DEVELOPMENTAL BIOLOGY. For the article “DMY gene induces male development in genetically female (XX) medaka fish,” by Masaru Matsuda, Ai Shionomiya, Masato Kinoshita, Aya Suzuki, Tohru Kobayashi, Bindhu Paul-Prasanth, En-lieng Lau, Satoshi Hamaguchi, Mitsuru Sakaizumi, and Yoshitaka Nagahama, which appeared in issue 10, March 6, 2007, of Proc Natl Acad Sci USA (104:3865–3870; first published February 28, 2007; 10.1073/pnas.0611707104), due to a printer’s error, in Table 4, column 3, the number of DMRT1 embryos hatched was given as “30”; it should instead be “80.” Also, in Table 4, column 6, the number of DMY transgenic XX females was given as “−4”; it should instead be “4.” The corrected table appears below.

### Table 4. CMV promoter-directed overexpression of DMY and DMRT1

<table>
<thead>
<tr>
<th>cDNA</th>
<th>Embryos injected</th>
<th>Embryos hatched</th>
<th>Hatching rate, %</th>
<th>XY male</th>
<th>XX female</th>
<th>XX male</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMY</td>
<td>195</td>
<td>86</td>
<td>44.1</td>
<td>20</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>DMRT1</td>
<td>139</td>
<td>80</td>
<td>57.6</td>
<td>30</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

www.pnas.org/cgi/doi/10.1073/pnas.0702707104

MEDICAL SCIENCES. For the article “The omega-3 fatty acid docosahexaenoate attenuates endothelial cyclooxygenase-2 induction through both NADP(H) oxidase and PKCε inhibition,” by Marika Massaro, Aida Habib, Laura Lubrano, Serena Del Turco, Guido Lazzерини, Todd Bourcier, Babette B. Weksler, and Raffaele De Caterina, which appeared in issue 41, October 10, 2006, of Proc Natl Acad Sci USA (103:15184–15189; first published October 3, 2006; 10.1073/pnas.0510086103), the authors note that the following should be added as an affiliation for Marika Massaro: Department of Biological and Environmental Sciences and Technologies, University of Lecce, Ecotekne, 73100 Lecce, Italy, The corrected author and affiliation lines, and related footnotes, appear below.

Marika Massaro**†‡, Aida Habib‡§, Laura Lubrano¶, Serena Del Turco¶, Guido Lazzерини, Todd Bourcier¶, Babette B. Weksler**, and Raffaele De Caterina††‡‡

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**M.M. and A.H. contributed equally to this work.

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www.pnas.org/cgi/doi/10.1073/pnas.0702704104

MICROBIOLOGY. For the article “Specific polysaccharide conjugate vaccine-induced IgG antibodies prevent invasion of *Shigella* into Caco-2 cells and may be curative,” by Yehuda Chowers, Joachim Kirschner, Nathan Keller, Iris Barshack, Simon Bar-Meir, Shai Ashkenazi, Rachel Schneerson, John Robbins, and Justen H. Passwell, which appeared in issue 7, February 13, 2007, of Proc Natl Acad Sci USA (104:2396–2401; first published February 7, 2007; 10.1073/pnas.0610833104), the authors note an error in the title. The title should read: “O-specific polysaccharide conjugate vaccine-induced antibodies prevent invasion of *Shigella* into Caco-2 cells and may be curative.” The online version has been corrected. Additionally, on page 2396, in the first line of the Abstract, in the first line of the second paragraph of the main text, and in the Abbreviations footnote, “O-specific polysaccharide” should instead appear as “O-specific polysaccharide.”

Microbiology. For the article “DgrA is a member of a new family of cyclic diguanosine monophosphate receptors and controls flagellar motor function in *Caulobacter crescentus*,” by Matthias Christen, Beat Christen, Martin G. Allan, Marc Folcher, Paul Jenö, Stephan Grzesiek, and Urs Jenal, which appeared in issue 10, March 6, 2007, of Proc Natl Acad Sci USA (104:4112–4117; first published February 27, 2007; 10.1073/pnas.0607738104), on page 4112, column 1, the key term “c-di-Gmp” should instead appear as “c-di-GMP.” The online version has been corrected.

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www.pnas.org/cgi/doi/10.1073/pnas.0702705104
DMY gene induces male development in genetically female (XX) medaka fish

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Communicated by Howard A. Bern, University of California, Berkeley, CA, January 3, 2007 (received for review June 20, 2006)

Although the sex-determining gene SRY/Sry has been identified in mammals, homologues and genes that have a similar function have yet to be identified in nonmammalian vertebrates. Recently, DMY (the DM-domain gene on the Y chromosome) was cloned from the sex-determination region on the Y chromosome of the teleost fish medaka (*Oryzias latipes*). DMY has been shown to be required for the normal development of male individuals. In this study, we show that a 117-kb genomic DNA fragment that carries DMY is able to induce testis differentiation and subsequent male development in XX (genetically female) medaka. In addition, overexpression of DMY cDNA under the control of the CMV promoter also caused XX sex reversal. These results demonstrate that DMY is sufficient for male development in medaka and suggest that the functional difference between the X and Y chromosomes in medaka is a single gene. Our data indicate that DMY is an additional sex-determining gene in vertebrates.

sex differentiation | sex-determining gene | *Oryzias latipes* | sex reverse | transgenic

The sex of an individual is decided by the sex of the gonad, and in most cases the information required for a gonad to become either a testis or an ovary is encoded in the genome. The gene at the top of the sex-determination cascade for mammals is located on the Y chromosome and is called SRY. This gene was first identified during deletion analysis of the human Y chromosome (1). Furthermore, Sry, which is the mouse homologue of SRY, has been shown to be sufficient for the induction of male development in transgenic mice (2). In nonmammalian vertebrates, which also have a male heterogametic (XX-XY) sex-determining system, neither a homologue of SRY nor any other candidate genes recruited in sex determination was found until recently.

Recently, we identified a single candidate gene at the top of the sex determination cascade in the teleost medaka, *Oryzias latipes*, by positional cloning in the sex-determining region of the Y chromosome, and we named this gene DMY (3), although it has also been designated as dmrY (4). This sex-determining region originated from a duplication of an autosomal region and it spans 258 kb, carrying only the DMY gene (4, 5). The expression of DMY is restricted exclusively to the somatic cells that surround the germ cells in the XY gonads, and the gene contains the highly conserved DM domain, which was originally described as a DNA-binding motif that is shared by doublesex (dsx) in *Drosophila melanogaster* and mb-3 in *Caenorhabditis elegans* (6). The involvement of DMY in the process of sex determination was confirmed by the advent of two naturally occurring sex-reversed mutants, in which DMY was either truncated or expressed at reduced levels (3). Nevertheless, it remains to be seen whether DMY is sufficient for the development of an individual into a male.

In this study, we performed overexpression experiments using the DMY genomic region or DMY cDNA, which can induce testis development in genetic females (XX). We used the d-rR (7) and the Qurt (8) strains of medaka. In both strains, the genetic sex can be distinguished on the basis of body color. These experiments were designed to show that DMY is sufficient for male development and, consequently, that DMY is the sex-determining gene in medaka.

Results

Overexpression of DMY from the DMY Genomic Region.

To confirm the mRNA expression of the DMY transgene, we examined the integration and expression of the transgene in newly hatched transgenic fry by genomic PCR-RFLP, RT-PCR, and in situ hybridization with DMY as the probe. The genomes of 16 newly hatched transgenic fry were examined, and all were found by genomic PCR-RFLP to harbor the DMY transgene. Of these 16 fish, 5 were XX and 11 were XY. The levels of mRNA expression in all XX and 27% of XY fry were examined by using RT-PCR (Table 3). All of the XX and XY transgenic embryos examined showed expression of the transgene.
We examined an additional 21 newly hatched transgenic fry for expression levels varied between individuals (data not shown). Transgenic construct of the DMY genomic region. (A) Transgenic construct derived from the BAC clone mCON051H1, which contains DMY*HNI and two SfiI sites. The red coloration of the BAC clone represents the insert. This fragment was digested with SfiI and ligated into the pCC1 vector by using linkers. (B) Genomic PCR products digested with StuI. The DMY*HNI allele is digested, whereas the DMY*drR allele is not digested. M represents the DNA marker. The arrowheads show the positions of the 1.5-kb and 1.0-kb DNA fragments. (C) Sequence chromatograms of the RT-PCR products of transgenic medaka. The DNA polymorphisms between DMY*HNI and DMY*drR are shown by arrowheads. Transgenic XX individuals have only the DMY*HNI allele, whereas transgenic XY individuals have both the DMY*HNI and DMY*drR alleles.

(DMY*HNI) in RT-PCR and direct sequencing experiments. The expression levels varied between individuals (data not shown). We examined an additional 21 newly hatched transgenic fry for DMY*HNI expression by in situ hybridization (Table 3 and Fig. 3). The sexes of these fry were assessed by genomic PCR-RFLP. Because the in situ hybridization method cannot distinguish the DMY*drR (recipient) and DMY*HNI (transgene) alleles, we were unable to estimate transgene involvement in the signals obtained from the XY embryos. However, 26.7% of the XX transgenic embryos examined showed expression of the DMY*HNI transgene. The signals were found in somatic cells that surrounded the germ cells (pre-Sertoli cells), which resembles the pattern of endogenous expression of DMY in normal XY embryos.

To elucidate sex reversal during the overexpression of DMY, we analyzed histologically the gonads of the d-rR fish at 20 and 30 days after hatching (DAH). Genetic sexing was performed on the basis of body color. We analyzed 24 (12 XX and 12 XY) and 32 (15 XX and 17 XY) individuals at 20 and 30 DAH, respectively. All of the XY medaka were found to be normal. For the XX medaka, 8.3% (20 DAH) and 6.3% (30 DAH) displayed the acinus structure (a globular structure that is the seminiferous tubule precursor), whereas the remaining medaka had ovaries. However, we found that some of the XX fish had slowly developing ovaries, with either low numbers of germ cells or with incomplete follicles (see Discussion).

The first morphological sex difference manifested in the gonads is reflected in the number of germ cells (9). The number of germ cells in a DMY mutant identified from a wild population resembled that of the female (3). Therefore, we evaluated the effect of DMY on germ cell number in the transgenic F0 generation. The genomic DNA fragment with DMY*HNI or Yamamoto’s solution alone (control) was injected into one-cell-stage medaka embryos of the Qurt strain. The hatched fry were dissected into the head part, which was used for checking the genetic sex by genomic PCR-RFLP, and the body region, which was used for histological observation of the gonad (Fig. 4A). The numbers of germ cells and their stages in fry that overexpressed DMY were compared with those of the control fry (Fig. 4 B–D). The DMY-injected XX fry had fewer germ cells than the controls at both 0 DAH (Fig. 4B) and at 5 DAH (Fig. 4C). Interestingly, the DMY-injected XY fry also had fewer germ cells than the control at 0 DAH. These differences were confirmed as significant by the t test (P < 0.05). In DMY-injected XX fry at 5 DAH, the numbers of germ cells were reduced at various stages of germ cell development (Fig. 4D).
Overexpression of DMY Using the CMV Promoter. The overexpression of DMY using the DMY genomic region induced sex reversal. However, because the genomic region used was large (117 kb), it could not be ruled out that a region within this 117-kb DNA segment but outside the DMY open reading frame (ORF) was involved in the induction of sex reversal. Therefore, to investigate the ability of the DMY ORF to induce sex reversal, we constructed overexpression vectors in which CMV controlled the DMY or DMRT1 cDNA. These constructs were injected into one-cell-stage medaka embryos of the Hdr-R strain, and the injected embryos were reared until the secondary sexual characteristics became apparent. Sex-reversed fish were obtained from the embryos that overexpressed DMY, whereas no sex-reversed fish were obtained from the embryos that overexpressed DMRT1 (Table 4). The sex-reversed medaka were fertile (data not shown).

Table 1. Genotyping and phenotyping (secondary sexual characteristics) of transgenic fish using the DMY genomic region

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>Female (%)</th>
<th>Male (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XY</td>
<td>57</td>
<td>0 (0)</td>
<td>57 (100)</td>
</tr>
<tr>
<td>XX</td>
<td>58</td>
<td>45 (77.6)</td>
<td>13 (22.4)</td>
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</table>

Table 2. Assessments of fertility of F₀ transgenic fish using the DMY genomic region

<table>
<thead>
<tr>
<th>n</th>
<th>Fertile</th>
<th>Sterile</th>
<th>Not assessed</th>
</tr>
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<tbody>
<tr>
<td>XY male</td>
<td>57</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>XX female</td>
<td>45</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>XX male</td>
<td>13</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

Discussion

A previous study has demonstrated that the DMY gene is necessary for normal male development (3). The present study shows that the overexpression of DMY by injecting the genomic region into XX individuals is sufficient to induce male development by reversing the sex of that individual. Furthermore, the overexpression of the DMY cDNA under the control of the CMV promoter also resulted in male development in XX individuals, which indicates that the protein encoded by the DMY ORF is sufficient for the induction of male development in XX medaka. Taken together with the previous data, our results indicate that DMY is the sex-determining gene in medaka. Thus, DMY is the first sex-determining gene to be identified in nonmammalian vertebrates.

Two lines of evidence suggest that DMY arose from a recent duplication event of the autosomal DMRT1 genomic region. First, Y chromosome-linked DMY appears to have originated from a duplicate copy of autosomal DMRT1 (4, 5, 10, 11), and then, in the Y chromosome, the duplicated DMRT1 acquired a new function as a sex-determining gene, DMY. Second, DMY is also found in Orzias curvinotus, which is most closely related to medaka (12), but is not found in other Orzias species (O. celebensis, O. mekongensis) or in other fishes (guppy, tilapia, zebrafish, and fugu) (13). These results suggest that DMY is a recently evolved gene specific to some species of the genus Orzias.

DMY represents a strong motive force for testis development in gonads. In transgenic experiments, F₀ embryos injected with DNA were typically mosaic. Likewise, F₀ embryos injected with the DMY genomic fragment were expected to have mosaic gonads. This situation is comparable to the XX recipient and XY donor chimeras of medaka, some of which developed as males despite having only a few XY donor cells and XX recipient cells in the gonad (14). It was found that some of the chimeras with only XX germ cells also developed into males. It is evident that relatively few XY somatic cells are sufficient to reverse the sex of the germ cells and somatic cells of the XX recipient gonad. These results suggest that even if DMY is present in only a minority of somatic cells, the gonad can ultimately develop into a testis. We believe that this is why we observed a low masculinization rate in the experiments in which gonad histology was examined at 20 and 30 DAH, whereas we observed a high masculinization rate for the secondary sex characteristics of the adult stage.

Some of the XX fish had slowly developing ovaries at 20 and 30 DAH. In this case, it appeared that the level of DMY expression in the XX gonad was low, and the gonad initially developed into an ovary. However, some of the somatic cells carried DMY, the expression of which should lead to testis development. DMY plays a role in the development of germ cells in males. The number of germ cells in many nonmammalian females is greater than in males at around the time of morphological sex differentiation (15–17). The germ cells in the females continue to proliferate and subsequently enter meiosis, in contrast to the male germ cells, which arrest in mitosis (9, 18). Kobayashi et al. (2004) demonstrated that the first appearance of a sex difference in germ cell number occurs at stage 38, before the hatching of medaka. Furthermore, in the XY gonads of medaka, the formation of the acinous structure occurs ∼10 DAH (19). These events are the first morphological signs of sex differentiation, as well as of testicular differentiation. Nevertheless, DMY expression starts in the somatic cells surrounding the germ cells, which are found in the coelomic epithelium under the nephric duct at stage 34 (9). This phenomenon occurs before the emergence of any sex differences in terms of germ cell number. When DMY does not function (e.g., a DMY mutant), the germ cells in XY embryos proliferate and enter meiosis, just like the XX embryos. In the DMY overexpression experiments, the total number of germ cells at 0 DAH was significantly reduced in both the XX and XY fry. In the 5 DAH XX fry injected with DMY, not only was the total germ cell number reduced but the number of germ cells at various stages of development was also reduced. Because the total number of germ cells reflects the outcome of active mitosis, the reduced number of germ cells in the transgenic fry may be due to a signal or signals from the surrounding somatic cells that express DMY.

In mammals, the function of the X chromosome differs from that of the Y chromosome. The male-specific region of the Y chromosome contains 156 known transcriptional units, which include 78 protein-coding genes that collectively encode 27 distinct proteins, including 10 testis-specific genes and SRY (20). Chromosomally female transgenic mice that carry Sry develop into males that are sterile (2), which suggests that Sry is insuf-
somes of medaka have also suggested that DMY appears to be the only functional gene (5). Because most vertebrate species have chromosomal (genetic) sex-determining systems and no morphologically distinct sex chromosomes, as is the case with medaka, it is possible that the functional difference between the sex chromosomes is a single gene that determines the sex of the respective species.

Materials and Methods
Strains. We used the three strains d-rR, Hd-rR, and Qurt. The d-rR and Hd-rR strains, in which the wild-type allele R of the r locus (a sex-linked pigment gene) is situated on the Y chromosome, was used to generate the transgenic fish with the DMY genomic region. In this case, the female XX had white body color, whereas the male XYY had orange-red body color (7). Another strain, Qurt [b/b, guigu, r/r, X(f)/Y(+)], in which the genetic sex of the XX and XY fish can be distinguished by the presence or absence of leucophore (8), was also used for the generation of transgenic fish.

Transgenic Constructs. The constructs for DMY transgenic fish were prepared by subcloning the BAC clone that was derived from the Y congenic strain Hd-rR,YHNI (3), which contains the sex-determining region from the Y chromosome of the HNI strain and has the genetic background of the Hd-rR strain. The BAC clone (mCON051H1) containing DMY was digested with SfiI, recognition sites for which were located ~1.4 kb downstream of DMY exon 6 and the vector sequence (Fig. 1). A biased sinusoidal field gel electrophoresis system (GENOFIELD; Atto Co., Tokyo, Japan) was used to isolate the DNA fragment that contained DMY. The gel electrophoresis conditions were as follows: 1% low-melting-point agarose gel in 0.5× TBE (44.5 mM Tris/44.5 mM boric acid/1 mM EDTA, pH 8.0) at 20°C, dc 1.6 V/cm and ac 9.6 V/cm, and log-pulse time ramp from 0.01 to 0.2 Hz for 20 h. The DNA fragment was purified by using GELase (Epicentre Technologies, Madison, WI) and then ligated with the linker-ligated CopyControl pCC1 vector (Epicentre Technologies). This system combines the clone stability afforded by single-copy cloning with the advantages of the high yields of DNA obtained by “on-demand” induction of the clones to high copy number. The pCC1 vector was digested with HindIII and EcoRI and ligated with the Sfi-Hind linker (AGCTGAG) and
Sfi-Eco linker (AATGGG). TransforMax EPI300 electro-competent cells (Epiconcept Technologies) were used for transformation. Recombinant clones were grown in culture and induced by the addition of the CopyControl Induction Solution (Epiconcept Technologies) to generate high plasmid copy numbers, according to the manufacturer’s instructions. The clones were purified by using either a Large-Construct kit (Qiagen, Valencia, CA) or CsCl-ethidium bromide gradient ultracentrifugation, which was preceded by purification by using the QIAfilter Plasmid Maxi kit (Qiagen).

To construct CMV promoter-controlled overexpression vectors, the ORFs of DMY and DMRT1 were amplified from the total RNA of whole embryos for DMY and of adult testes for DMRT1 from the Hd-r strain by using a OneStep RT-PCR kit (Qiagen) with the following primer sets: PG17.25 (CCC ACC AGA TCC TAT ACA AGT GAC) and PG17.89 (CAG CTT GTC GAC ATT TGC CCA) for DMY, and PG17.5 (GGA CCC GCT GA) and PG17.20 (GCA TCT GCT GGT ACT GCT GGT AGT TG) for DMRT1. Primer PG17.25 is located upstream of the ATG start site. Primers 17.89 and 17.95 (CAG CTT GTC GAC ATT TGC CCA) and PG17.89 (CAG CTT GTC GAC ATT TGC CCA) were used, and 100 ng of total RNA was used as the template in a 25-μl volume. The PCR conditions were as follows: 5 min at 94°C, followed by 30 cycles of 15 sec at 96°C, 60 sec at 68°C, and a final step of 5 min at 72°C. To distinguish the DMY^(h-r)^ and DMY^(h-n)^ alleles, the PCR products were digested with Stul and electrophoresed in a 2% agarose gel.

RT-PCR was performed by using a OneStep RT-PCR kit (Qiagen). For the RT-PCR, the PG17.25 (CCC ACC AGA TCC TAT ACA AGT GAC) and PG17.48 (GCC TCT GGT TAG AAG TGT TAG TAG GAG GTT T) primers were used, and 100 ng of total RNA was used as the template in a 25-μl volume. The PCR conditions were as follows: 30 min at 55°C, 15 min at 95°C, followed by 30 cycles of 20 sec at 96°C, 30 sec at 55°C, 60 sec at 72°C, and a final step of 5 min at 72°C. The RT-PCR products were directly sequenced.

Fertility Checking. To check the fertility of F0 transgenic medaka, transgenic F0 males were pair-mated with normal females or transgenic F0 females.

Histological Analyses. For the histological analysis and counting of germ cell numbers, the embryos that were injected with the DMY genomic region were dissected into head and body segments. The body portions were fixed overnight in Bouin’s fixative solution and then embedded in paraffin. Each dissected head was used to determine the genetic sex, according to the protocol listed in the Sexing section. Cross-sections were cut serially at 5-μm thickness, and after H&E staining, all of the germ cells were counted for each fry. After cell counting, the mean and standard error were calculated for each sex at each stage, and the differences between the sexes were evaluated statistically by using the paired t test for each stage.

In Situ Hybridization. After the head part had been removed from the hatching fry, the body region with the gonad were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) at 4°C overnight. In situ hybridization was performed as described previously (3, 9).

We thank Ms. E. Uno for technical assistance. This work was supported in part by grants-in-aid for Scientific Research on Priority Areas from the Ministry of Education, Science, Sports, and Culture of Japan; and the Sorst Research Project of Japan Science and Technology Agency; and Environment Endocrine Disruptor Studies from the Ministry of the Environment.

### Table 4. CMV promoter-directed overexpression of DMY and DMRT1

<table>
<thead>
<tr>
<th></th>
<th>Embryos injected</th>
<th>Embryos hatch</th>
<th>Hatching rate (%)</th>
<th>XY male</th>
<th>XX female</th>
<th>XX male</th>
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<tbody>
<tr>
<td>DMY</td>
<td>195</td>
<td>86</td>
<td>44.1</td>
<td>20</td>
<td>-4</td>
<td>4</td>
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<tr>
<td>DMRT1</td>
<td>139</td>
<td>30</td>
<td>57.6</td>
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