syndrome), which are the severe consequences of infection.[10] Yet an effective treatment remains frustratingly elusive. Infection with *E. coli* O157:H7 is potentially fatal, and children bear the brunt of the complications. The basis of therapy remains supportive — correcting and maintaining fluid and electrolyte balance, avoiding the use of antimicrobial and antimotility agents, and managing complications swiftly as they arise.[11] During a large outbreak of *E. coli* O157:H7 infection in central Scotland in 1996, a community clinic was established in the short term to monitor patients with suspected infection and to refer them for hospital treatment in a consistent and timely manner.[12] A total of 1198 people from the local community presented to the clinic, and the experience gained during this episode led to the development of a clinical monitoring protocol.[12]

Given the seriousness of human infection with *E. coli* O157:H7, the lack of therapeutic options, and the absence of control measures for the animal reservoir, blocking transmission pathways is essential for reducing morbidity and mortality. Initiatives such as the creation of a temporary community clinic illustrate the importance of cooperation between clinicians and public health departments. Clinicians are on the front line in detecting sporadic disease or clusters of infections.[4] As new discoveries about *E. coli* O157:H7 are made, the range of possibilities that must be included in taking a history becomes much wider. Clinical acumen combined with appropriate laboratory tests and early alerting of the health department allows public health professionals to assess whether or not a seemingly sporadic case is genuinely that and, if it is not, to begin the detective work necessary to track an outbreak to its source. Typing of strains is important, both for linking together over a wide geographic area what might appear locally to be sporadic cases and to provide the evidence needed for the selection of specific interventions.[13]

Like all infections, *E. coli* O157:H7 infection does not respect administrative, geographic, or professional boundaries. The synergy among clinical medicine, laboratory sciences, veterinary medicine, epidemiology, and public health has vastly expanded our knowledge about *E. coli* O157:H7 over the past 19 years, and each new discovery has unlocked fresh opportunities for prevention. There is no doubt that this particular jigsaw puzzle is much more complicated than it first appeared to be, and it is unlikely that the latest pieces that have been added are going to be the last.

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ANOTHER SURPRISE FROM THE MITOCHONDRIAL GENOME

ADVANCES in the field of mitochondrial genetics have challenged the general principles of molecular biology on several occasions. The universality of the genetic code that relates triplet-nucleotide sequences in DNA to specific amino acids in proteins was overturned by the discovery that the translation of mitochondrial proteins involves different coding rules.[1] Studies of mitochondria led to the surprising discoveries of autocatalytic RNA (RNA with enzymatic activity in the absence of proteins), RNA editing (post-transcriptional modification of the nucleotide sequence in messenger RNA [mRNA]), and trans-splicing (the joining of two separate primary RNA transcripts to form a single mRNA molecule).[2-4] In this issue of the *Journal*,[5] a case report by Schwartz and Vissing of a young man with a myopathy due to a defect in mitochondrial DNA (mtDNA) provides yet

another surprise by revealing an exception to the principle of maternal inheritance of mtDNA in humans.

Small but elegant, the human mitochondrial genome encodes a dozen proteins as well as a complete set of ribosomal and transfer RNA, densely packed along with transcriptional promoters and nucleotide sequence motifs that serve as defined origins of DNA replication into its approximately 16,000 nucleotide base pairs. Dwarfed by the 3,000,000,000 nucleotides and 50,000 protein-encoding genes of the human nuclear genome, the mitochondrial genome nonetheless encodes protein products essential for cellular respiration. Defective variants of mtDNA are the cause of several rare but biologically informative human diseases. Phenotypic manifestations of mitochondrial-gene defects most commonly affect tissues with high physiologic demands for oxidative phosphorylation, so neurologic disease, cardiomyopathy, and skeletal myopathy dominate the clinical picture.[6]

Organelle DNA, found in the mitochondria of all eukaryotes and in the chloroplasts of photosynthetic plants, is thought to be a relic of the primeval origin of eukaryotes: the engulfment of one unicellular bacterium by another established a symbiotic relationship of great selective advantage, ultimately leading to the formation of multicellular life forms. Mitochondrial genes are replicated, transcribed, and translated within the mitochondrial matrix, and these processes are catalyzed by enzymes generated as products of nuclear genes and imported into the mitochondria.[7] Every human cell contains many copies of mtDNA, which is replicated independently of nuclear DNA. Copies of mtDNA with deletions or other mutations can be detected at a low frequency (less than 1 percent) in cells from normal human tissues and increase in frequency with advancing age, even in healthy persons.[8] Degenerative conditions, such as ischemic heart disease and Parkinson's disease, accelerate the rate at which variant forms of mtDNA are generated in human tissues.[9] The persistence of multiple copies of normal mtDNA in cells that also harbor mtDNA mutations (i.e., heteroplasmy) usually protects those cells from respiratory insufficiency until defective mtDNA variants exceed 85 to 90 percent of the total pool of mtDNA within the cell.

In familial cases of disease caused by gene defects in mtDNA, inheritance is nonmendelian and passes from mother to offspring. Families with a mendelian pattern of inheritance of mitochondrial-gene defects have been described. However, these cases appear to be attributable to defects in the nuclear genes that encode proteins responsible for the fidelity of mtDNA replication or the maintenance of mitochondrial genomes, rather than attributable to direct inheritance of defective forms of mtDNA.[10] Maternal inheritance of mtDNA also has been uniformly observed in healthy humans. Several mechanisms have been proposed to explain this observation.[11] Mitochondria that are abundant in the tail structures of sperm fail to gain access to the interior of the oocyte. Any paternal mtDNA molecules that do enter the oocyte may ultimately be diluted by a vastly greater abundance of oocyte mtDNA molecules or may be eliminated from the zygote by molecular surveillance mechanisms.

Schwartz and Vissing[5] describe a patient with exercise intolerance, lactic acidosis after minimal exertion, and ragged-red muscle fibers, a histologic hallmark of mitochondrial myopathy, in a biopsy specimen of the quadriceps muscle. Sequencing of mtDNA from the patient's muscle showed a 2-bp deletion resulting in a frame-shift mutation in the *ND2* gene, which encodes an essential subunit of the mitochondrial NADH dehydrogenase complex. This variant form of mtDNA accounted for more than 90 percent of the total pool of mtDNA within the muscle tissue and may reasonably be assumed to have caused the clinical phenotype. The 2-bp deletion was not present in mtDNA extracted from the patient's circulating lymphocytes, illustrating the interesting but well-known phenomenon that defective forms of mtDNA may accumulate preferentially in different tissues within a single person. Together, these clinical and genetic findings would be considered characteristic of a mitochondrial myopathy.[12] However, more complete sequencing analysis of mtDNA from the patient and his healthy parents led to a remarkable and unanticipated finding.

The sequencing analysis was sufficiently detailed to identify the mitochondrial genotype at multiple polymorphic sites and thus to determine the mitochondrial haplotype. The analysis of DNA extracted from the patient's lymphocytes confirmed the expected transmission of mtDNA from his mother. Surprisingly, however, the mitochondrial haplotype in the patient's muscle matched that of his father (Fig. 1). The 2-bp deletion causing disease was unique to the patient, apparently representing a new mutation arising in the paternal germ line or during embryonic development. There is no strict selection against defective forms of mtDNA in the cells of early embryos,[13] apparently because the metabolic needs of the embryo are met primarily by glycolysis. Thus, the disease-causing mutation occurred on the background of mtDNA derived from the father — a finding that demonstrates paternal transmission of mtDNA in a human family. The authenticity of paternal inheritance was supported by the multisite haplotype analysis and by the haplotype analysis of nuclear DNA from the same tissue and blood specimens that confirmed parentage and that ensured that the samples had not been mislabeled or mixed up.

The inheritance of organelle DNA from only one
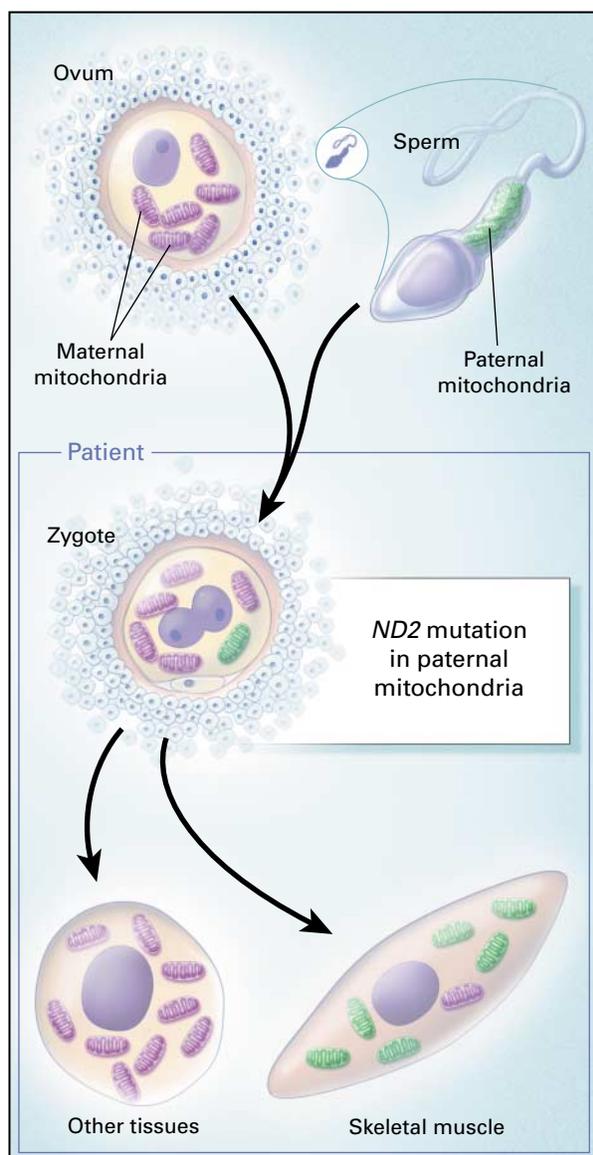
Figure 1. Paternal Inheritance of Mitochondrial DNA.

Schwartz and Vissing describe a patient who had mitochondrial myopathy due to a spontaneous mutation in *ND2,* a gene encoding a subunit of enzyme complex I of the mitochondrial respiratory chain, and whose skeletal-muscle mitochondrial DNA was derived from his father. The authors postulate that the presence of the mutation may have led to selective replication of paternally derived DNA (green) in muscle. In contrast, mitochondria in other tissues were inherited from the mother (purple). Normally, all mitochondrial DNA is maternally inherited.

parent is not a fundamental biologic principle. Plants frequently exhibit a mixture of maternal, paternal, and biparental progeny. In mammals, paternal inheritance of mtDNA has previously been reported as a rare phenomenon (incidence, 1×10^{-5} 5×10^{-5} per generation) in crosses of different strains of laboratory mice.[14] Previous studies of healthy humans have revealed no evidence of paternal inheritance, but the samples studied may have been too small to allow detection of such low rates of paternal transmission. Patients with mtDNA disorders are rare, and mitochondrial haplotypes are rarely defined in the manner described in the current case. Thus, it is not possible at this time to estimate with confidence the frequency at which paternal inheritance of mtDNA occurs in humans.

Nevertheless, even a single validated example of paternal mtDNA transmission suggests that the interpretation of inheritance patterns in other kindreds thought to have mitochondrial disease should not be based on the dogmatic assumption of absolute maternal inheritance of mtDNA. Likewise, the possibility of paternal inheritance of mtDNA should be accommodated in statistical models that analyze sequence variations in mtDNA in different human or primate populations[15] in order to draw inferences about human evolution or migration. The unusual case described by Schwartz and Vissing is more than a mere curiosity.

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Editor's note: Dr. Williams is on the scientific advisory board of Sequenom, which makes instruments for DNA analysis, and also holds equity in that company. He holds a patent on a method for transferring genes to mitochondria.

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