quent (depending on the severity of the retinopathy) (3). Our data relate to patients <20 years old and cannot be
generalized to the adult population. Ste-
fansson states that in Iceland, no patient progressed from “no retinopathy” to “vi-
sion-threatening retinopathy” within 2 years. However, since collecting the orig-
nal data (1990–2002), we have been in-
formed of two former patients who had
rapid progression from level 31 and level 45 retinopathy to blindness in <2 years. These patients were 21 and 23 years old when blindness occurred (therefore out-
side of our study group), and both had
significant risk factors for retinopathy
(persistently high HbA1c and diabetes du-
ration 17 years).

Stefánsson describes a decrease in le-
gal blindness due to retinopathy in the
Icelandic population. Although this may be due to improved management of reti-
nopathy, it may also indicate a reduction in retinopathy due to intensive insulin
therapy. This would be in keeping with the trend in our population, in which the
incidence of retinopathy has decreased over the last decade from 49 to 24% in
patients of 8 years’ diabetes duration (4). However, despite the declining incidence of retinopathy in our population, adoles-
cents should be advised of the serious and
real risk of blindness due to diabetic reti-
nopathy. Indeed, blindness occurred in
the two patients mentioned above in 2003 and 2004. Clinicians must not underesti-
mate the risk of future blindness from reti-
nopathy for adolescents.

**ANN M. MAGUIRE, MB, BAD, BCH**
**JANINE M. CUSUMANO**
**MARIA E. CRAIG, PHD**
**KIM C. DONAGHUE, PHD**

From the 1Institute of Endocrinology and Diabetes, The Children’s Hospital at Westmead, Sydney, Aus-
tralia; the 2Department of Paediatrics and Child
Health, University of Sydney, Sydney, Australia; and the
3School of Women’s and Children’s Health, Uni-
versity of New South Wales, Sydney, Australia.

Address correspondence to Dr. Ann Maguire, In-
stitute of Endocrinology and Diabetes, The Chil-
dren’s Hospital at Westmead, Locked Bag 4001,
Sydney, NSW 2145, Australia. E-mail: annm4@chw.
edu.au.

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**References**

1. Stefánsson E: The case for biennial reti-
nopathy screening in children and adoles-
cents (Letter). Diabetes Care 29:178, 2006
2. Kristinsson JK, Gudmundsson JR, Stefán-
ssoon E, Jonasson F, Gislason I, Thorsson
AV: Screening for diabetic retinopathy:
initiation and frequency. Acta Ophthalmol
Scand 73:525–528, 1995
3. Maguire AM, Chan AKF, Cusumano J,
Hing S, Craig ME, Silink M, Howard NJ,
Donaghue KC: The case for biennial reti-
nopathy screening in children and adoles-
4. Mohsin F, Craig ME, Cusumano J, Chan
AKF, Hing S, Lee JW, Silink M, Howard
NJ, Donaghue KC: Discordant trends in
microvascular complications in adoles-
cents with type 1 diabetes from 1990 to

**Letters**

**Of Genes and Men: The Alternative View of Sex Differences in Cystic Fibrosis**

Response to Sims et al. and Milla et al.

Female subjects with cystic fibrosis–
related diabetes have a worse prog-
nosis than male subjects according to
two independent studies recently pub-
lished in Diabetes Care (1,2). It has been
known for some time that females with
cystic fibrosis generally have a signifi-
cantly higher mortality than males from
age 1 to 20 years (3), a sex difference that
remains despite radical improvement in
survival rates through the years (4). Are
these differences a result of evolutionary,
sex-specific selective pressures? We pro-
pose an evolutionary explanation for the
observed sex differences in cystic fibrosis.

Congenital bilateral absence of the
deries (CBAVD), a cause of infertil-
ity in 1–2% of European men, is a clinical
sign of cystic fibrosis. Conversely, muta-
tions in the cystic fibrosis transmembrane
regulator (CFTR), the cause of cystic fi-
brosis, are also found in 80% of patients
with isolated CBAVD (5,6). Indeed, the
observation that the vas deferens is abnor-
mal in almost all male cystic fibrosis pa-
tients led to the suggestion that CBAVD is
an incomplete form of cystic fibrosis (7).

To account for the high incidence of
CFTR mutations in the population, it is
generally assumed that there are selective advantages in being a heterozygous car-
rier, perhaps in the form of resistance
against typhoid fever (8); such CFTR mu-
tations must, however, simultaneously
place an enormous selective pressure against men carrying these same “infertil-
ity” alleles even in heterozygosity. This se-
lective pressure is much less pronounced in female carriers.

We postulate that compensatory mu-
tations in the Y chromosome have arisen
to ensure that CFTR mutations do not lead to sterility in men; such mutations will
preserve the selective advantage of
CFTR mutations. As an evolutionary
consequence, the phenotype of cystic fibrosis
will be skewed toward less severe manifesta-
tions of the disease in men. Further-
more, these protective effects of alleles in
the Y chromosome may be reflected in the
extreme cases of CBAVD patients lacking
clinical evidence of cystic fibrosis who
harbor “serious,” homozygous CFTR mu-
tations (5).

Our postulate could help explain ep-
idemiological findings such as unequal
sex distribution among diagnosed cystic
fibrosis patients and prevalence of women
diagnosed later in life (9). What is our
suggested explanation for this observa-
tion? Simply, females homozygous for
mutations in the CFTR gene diagnosed as
adults still have penetrant cystic fibrosis,
whereas age-matched males do not, and
are therefore never diagnosed, except,
perhaps, if these males have CBAVD or
pancreatitis (10).

In view of the recent findings re-
ported by Sims et al. and Milla et al., we
believe that searching for alleles in the Y
chromosome that confer resistance to
CBAVD, cystic fibrosis, and cystic fibro-
sis–related diabetes may be of consider-
able scientific value. In conclusion, rather
than decreased lung function and survival in
women, we should view the published
results as better survival and lung func-
tion in men.

**MARC CREUS, PHD**
**WOLFGANG VOGEL, MD**
**HEINZ ZOLLER, MD**

From the Clinical Division of Gastroenterology and
Hepatology, Department of Medicine, Innsbruck
Medical University, Innsbruck, Austria.

Address correspondence to Heinz Zoller, MD,
Innsbruck Medical University, Clinical Division of
Gastroenterology and Hepatology, Department of
Medicine, Anichstrasse 33, A-6020 Innsbruck, Aus-
tria. E-mail: heinz.zoller@uibk.ac.at.

© 2006 by the American Diabetes Association.

**References**

1. Sims EJ, Green MW, Mehta A: Decreased
lung function in female but not male sub-
jects with established cystic fibrosis–re-
lated diabetes. Diabetes Care 28:1581–
1587, 2005
2. Milla CE, Billings J, Moran A: Diabetes is
associated with dramatically decreased
survival in female but not male subjects
with cystic fibrosis. Diabetes Care 28:
2141–2144, 2005
Letters


Of Genes and Men: The Alternative View of Sex Differences in Cystic Fibrosis

Response to Creus et al.

Creus et al. (1) offer an intriguing hypothesis, namely that protective genes on the Y chromosome confer a survival advantage to men with cystic fibrosis. While there are aspects of this theory that are attractive, its does not explain the fact that in our series of >1,000 patients, survival was only decreased in women with both cystic fibrosis and diabetes (2). Survival in women without diabetes did not significantly differ from that of men with or without diabetes. While this does not preclude a genetic explanation, it suggests that excess mortality in cystic fibrosis is related to the relationship between diabetes and sex rather than sex per se. Perhaps this is a direct negative interaction between diabetes and some factor associated with female physiology. Alternatively, there may be negative effects of diabetes that men but not women are able to overcome. These might be due to hormonal or other differences found in all men, but one could speculate that there may be protective genetic factors specific to men with cystic fibrosis. While diabetes affects men and women differentially in the general population, the sex difference in cystic fibrosis is certainly more dramatic, and it is possible that genes on the Y chromosome may modify survival in men with cystic fibrosis–related diabetes.

CARLOS E. MILLA, MD
JOANNE BILLINGS, MD
ANTOINETTE MORAN, MD

From the Minnesota Cystic Fibrosis Center, Departments of Pediatrics and Medicine, University of Minnesota, Minneapolis, Minnesota.

Address correspondence to Antoinette Moran, MD, Department of Pediatrics, MMC 742, University of Minnesota, 420 Delaware St. SE, Minneapolis, MN 55455. E-mail: moran001@umn.edu.

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References

We thank Creus et al. (1) for their interesting comments on our proposal that female subjects with cystic fibrosis–related diabetes develop worse lung function compared with age- and genotype-matched male peers. They ask whether these differences are a result of “evolutionary, sex-specific selective pressures.” They then make the assertion that cystic fibrosis heterozygosity must “simultaneously place an enormous selective pressure against men carrying these same ‘infertility’ alleles even in heterozygosity.” The difficulty we face in accepting this notion of selective negative pressure on the Y chromosome is that most heterozygote males are perfectly fertile, but for reasons unknown, more males are diagnosed with cystic fibrosis than females (1.1 to 1.0). The latter ratio is higher than the accepted male preponderance at birth in the population as a whole (1.05 to 1.0), which is offset back toward unity by a higher male mortality in childhood (2).

We accept that it is not fully understood why some patients with apparently “severe genotypes” do not develop classical cystic fibrosis, although intronic/exonic boundary structure, modifier genes, and environmental factors have all been implicated (3). However, although Rodman et al. (3) reported that females outnumbered males by three to one in their late-diagnosed cohort, females formed a smaller proportion of their early-diagnosed cohort. But, Rodman et al.’s results contradict the recognized excess of female cystic fibrosis mortality (4). Indeed, we have recently submitted a manuscript responding to Rodman et al.’s findings and report that for a national population of 135 patients aged >40 years, comparable male-to-female ratios were found in pediatric- and adult-diagnosed cohorts (J.M., personal communication). The different findings between our work and that of Rodman et al. could indicate a possible unknown bias in a single-center approach (3). Finally, Creus et al. (1) also suggest that “rather than decreased lung function and survival in women, we should view the published results as better survival and lung function in men.” We suggest that the imminent imposition of neonatal screening across the U.K. and France provides an opportunity to test the ideas proposed by the correspondents, but we feel it is premature to envisage a change in the title of our report (5).

ERIKA J. SIMS, PHD
JONATHAN MCCORMICK, MRCP
ANIL MEHTA, FRCP (EDIN)