ulin (a putative megalin ligand) was also detected in this patient, but immunohistochemical analyses revealed no apparent change in its uptake (Fig. S4E and S4F in the Supplementary Appendix), which suggested β_2_-microglobulin is also a shared ligand. Consequently, we tested the binding capacity of α_1_-microglobulin to cubilin (with the use of surface-plasmon-resonance analyses, as described in the Supplementary Appendix and shown in Fig. S3B) and found that α_1_-microglobulin is also a cubilin ligand.

Studies in rodents have shown that both cubilin and amnionless are essential to normal embryonic development. However, no lethal phenotype or malformations were observed in the dogs deficient in amnionless in the above-mentioned model. Since our patient has no additional apparent developmental abnormalities or physical disabilities, it appears that cubilin is not essential for human embryonic development. Furthermore, the functional immunohistochemical analyses of specimens from this patient’s kidney indicate that cubilin and amnionless also have an interdependent relationship in humans.

Tina Storm, M.Sc.
University of Aarhus
Aarhus, Denmark

Francesco Emma, M.D.
Ospedale Bambino Gesù
Rome, Italy

Pierre J. Verroust, M.D.
University of Aarhus
Aarhus, Denmark

Jens Michael Hertz, M.D.
Aarhus University Hospital
Aarhus, Denmark

Rikke Nielsen, Ph.D.
Erik I. Christensen, M.D.
University of Aarhus
Aarhus, Denmark
eic@ana.au.dk

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


A SOX9 Duplication and Familial 46,XX Developmental Testicular Disorder

TO THE EDITOR: Female-to-male sex reversal in humans is rare, and when it is familial, it is extremely rare. We describe a family with a 46,XX testicular disorder of sex development in which three adult males (two brothers and a paternal uncle) were determined to be female according to karyotype (46,XX) and were negative for the SRY gene (Fig. 1). The secondary sexual characteristics, behavior, growth and development, and skeletal development in these men were all normal male. Their general health and intelligence were normal. All three affected men were infertile with azoospermia. In two men, the testes were removed and prostheses were placed during their 20s because of testicular pain secondary to testosterone replacement. Histologic examination showed the presence of Leydig and Sertoli cells, severely diminished and atrophied seminiferous tubules, and no spermatogenesis.

Male development is normally triggered by the transient expression of the Y chromosome gene SRY, which initiates a cascade of gene interactions orchestrated by SOX9, leading to the formation of testes from bipotential gonads.\(^1,2\) The essential and nonredundant role of Sox9 in male development was initially detected in mice. Ectopic expression of Sox9 in the female gonad of XX mice caused complete female-to-male sex reversal, demonstrating that Sox9 is sufficient to trigger testis differentiation in the absence of Sry.\(^3,4\)
We used single-nucleotide-polymorphism microarray analysis, in situ hybridization, and a long-range polymerase-chain-reaction assay to evaluate the family (Fig. 1). The proband and his uncle had an approximately 178-kb duplication that was 600 kb upstream of \textit{SOX9}. The duplication was arranged in tandem in wild-type orientation, and the joining points of the duplicated segments were uncorrupted. All affected family members carried the duplication, as did the proband's healthy, fertile 46,XY father. Neither his fertile daughter nor his fertile son carried the duplication. Of note, the 1.9-Mb region of chromosome 17 upstream of \textit{SOX9} contains no other genes and is evolutionarily highly conserved in mammals. \textit{SOX9} is a transcription factor essen-
tial for both sex and skeletal development, and various perturbations to this 1.9-Mb region give rise to a range of phenotypes.5

The pattern of autosomal dominant sex-limited inheritance in this family with transmission by a man with a normal male phenotype appears to be unique. Although SRY is normally needed for SOX9 activation and the male phenotype, in this family a small duplication alone seemed to be sufficient to override this fundamental genetic process. Only the sex-dependent expression of SOX9 was affected, presumably through specific enhanced promoter activity. This duplication, 600 kb distant from SOX9, exemplifies the complexities of transcription-factor control and illustrates the use of human studies in understanding developmental mechanisms.

James J. Cox, Ph.D.
Cambridge Institute for Medical Research
Cambridge, United Kingdom

Lionel Willatt, Ph.D.
East Anglian Medical Genetics Service
Cambridge, United Kingdom

Tessa Homfray, M.B., Ch.B.
St. George’s Hospital
London, United Kingdom

C. Geoffrey Woods, M.B., Ch.B.
Cambridge Institute for Medical Research
Cambridge, United Kingdom
cw347@cam.ac.uk

Drs. Cox and Willatt contributed equally to this letter.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


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CORRECTIONS

In-Center Hemodialysis Six Times per Week versus Three Times per Week (December 9, 2010;363:2287-300). In Table 4 (page 2298), the 10th row under “Outcome” should have been “Episodes of hypotension,” rather than “Episodes of hypertension.” We regret the error. The article is correct at NEJM.org.

Effect of Home Testing of International Normalized Ratio on Clinical Events (October 21, 2010;363:1608-20). In Table 1 (page 1613), in the Self-Testing Group column, the parenthetical percentages given for “CHAD, score for patients who had AF without MHW” were incorrect for patients with scores of 1 to 5. Also, in the final paragraph of the Secondary End Points subsection of Results (page 1616), the second sentence should have ended “... with a mean interval between tests of 7.6±5.4 days...”, rather than “... with a mean interval between tests of 5.6±5.4 days...”. The article is correct at NEJM.org.

A Tuba Player with Air in the Parotid Gland (February 12, 2009;360:710). In Panel A (page 710), no arrowhead should have appeared, and there should have been no parenthetical mention of it in the text. The article is correct at NEJM.org.

NOTICES

Letters submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the Journal’s Web site (NEJM.org/medical-conference). The listings can be viewed in their entirety or filtered by specialty, location, or month.

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