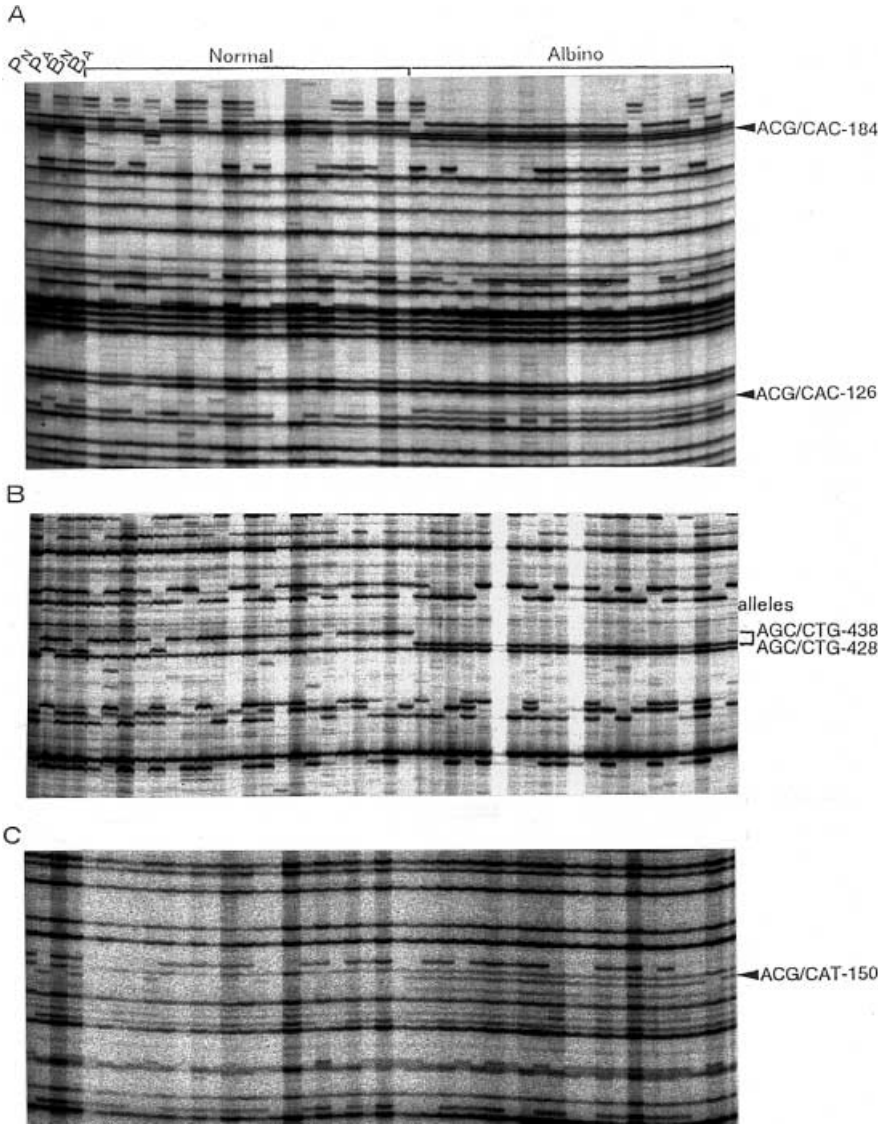

Fig. 1A–C AFLP markers linked to the dominant albino locus. The first four lanes on the *left* show the Bulked Segregant Analysis (BSA). Lanes P_N and P_A correspond to the normal pigmented and albino parents, B_N and B_A correspond to the normal and albino bulks. The AFLP markers generated with the primer combinations E-ACG/M-CAC (**A**), E-AGC/M-CTG (**B**), and E-ACG/M-CAT (**C**) are indicated by the *arrowheads*. Alleles AGC/CTG-428/-438 in **B** belong to a single locus

Table 1 Linkage analysis of markers associated with the dominant albino locus in the Alb×Nor-97 family

Locus	Map distance (±SE)[a]	LOD score
AGC/CAC-126	0	27.4
ACG/CTG-428	1.11±1.10	24.7
AGC/CAC-184	2.20±1.54	23.2
AGC/CAT-150	4.44±2.17	20.0

[a] Map distance in centimorgans (cM) between the marker and the albino locus

correlated with normal and absence with the albino phenotype) except in one individual (Fig. 1B). These two bands represented the maternal alleles and alternated on the profiles. Interestingly, sequencing analysis revealed that these bands differed only in the number of pentanucleotide repeats (GGAGT) they contained. Thus, it can be concluded that these bands represented two AFLP alleles of the same genetic locus. Specific primers were designed from one at the sequences and designated as OmyD-AlbnTUF. The sequence of the forward primer was 5′-GAATTCACGGGAGTGGAGTG-3′ and the reverse primer was 5′-TCCATGATTGCCACGG-GATTCT-3′. The band patterns obtained with this primer pair in the test family are shown in Fig. 2 and were the same as the result obtained from AFLP. The lower band in Fig. 2 was the paternal allele and all progeny had inherited it. Upon sequencing, this band was also found to contain pentanucleotide repeats as expected. DNA samples from 21 unrelated salmonids were tested for this GGAGT-repeat microsatellite, and polymorphism was confirmed and proven to be highly informative (Nakamura et al., unpublished results).

Placement of the dominant albino locus on the rainbow trout linkage map

Analysis of linkage between the dominant albino locus and known microsatellite markers was then performed. The highest LOD score of 1.8 was obtained with Ots4BML, which is located on linkage group G in the male rainbow trout map but not in the female (Sakamoto et al. 2000). To verify the association with linkage group G, we examined the linkage between Ots4BML and OmyD-AlbnTUF, the marker developed from one of the AFLP markers found to be linked to dominant albino locus, using another backcross family (97K2-2, Ozaki et al. 2001) unrelated to albino. In the male map, no recombinant was detected (LOD = 15.7) between OmyD-AlbnTUF, Ots4BML and another marker (OmyRGT36TUF) mapped on the linkage group G (Sakamoto et al. 2000). These results showed that OmyD-AlbnTUF is also located on linkage group G (Fig. 3).

Discussion

A location for the gene which is responsible for autosomal dominant albinism in rainbow trout was confirmed on the reference linkage map of rainbow trout. This result showed that BSA/AFLP approach can be used to identify genetic markers that facilitate positional cloning of genes for monogenic traits in teleosts.

As it has in plants, the combination of BSA and AFLP proved in our study to be a useful tool for increasing marker density in a target region and identifying specific genes (Ballvora et al. 1995; Cervera et al. 1996; Cnops et al. 1996; Barcaccia et al. 1998; Hartl et al. 1999; Schwarz et al. 1999). Four AFLP markers that are tightly linked to the dominant albino locus in rainbow trout were identified by this means, thus showing it to be a powerful way of locating loci of interest in fish. In addition, the development of a microsatellite marker, OmyD-AlbnTUF, which was designed on the basis of DNA sequence to amplify AFLP bands by PCR amplification, facilitated the placement of the dominant albino locus on a linkage map. Although the conversion of AFLPs to sequence-tagged-site (STS) markers has

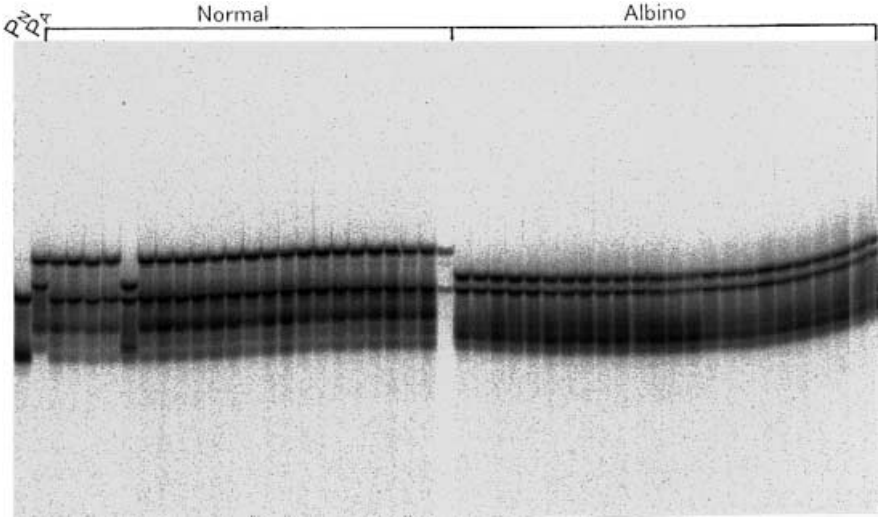

Fig. 2 Microsatellite analysis using OmyD-AlbnTUF on the same individuals tested with the AFLP technique. All individuals are non-recombinant, except the fifth normal individual from the *left*. It was confirmed that the lowest band was one of the alleles of this locus

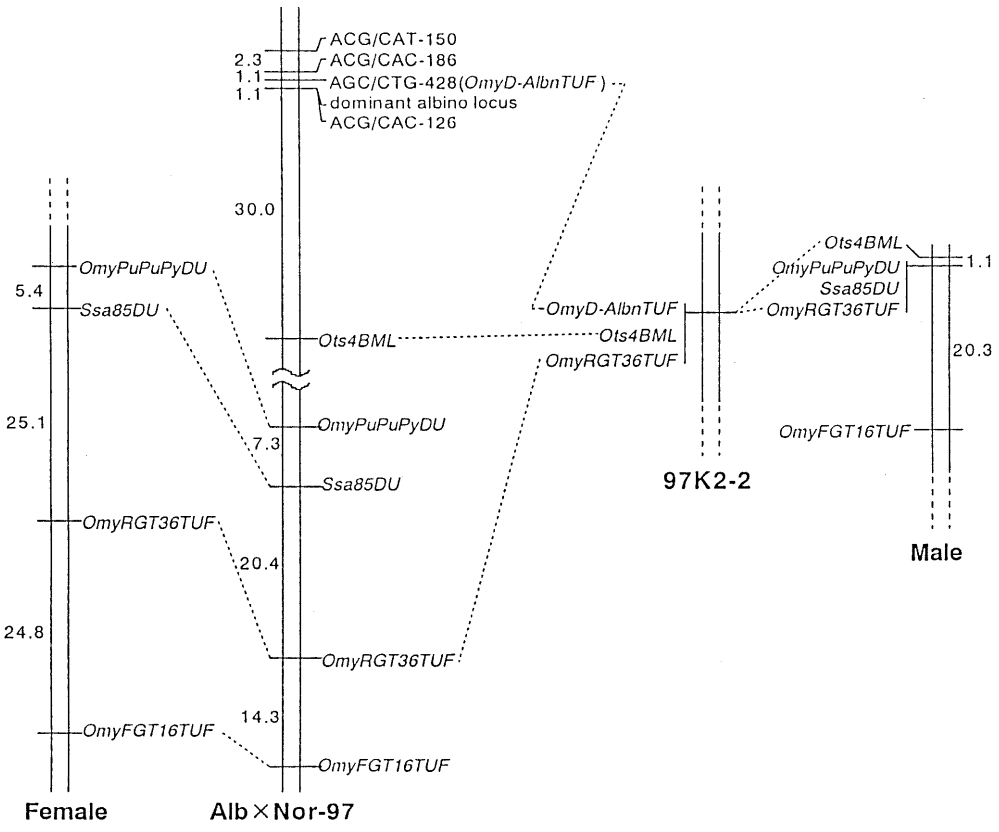

Fig. 3 Comparison of the genetic linkage maps of part of rainbow trout linkage group G in the Alb×Nor-97 family, a second unrelated family (97K2-2) and sex-specific linkage maps (female and male) constructed by Sakamoto et al. (2000). Map distances are given in centimorgans (cM)

been described in several reports (Meksem et al. 1995; Bradeen and Simon 1998; Qu et al. 1998; Shan et al. 1999), our result represents a rare case of the conversion of three putatively homologous AFLP markers to a pentanucleotide repeat microsatellite marker.

This marker, OmyD-AlbnTUF, derived from an AFLP marker tightly linked to the dominant albino locus, was not directly mapped on a reference map of rainbow trout (Sakamoto et al. 2000). However, the use of a different backcross family helped to map the locus of the dominant albino gene on the reference map because their microsatellite markers were highly conserved (Sakamoto et al. 1994). In the reference map, microsatellite marker Ots4BML, which showed the closest linkage to the dominant albino locus in the albino family tested, was located on linkage group G of the male linkage map but not located in the female map. The distance between Ots4BML and the dominant albino locus was 30 cM, as found in our female linkage map (Alb×Nor-97), but no recombinant was detected between OmyD-AlbnTUF, Ots4BML and OmyRGT36TUF in another unrelated family, 97K2-2 (Ozaki et al. 2001; male linkage map) (Fig. 3) confirming that the dominant albino locus maps on linkage group G. This result indicates that recombination rates in females are much higher than in males, and this is consistent with the large sex-specific recombination differences reported by Sakamoto et al. (2000). OmyD-AlbnTUF mapped further than Ots4BML (Fig. 3) from two possible centromeric positions, Ssa85DU and OmyRGT36TUF, suggesting that the linkage group G of the female linkage map established by Sakamoto et al. (2000) should be extended, and estimates of the recombination rates may therefore increase.

Tyrosinase has long been known to be a key enzyme in melanogenesis, and its functions in the melanogenic pathway involve tyrosine hydroxylation, DOPA oxidation and DHI oxidation (Hearing 1998). Most reported mutations associated with albinism are in the tyrosinase gene associated with OCA1 (Oetting and King 1999). Our study using an intragenic microsatellite marker for tyrosinase to perform linkage analysis found no association between the tyrosinase gene and dominant albinism of rainbow trout. Moreover, the dominant albino locus and the tyrosinase locus were mapped to different linkage groups. These results suggest that the dominant albinism phenotype is not due to a mutation in the tyrosinase gene, at least in rainbow trout. There are two types of melanin that are related to albinism, the black or brown eumelanin and the yellow or red pheomelanin (Prota et al. 1995). Eumelanin is believed to confer greater protection against UV radiation than pheomelanin. The albino genotype we studied has a yellow phenotype. The product of the mutant allele therefore appears not to inhibit the function related to pheomelanogenesis but to interfere with eumelanogenesis, suggesting that it results in the effective loss-of-function of (a) gene(s) related to eumelanogenesis. However, the chemical structures and properties of the different types of melanin are not yet understood completely and the switching mechanism

used in the melanogenic pathway to produce eu- or pheomelanins is still unclear (Hearing 1999).

Dominant albinism is due to a "dominant negative" mutation, where the mutant product of one allele inhibits the activity of the remaining wild-type product in the heterozygote. Various dominant-negative effects have been described in many types of proteins with signaling or transcriptional functions (Wilkie 1994), but the underlying effect in dominant albinism is still unknown. Since genes involved in pigmentation are conserved in vertebrates – in fact, the members of the tyrosinase-related gene family are conserved (Inagaki et al. 1994) – the progress of our study will facilitate clarification of the cause of human autosomal dominant OCA. The dominant negative effect that results in albinism will hopefully be understood at molecular level in the near future, thanks to the further analysis of autosomal dominant albinism in the rainbow trout.

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