2017

Tay-Sachs and its Prevalence in the Ashkenazi Jewish, French-Canadian, and Louisiana Cajun Population

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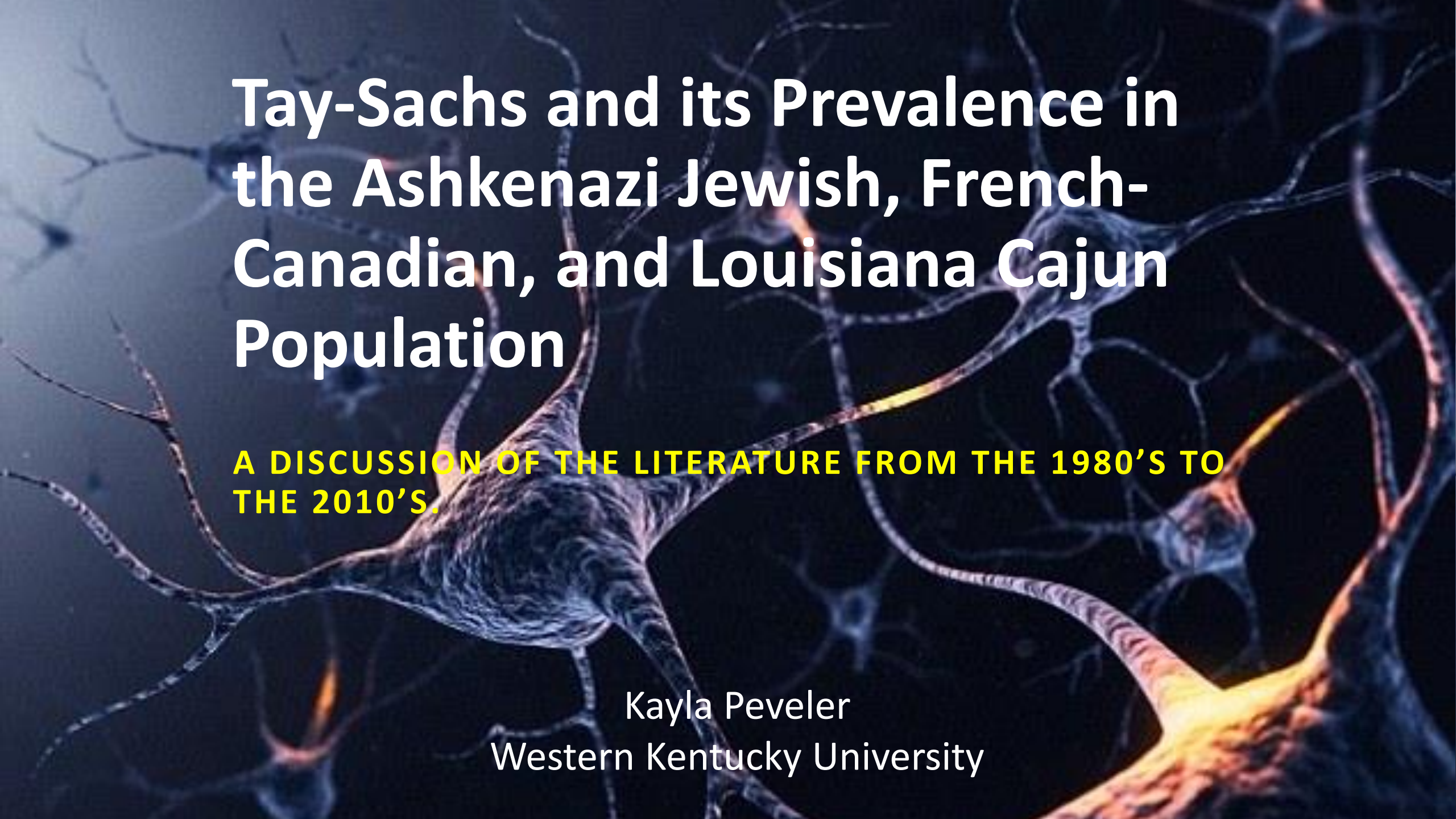


Tay-Sachs and its Prevalence in the Ashkenazi Jewish, French-Canadian, and Louisiana Cajun Population

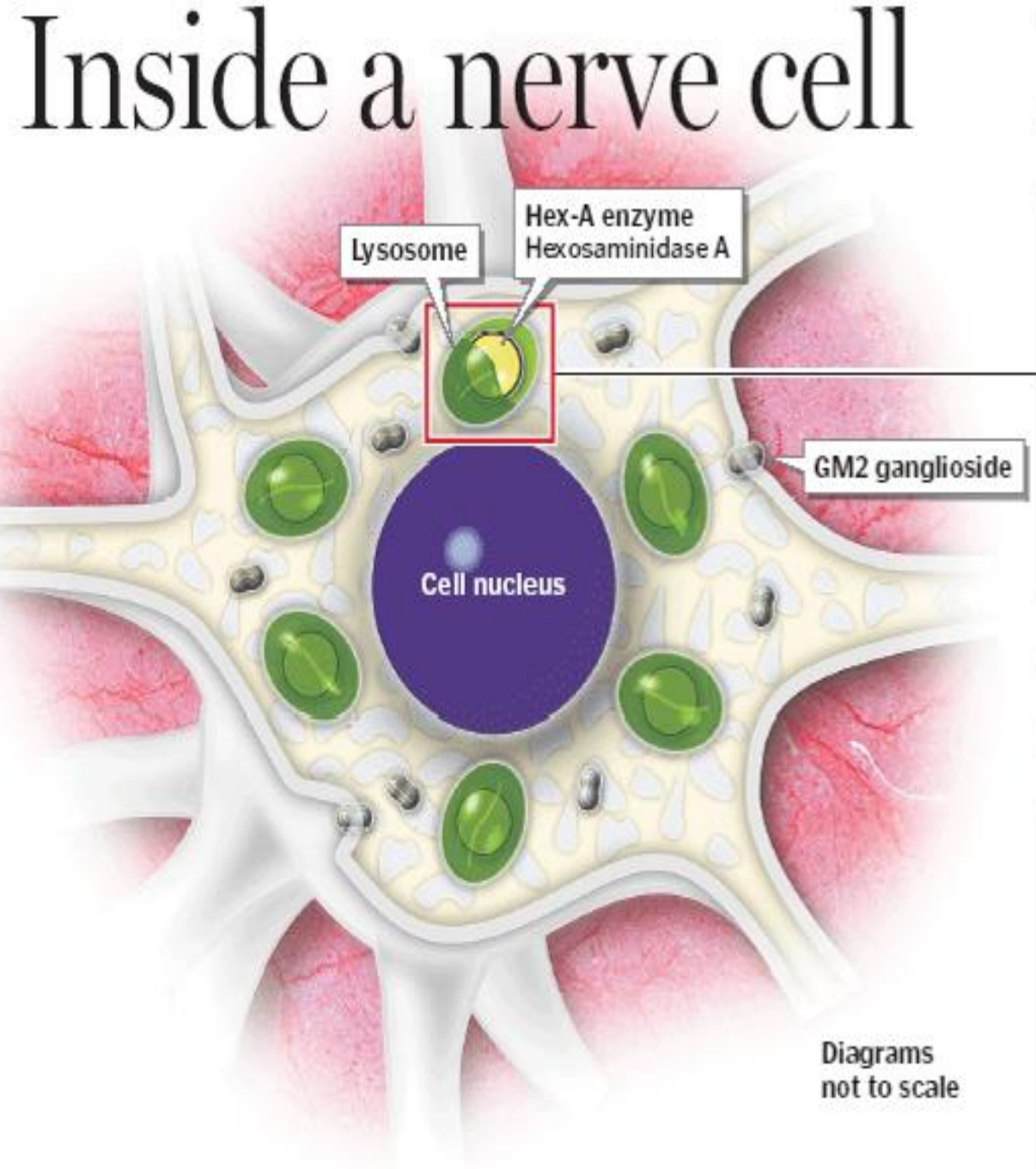
A DISCUSSION OF THE LITERATURE FROM THE 1980'S TO THE 2010'S.

Kayla Peveler
Western Kentucky University

What is Tay-Sachs Disease?

- Autosomal, recessive disease
- Chromosome 15, HEXA gene
- Beta-hexosaminidase A
  - Breaks down GM2 gangliosides used for neuron cell membrane production
  - Lysosomes
- Results in toxic levels of GM2 gangliosides, destroys nerve cells

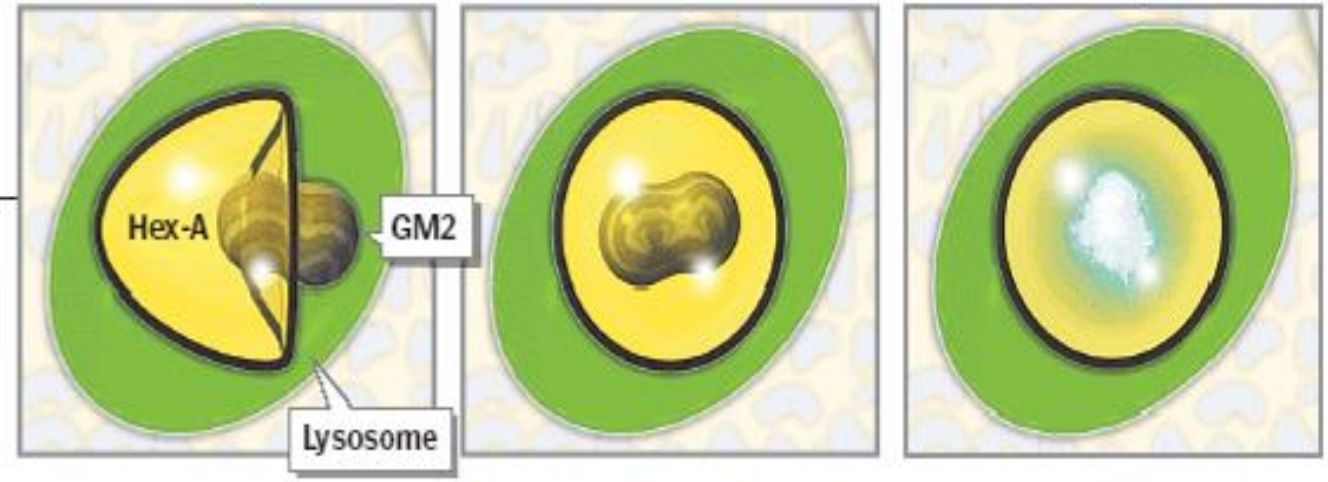
Inside a nerve cell



Cells in healthy children

In a healthy child, a lipid, or fat, called GM2 ganglioside enters the nerve cell as a source of food. Among the components of the cell are lysosomes, which might be thought of as the "stomachs" of the cell. They contain an enzyme called Hexosaminidase A, or Hex-A, that digests the GM2.

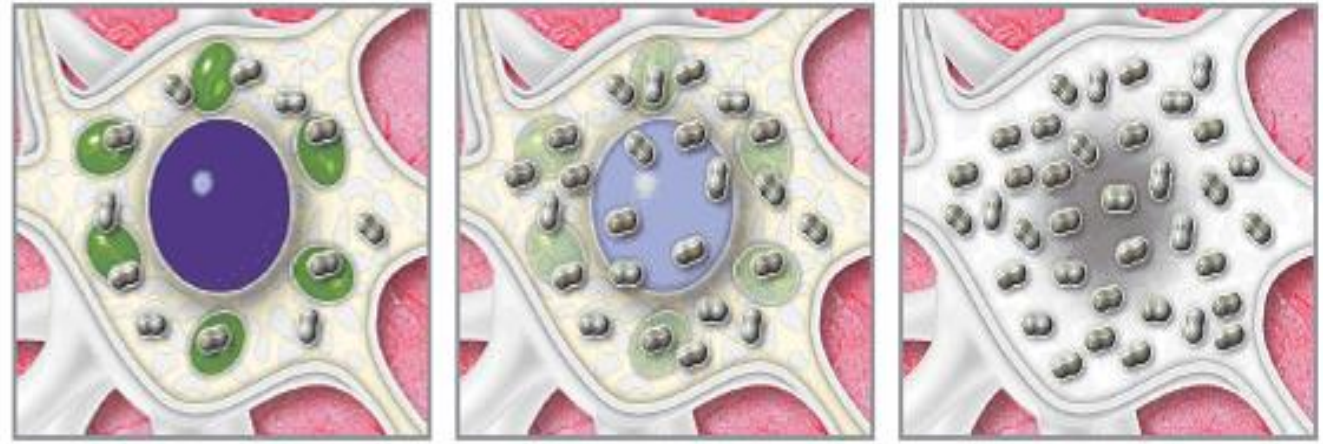
GM2 enters the lysosome ... ... where it is engulfed ... ... and digested by the Hex-A.



Cells in children with Tay-Sachs disease

Children with Tay-Sachs lack Hex-A, so the GM2 proliferates to such a degree that it eventually kills the cell, gradually shutting down the central nervous system.

If Hex-A enzyme is not present ... ... GM2 accumulates ... ... and in time chokes off the cells.



University Hospitals; The National Tay-Sachs & Allied Diseases Association; healthline.com; howstuffworks.com

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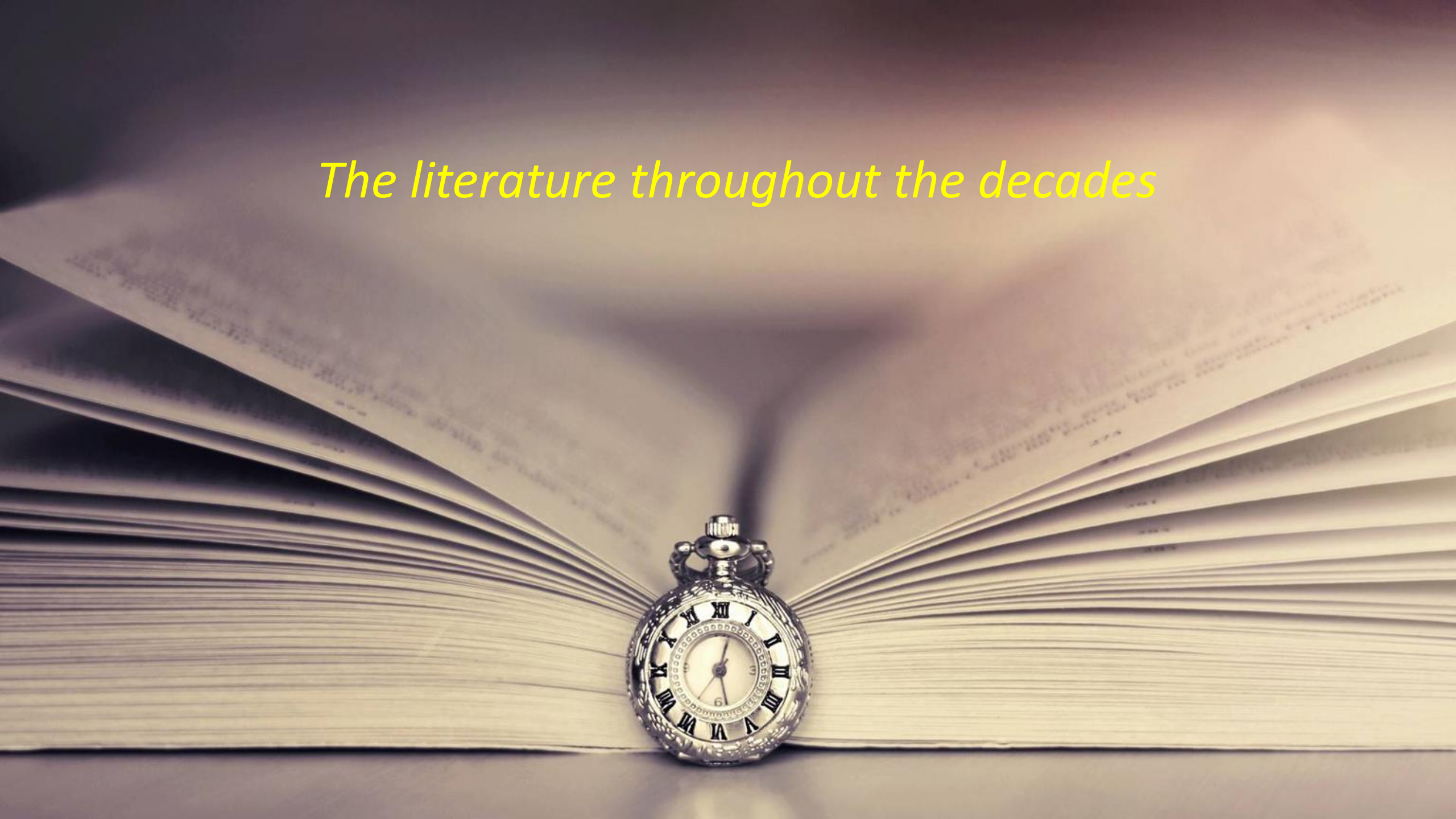
The literature throughout the decades



1981

- The *American Journal of Human Genetics*
- Purpose:
  - Do carriers have an heterozygous advantage?
    - TB resistance?
- Population Studied:
  - Ashkenazi Jewish
- Method:
  - Questionnaires sent to 400 carriers
  - Control group of non-Carriers randomly selected
  - Questions asked
    - Carrier or non-carrier?
    - Cause of death of both maternal and paternal grandparents?

Spyropoulos, B., Moens, P. B., Davidson, J., & Lowden, J. A. (1981). Heterozygous advantage in Tay-Sachs Carriers? *The American Journal of Human Genetics, 33,* 375-380. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1685035/pdf/ajhg00363-0049.pdf

1981 Cont.

- Findings:
  - Mathematically, grandparents of Tay-Sachs carriers die from the same reasons as non-carriers of the disease
- Conclusion:
  - Founder effect resulting in genetic drift
- Problems:
  - Ashkenazi Jewish?
  - Grandparents didn’t undergo carrier screenings
  - Grandparents of one family could be closely related to the grandparents of another family
  - Grandchildren could have been inaccurate

Spyropoulos, B., Moens, P. B., Davidson, J., & Lowden, J. A. (1981). Heterozygous advantage in Tay-Sachs Carriers? *The American Journal of Human Genetics, 33,* 375-380. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1685035/pdf/ajhg00363-0049.pdf

1992

- The *American Journal of Human Genetics*
- Purpose:
  - Determine origins of Tay-Sachs mutations in southwest Louisiana
- Population Studied:
  - Louisiana Cajun
- Method:
  - Six Families Studied
  - Four Families
    - 90 Individuals Evaluated
    - Pedigrees Conducted for All Carriers

McDowell. G. A., Mulest. E. H., Fabacher. P., Shapira. E. & Blitzer, M. G. (1992). The presence of two different infantile Tay-Sachs Disease mutations in a Cajun population. The American Journal of Human Genetics, *51,* 1071-1077. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1682822/pdf/ajhg00069-0137.pdf

1992 Cont.

- Findings:
  - Exon 11 mutation
    - 11/12 TSD infantile alleles
    - Traced back to one couple from France
- Conclusion:
  - Exon 11 mutation originated 2 centuries ago
  - Intron 9 mutation
    - Recent
- Problems:
  - Not all members of each family had pedigrees made
  - Not enough information for intron 9 mutation

McDowell. G. A., Mulest. E. H., Fabacher. P., Shapira. E. & Blitzer, M. G. (1992). The presence of two different infantile Tay-Sachs Disease mutations in a Cajun population. The American Journal of Human Genetics, *51,* 1071-1077. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1682822/pdf/ajhg000690137.pdf

2012 (Research Paper)

- *Advances in Anthropology*
- Population Studied:
  - French-Canadian
- Hypothesis:
  - Co-evolution has occurred between two populations of French-Canadians in eastern Quebec due to heterozygous advantage.
- Reasoning:
  - Concentrated in eastern Quebec
    - Two mutant alleles
      - North shore
      - South shore
  - Alleles not present in France

Frost. P. (2012). Tay-Sachs and French Canadians: A case of gene-culture co-evolution? *Advances in Anthropology, 2(3),* 132-138. http://dx.doi.org/10.4236/aa.2012.23016

2012 (Research Paper) Cont.

- British conquest of 1759
  - Lack of American and British merchants
- Conclusion:
  - The high frequency of Tay-Sachs disease is inconsistent with a founder effect. Due to it's unique characteristics, the phenomenon occurring in the French-Canadian population in eastern Quebec is consistent with a heterozygous advantage.

Frost. P. (2012). Tay-Sachs and French Canadians: A case of gene-culture co-evolution? *Advances in Anthropology, 2(3),* 132-138. http://dx.doi.org/10.4236/aa.2012.23016

2014

- *Nature Communications*
- Population Studied:
  - Ashkenazi Jewish
- Purpose:
  - To determine the origins of the Ashkenazi Jewish population and, in-turn, determine the reasons for increased frequencies of diseases.
- Method:
  - Comparison of genomes
    - 128 AJ to non-Jewish Europeans

Carmi, S., Hui, K. Y., Kochav, E., Liu, X., Xue, J., Grady, F. … Pe'er, I. (2014). Sequencing an Ashkenazi reference panel supports population-targeted personal genomics and illuminates Jewish and European origins. *Nature Communications, 5: 4835*. doi: 10.1038/ncomms5835

2014 Cont.

- Findings:
  - Admixture
    - European and Middle Eastern
  - Bottleneck
    - 600-800 years ago
      - 350 Individuals
- Conclusion:
  - The AJ population was founded by a severe bottleneck during the late Middle Ages. They are almost an even admixture of Europeans and Middle Easterners.

Carmi, S., Hui, K. Y., Kochav, E., Liu, X., Xue, J., Grady, F. … Pe'er, I. (2014). Sequencing an Ashkenazi reference panel supports population-targeted personal genomics and illuminates Jewish and European origins. *Nature Communications, 5: 4835*. doi: 10.1038/ncomms5835

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