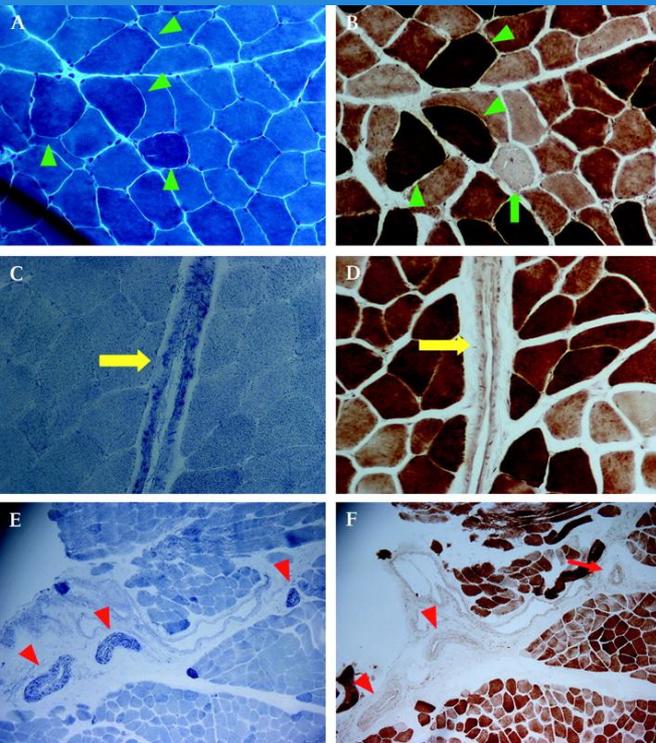
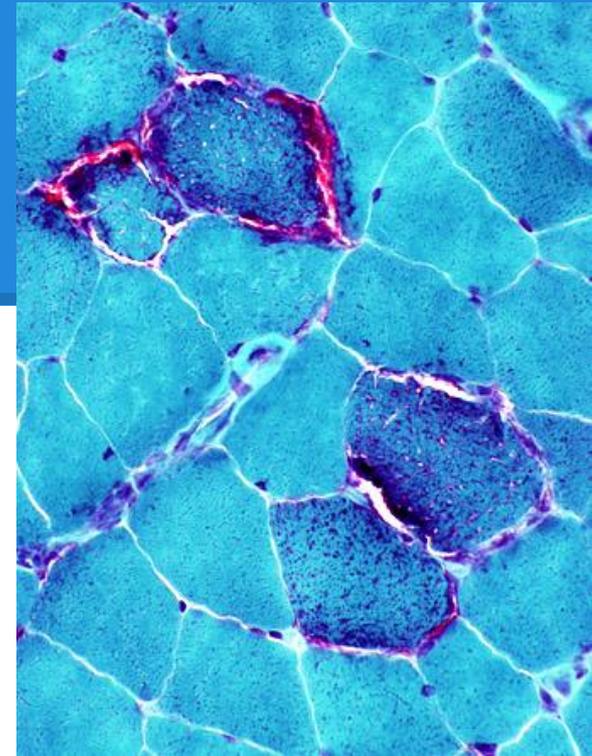


# Myoclonic Epilepsy with Ragged Red Fibers



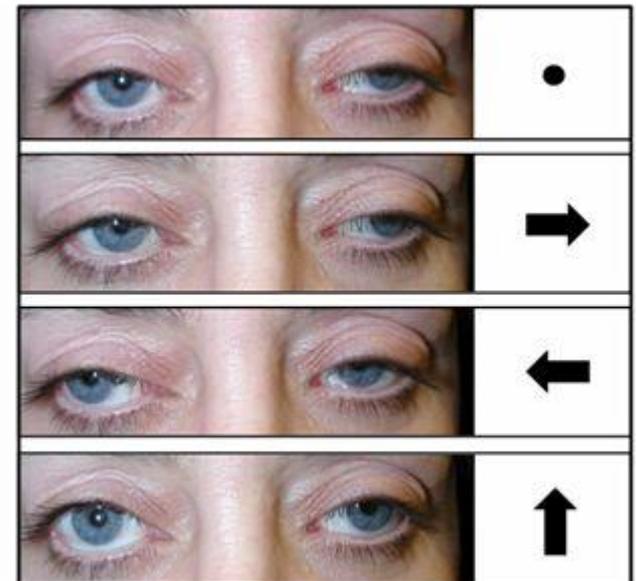
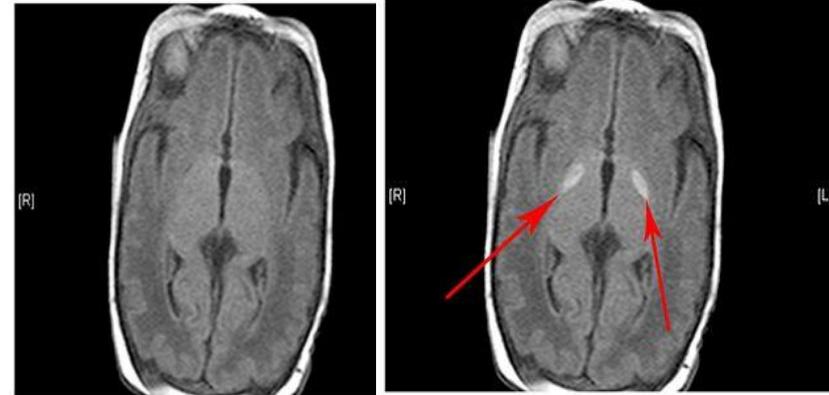
Shi Hui Ng (Fiona)  
Pd 6, #20  
May 29, 2013



# Physiology

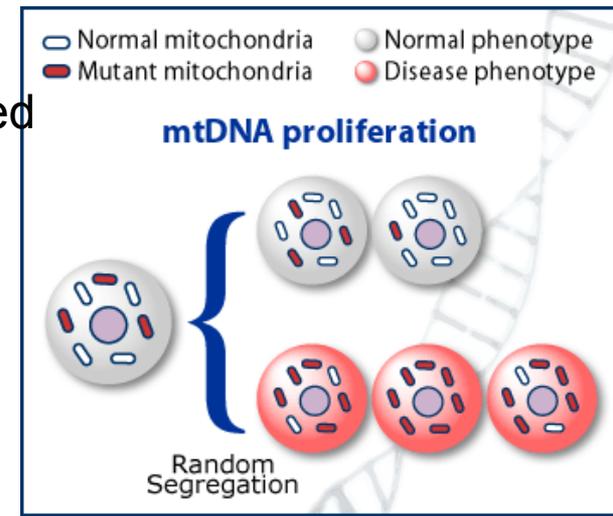
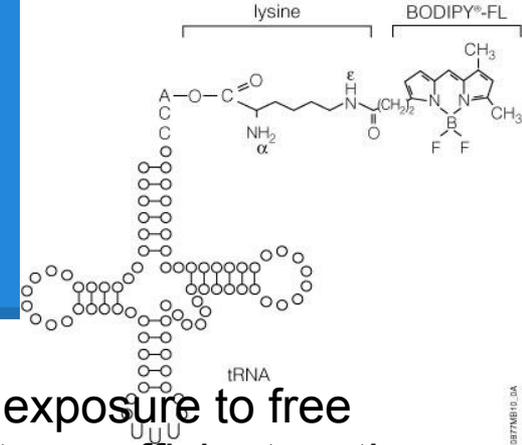
MERRF or Fukuhara Syndrome is a genetic disease that targets organs and systems with high dependence on mitochondria (brain, heart, skeletal muscles, kidney, liver, nervous and muscular systems).

- Affects 1 out of 400,000 people, mostly of European descent; inherited matrilineally, rarely spontaneous.
- Onset is from post early development to early adulthood.
- Severity varies due to heteroplasmy, even in families, but worsens with age.
- Symptoms are myoclonus, epilepsy, loss of coordination, short stature, elevated lactic acid levels, muscle weakness, stiffness, lipomas, dementia, and speech, sight, and hearing disorders.
- MRIs show parts of brain are calcified.
- Stained muscle biopsies show clumps of defective, red mitochondria.

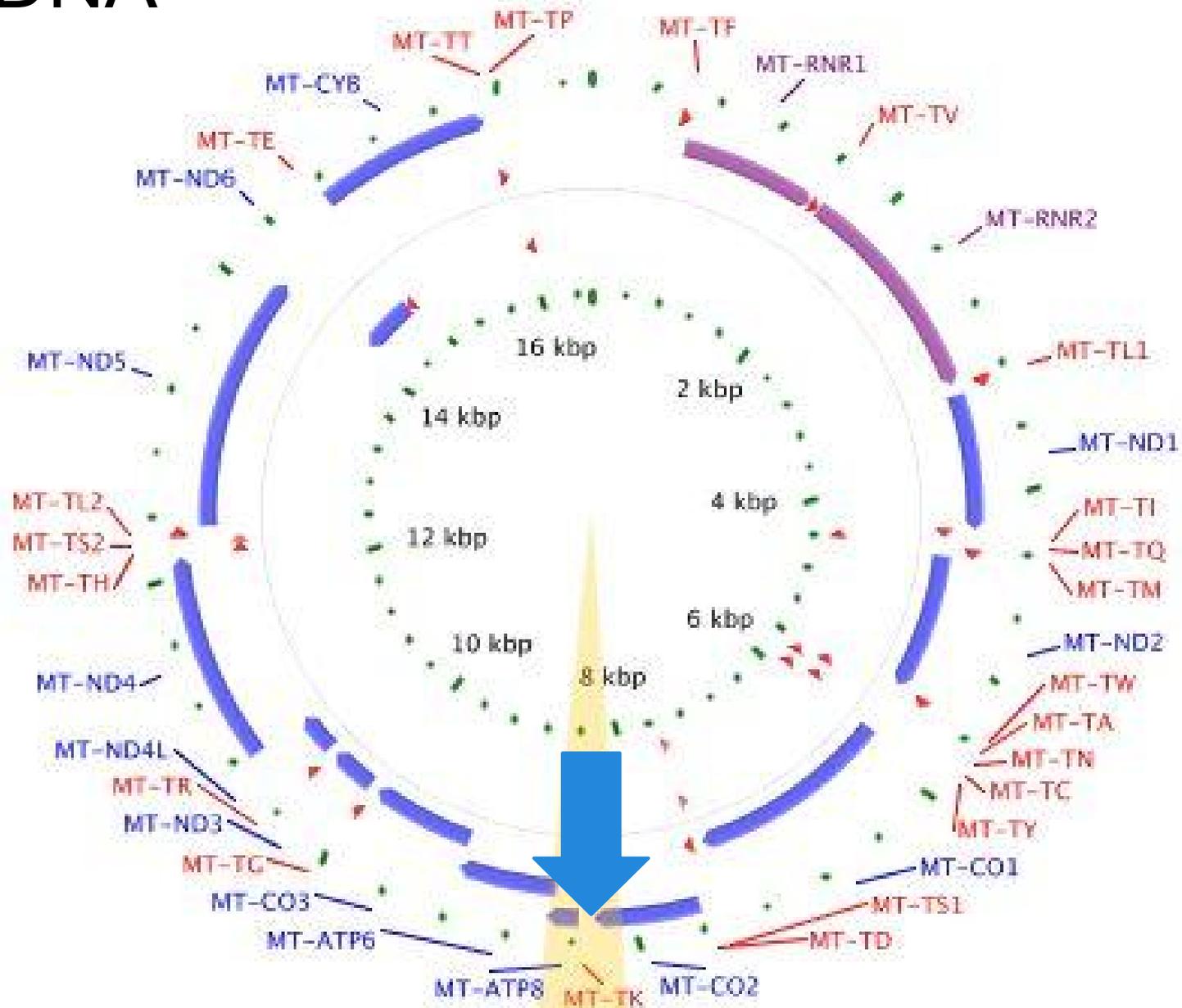


# Molecular Cause

- mtDNA has 37 genes, 22 of which encode tRNA.
- Cause: point mutation in mitochondrial DNA (mtDNA) due to exposure to free oxygen radicals, lack of histones, and repair mechanisms not as sufficient as those of nuclear DNA (nDNA).
- Over 80% of cases due to A8344G mutation in MT-TK gene, which codes for **tRNA<sup>Lys</sup>**, which brings lysine to ribosome. Due to the defective tRNA<sup>Lys</sup> not being able to carry lysine, the ribosome prematurely stops translating the protein needed for oxidative phosphorylation in complex I and IV in the mitochondrial matrix. This premature termination of translation happens near lysine codon.
- Other related mitochondrial genes are MT-TH (tRNA for histidine), MT-TL1, MT-TS1), MT-TS2, and MT-TF.
- **Heteroplasmy**-during replicative segregation, the mother's defective mitochondria are randomly segregated during cell division, so the child may not have the same proportion of mitochondria as the mother.
- Threshold effect is when MERRF manifestations occur only when a certain proportion of mutant mtDNA is reached.



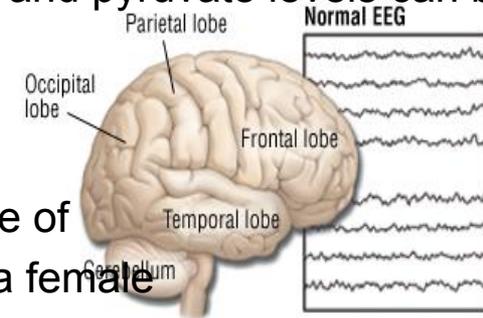
# mtDNA



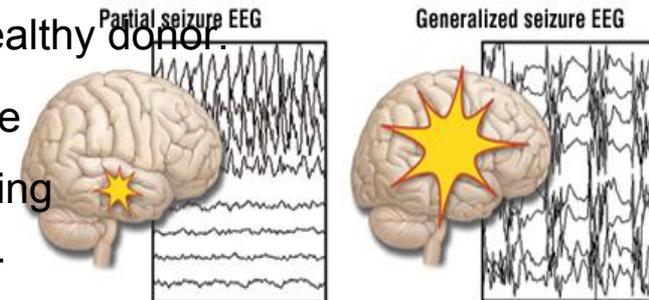
# Treatments/Risks and Limits



- There is currently no cure for MERRF, but there are medicines for its symptoms, which may include coenzyme Q10, L-carnitine, and various vitamins, often in a “cocktail” combination, to help with mitochondrial function. Anticonvulsant drugs, like levetiracetam, can help control epilepsy and myoclonus.
- Physical therapy and aerobic exercise can increase exercise tolerance, muscle strength, and coordination.
- Routine neurological exams, MRI, MR-spectroscopy, and electrophysiology (EEG) are recommended to diagnose prospective mothers. High lactate and pyruvate levels can be measured to show disruption of OXPHOS. MERRF can be detected most effectively in the mtDNA of blood leukocytes and skeletal muscle biopsies.



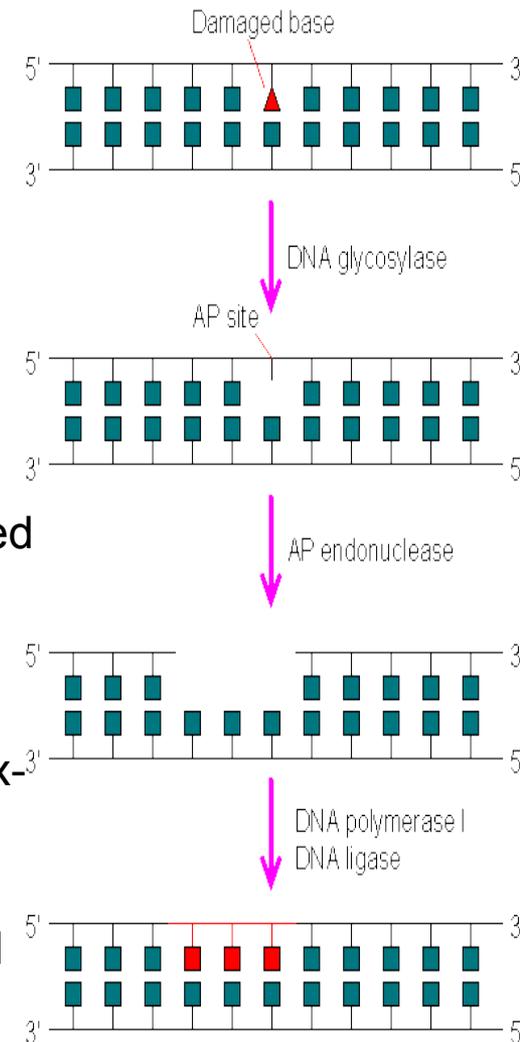
- **Maternal Spindle Transfer** prevents the embryo's inheritance of mother's mutation by placing the nucleus of the mother's egg into a female donor's healthy egg with its own nucleus removed, and then fertilizing the egg with the father's sperm. Make sure mother won't reject and healthy donor.



- Scientists in Taiwan are studying how cell-penetrating peptide Pep-1 can transfer mtDNA between cells that will encode functioning tRNA<sup>lys</sup> into cells with defective mitochondria. Detection is tedious.

# Proposed Cure/Limits

- Since nDNA can also code for tRNA<sup>lys</sup>, we can use a protein import pathway to import tRNA<sup>lys</sup> produced from the cytosol into the mitochondria via mitochondrial precursor protein. Yeast tRNA<sup>lys</sup>, not human tRNA, have been imported fully or partially into isolated mitochondria and were translated correctly. Also, we're not sure specific tRNAs can be imported.
- My proposal aims at repairing the point mutation by increasing the number of base excision repair (BER) proteins, like glycosylase and AP endonuclease with extensions at their N-terminus to act as mitochondrial-matrix targeting signals (sequences of 20 to 30 residues that fold into a positively charged amphiphilic helix with hydrophilic sides). The cytosolic proteins with targeting signals would be made on free ribosomes. After successfully translocating the proteins across the two mitochondrial membranes, the proteins can get rid of their matrix-targeting signals and go perform short-patch BER.
- If the cell releases too much DNA glycosylase and AP endonuclease, the patient may be exposed to alkylation induced tissue damage



# References

## Physiology

### Content

<http://herkules.oulu.fi/isbn9514255674/html/x287.html>

[Nussbaum](#), Robert L., [Roderick R. McInnes](#), [Huntington F. Willard](#), and [Margaret W. Thompson](#). *Thompson & Thompson Genetics in Medicine*. Philadelphia: Saunders, 2004. Clinical Case Studies #20, 244-46. Print.

### Images

<http://neuromuscular.wustl.edu/pics/biopsy/ mito/ melas/ mitogtlpsm.jpg>

[http://www.lhsc.on.ca/\\_images/Genetics/mitochondrialinheritance.jpg](http://www.lhsc.on.ca/_images/Genetics/mitochondrialinheritance.jpg)

## Molecular Pathway

### Content

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1223225/pdf/12467494.pdf>

"Myoclonic Epilepsy with Ragged-red Fibers." *Genetics Home Reference*. U.S. National Library of Medicine, 18 Mar. 2013. Web. 19 Mar. 2013.

<[ghr.nlm.nih.gov/condition/myoclonic-epilepsy-with-ragged-red-fibers](http://ghr.nlm.nih.gov/condition/myoclonic-epilepsy-with-ragged-red-fibers)>.

[Gredilla](#), Ricardo. "DNA Damage and Base Excision Repair in Mitochondria and Their Role in Aging." *Journal of Aging Research* 2011 (2011) *DNA Damage and Base Excision Repair in Mitochondria and Their Role in Aging*. [Hindawi Publishing Corporation](#), 2011. Web. 17 May 2013. Article ID 257093, doi:10.4061/2011/257093 <<http://www.hindawi.com/journals/jar/2011/257093/>>.

### Images

[http://lab.hirschey.org/research/files/page23\\_blog\\_entry0-oxphos.png](http://lab.hirschey.org/research/files/page23_blog_entry0-oxphos.png)

[http://ghr.nlm.nih.gov/html/images/chromosomeIdeograms/mitochondria/MT-TK\\_highlight.jpg](http://ghr.nlm.nih.gov/html/images/chromosomeIdeograms/mitochondria/MT-TK_highlight.jpg)

[http://www.promega.com/resources/product-guides-and-selectors/protocols-and-applications-guide/protein-expression/~Media/Images/Resources/PAGuide/0877MB10\\_0A.ashx](http://www.promega.com/resources/product-guides-and-selectors/protocols-and-applications-guide/protein-expression/~Media/Images/Resources/PAGuide/0877MB10_0A.ashx)

## Treatments/Risks and Limits

### Content

<http://bioscience.jpуб.com/cells/MBIO4134.aspx>

[DiMauro](#), Salvatore, MD, and [Michio Hirano](#), MD. "MERRF." *National Center for Biotechnology Information*. U.S. National Library of Medicine, 06 Mar. 2003. Web. 10 Mar. 2013. Bookshelf ID: NBK1520 PMID: 20301693 <[www.ncbi.nlm.nih.gov/books/NBK1520/](http://www.ncbi.nlm.nih.gov/books/NBK1520/)>.

[Pál](#), E. "Diagnosis and Therapy of Mitochondrial Diseases." *National Center for Biotechnology Information*. U.S. National Library of Medicine, 30 July 2012. Web. 9 Mar. 2013. PMID: 23074842 <[www.ncbi.nlm.nih.gov/pubmed/23074842](http://www.ncbi.nlm.nih.gov/pubmed/23074842)>.

### Images

[http://www.pharmer.org/files/images/Keppra%20\(Lvetiracetam\)%20500mg%20%20%20%20%20%20%20UCB%20Pharma.JPG](http://www.pharmer.org/files/images/Keppra%20(Lvetiracetam)%20500mg%20%20%20%20%20%20%20UCB%20Pharma.JPG)

## Proposed cure/Limits

### Content

<http://www.ncbi.nlm.nih.gov/pubmed/15317755>

<http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1003238#abstract1>

<http://hmg.oxfordjournals.org/content/13/20/2519.short>

[Roth](#), Stephen M. "Why Does Lactic Acid Build up in Muscles? And Why Does It Cause Soreness?" *Scientific American*, 23 Jan. 2006. Web. 20 Mar. 2013.

<[www.scientificamerican.com/article.cfm?id=why-does-lactic-acid-build](http://www.scientificamerican.com/article.cfm?id=why-does-lactic-acid-build)>.

[Jha](#), [Alok](#). "Mitochondria Donation Wins Ethical Approval for Fertility Treatments." *The Guardian*. Guardian News and Media, 11 June 2012. Web. 20 Mar. 2013.

<[www.guardian.co.uk/science/2012/jun/12/fertility-treatments-mitochondria-donation-ethical-approval](http://www.guardian.co.uk/science/2012/jun/12/fertility-treatments-mitochondria-donation-ethical-approval)>.

[Chang](#), JC. "Functional Recovery of Human Cells Harboring the Mitochondrial DNA Mutation MERRF A8344G via Peptide-Mediated Mitochondrial Delivery." *National Center for Biotechnology Information*. U.S. National Library of Medicine, 21 Sept. 2012. Web. 21 Mar. 2013. <[www.ncbi.nlm.nih.gov/pubmed/23006856](http://www.ncbi.nlm.nih.gov/pubmed/23006856)>.

[Robertson](#), AB, and A. [Klungland](#). "DNA Repair in Mammalian Cells: Base Excision Repair: The Long and Short of It." *National Center for Biotechnology Information*. U.S. National Library of Medicine, Mar. 2009. Web. 06 May 2013. PMID: 19153658 <<http://www.ncbi.nlm.nih.gov/pubmed/19153658>>.

[Calvo](#), JA, and CA [Moroski-Erkul](#). "Result Filters." *National Center for Biotechnology Information*. U.S. National Library of Medicine, Apr. 2013. Web. 18 May 2013.

<<http://www.ncbi.nlm.nih.gov/pubmed/23593019>>.

### Images

<http://www.web-books.com/MoBio/Free/images/Ch7G1.gif>