ANGIOMA ALLIANCE
because brains shouldn't bleed

Genealogy of the CCM2 Exon 2-10 Deletion Founder Mutation

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CCM2 Common Deletion

Am J Hum Genet. 2007 Jan; 80(1): 69–75.
Published online 2006 Nov 14. doi: 10.1086/510439
PMCID: PMC1785317
PMID: 17160895

Deletions in *CCM2* Are a Common Cause of Cerebral Cavernous Malformations

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Abstract

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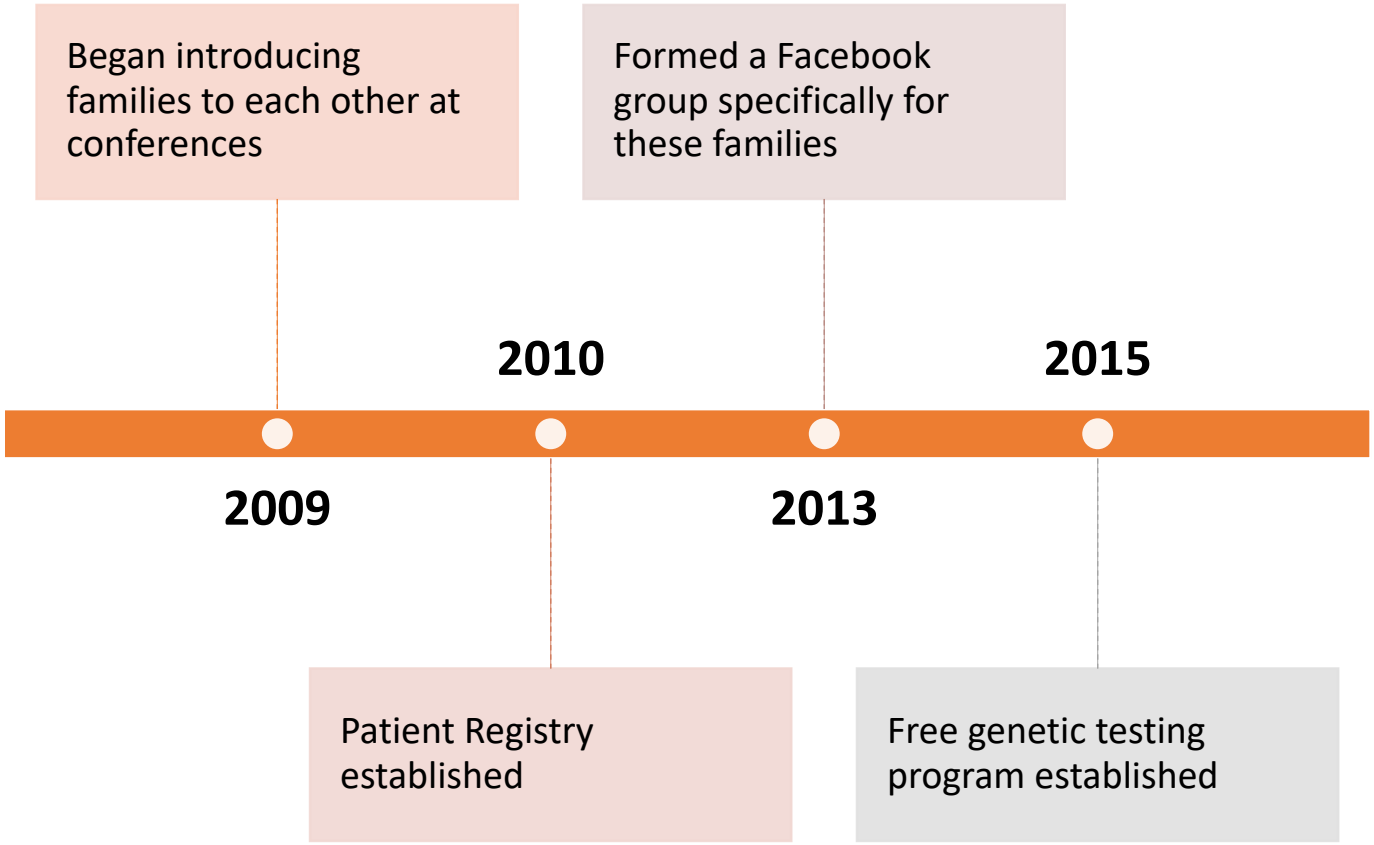
Cerebral cavernous malformations (CCMs) are vascular abnormalities of the brain that can result in a variety of neurological disabilities, including hemorrhagic stroke and seizures. Mutations in the gene *KRIT1* are responsible for CCM1, mutations in the gene *MGC4607* are responsible for CCM2, and mutations in the gene *PDCD10* are responsible for CCM3. DNA sequence analysis of the known CCM genes in a cohort of 63 CCM-affected families showed that a high proportion (40%) of these lacked any identifiable mutation. We used multiplex ligation-dependent probe analysis to screen 25 CCM1, -2, and -3 mutation-negative probands for potential deletions or duplications within all three CCM genes. We

13% of Cohort at Duke

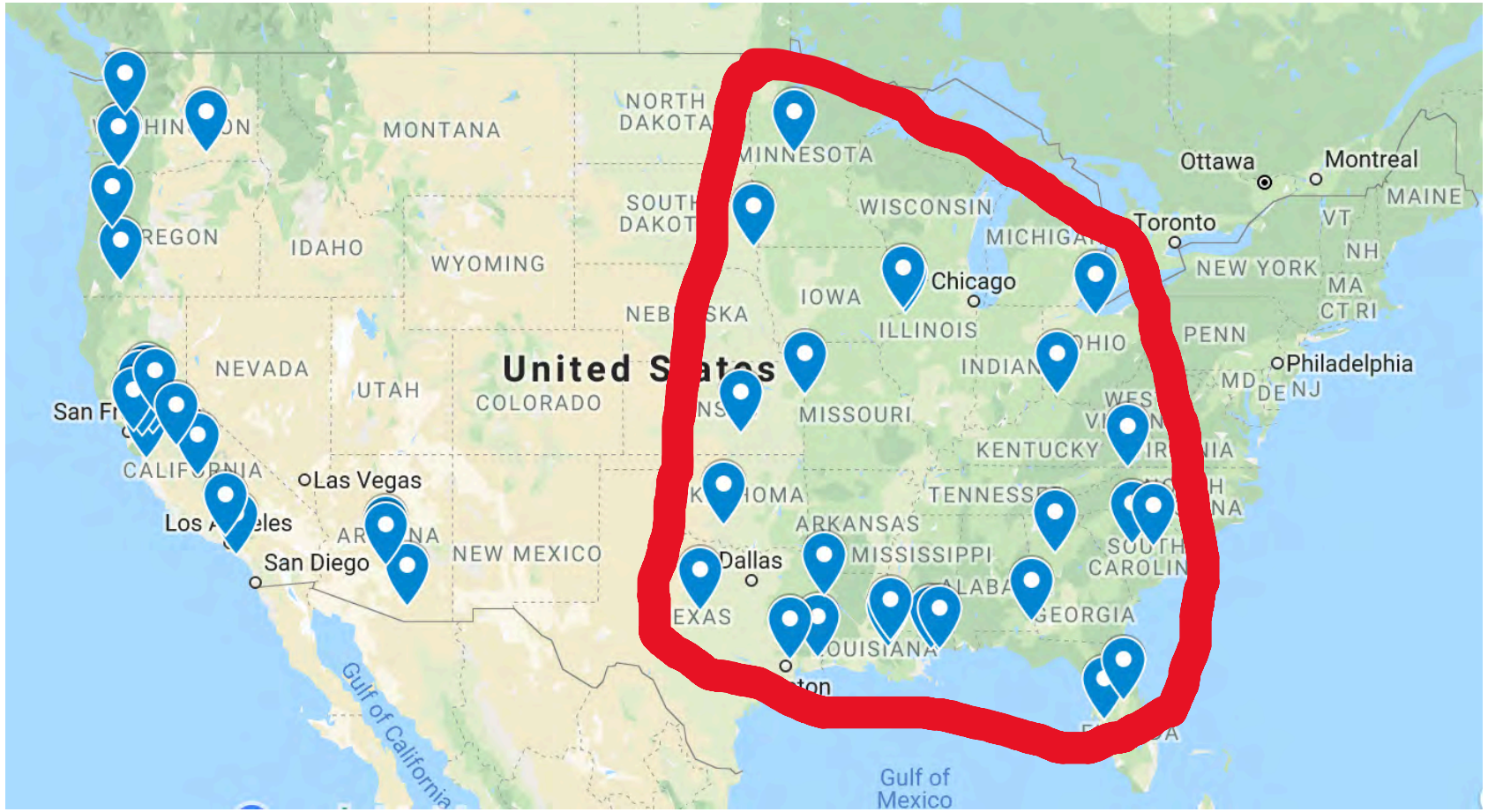
frequencies of 40% for CCM1, 38% for CCM2, 6% for CCM3, and 16% with no mutation detected. These data indicate that the prevalence of CCM2 is much higher than previously predicted, nearly equal to CCM1, and that large genomic deletions in the CCM2 gene represent a major component of this disease. A common 77.6-kb deletion spanning *CCM2* exons 2–10 was identified, which is present in 13% of our entire CCM cohort. Eight probands exhibit an apparently identical recombination event in the CCM2 gene, involving an *Alu*Sx in intron 1 and an *Alu*Sg distal to exon 10. Haplotype analysis revealed that this *CCM2* deletion occurred independently at least twice in our families. We hypothesize that these deletions occur in a hypermutable region because of surrounding repetitive sequence elements that may catalyze the formation of intragenic deletions.

Collecting Families

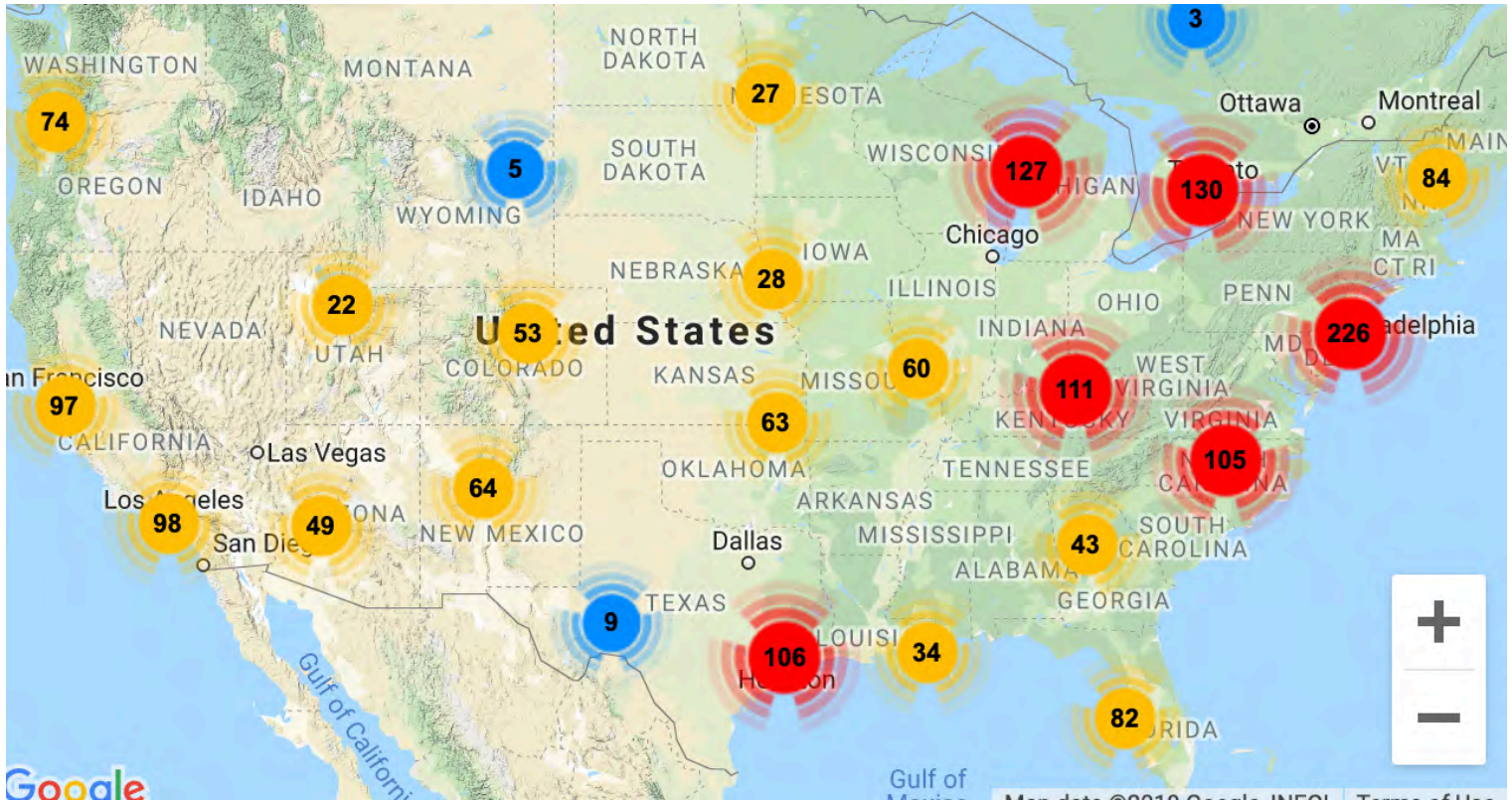


Where our families members live now

Northeast Entirely Omitted



Patient Registry Enrollees: Geography



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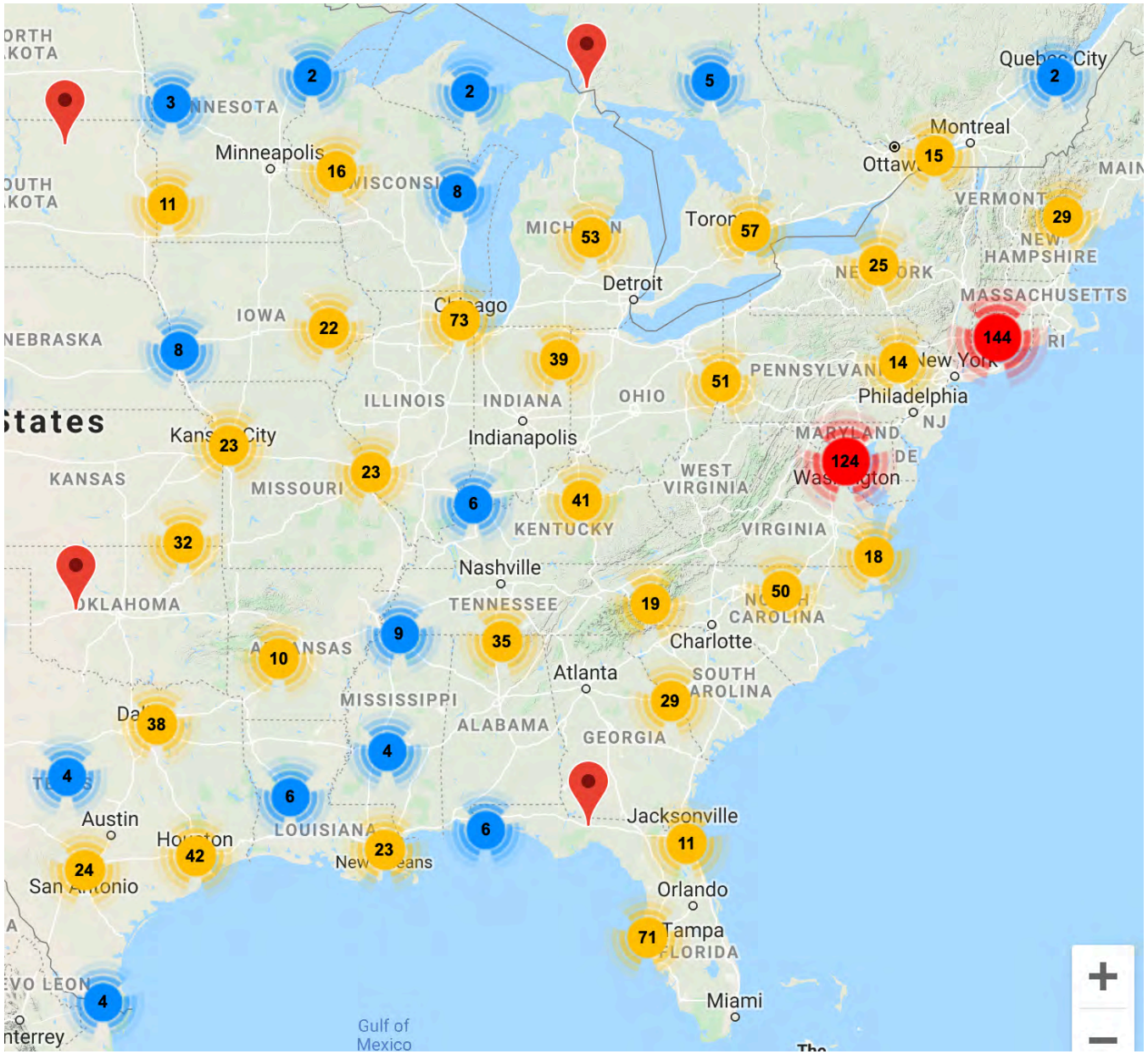
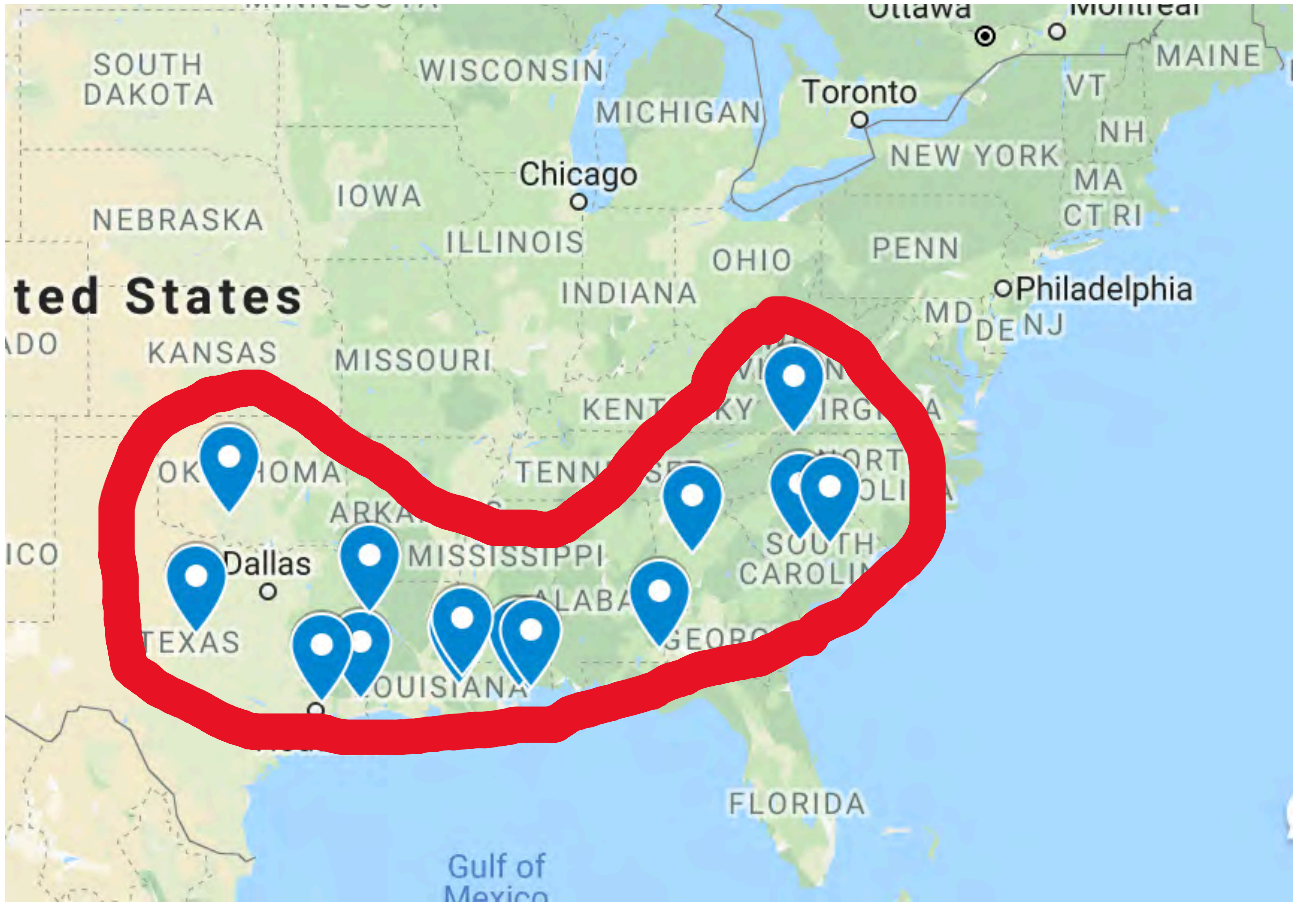


Origin of Most of Our Families



Connecting Genealogy, Finding a Founder

2013 – created Facebook group

We collected 30 separate families, total of 65 named patients, representing 400+ non-overlapping affected family members.

We already knew the Bates and Bowlin families intersected in the early 1900's because of previous genealogical work by a member. Founder was Abraham Bowlin, born 1876.

December 2018 - September 2019

With the addition of a new Florida/Louisiana family to our group, the families were able to make the first connection: they discovered that the Rushing family of South Carolina and the Bowlin family of Mississippi intersect around 1860 and both have the illness.

February 2019 – brought in professional genealogist (president of NM Genealogical Society whose husband is from NC). She is helping pro bono.

With research by a North Carolina family, we discovered that we could go back one more generation because Matthew Malachi Rushing Jr. had 2 children who had the illness (Caroline and Ephraim).

October 2019

Looking at our families again, corrected a mistaken link - this ended up taking the families back one more generation.

Now the identified founding couple is Matthew Malachi Rushing and Sarah Mae Harrell, both born around 1762 in NC.

Summary of connections

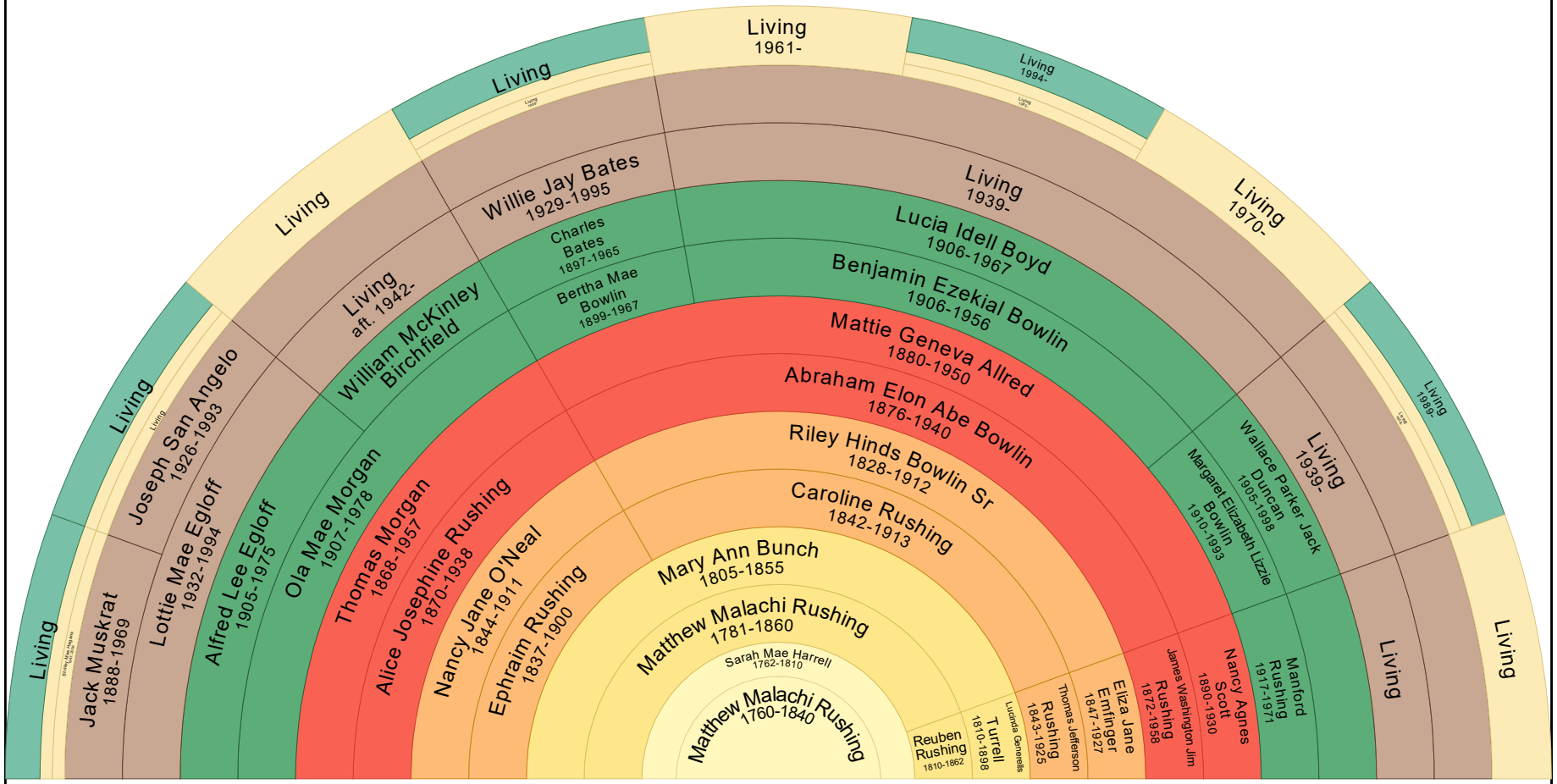
Matthew Malachi Rushing Sr. and Sarah Harrell had at least 2 affected sons, Matthew Malachi Jr. and Reuben.

Matthew Malachi Jr. had at least one affected daughter and one affected son, Caroline and Ephraim.

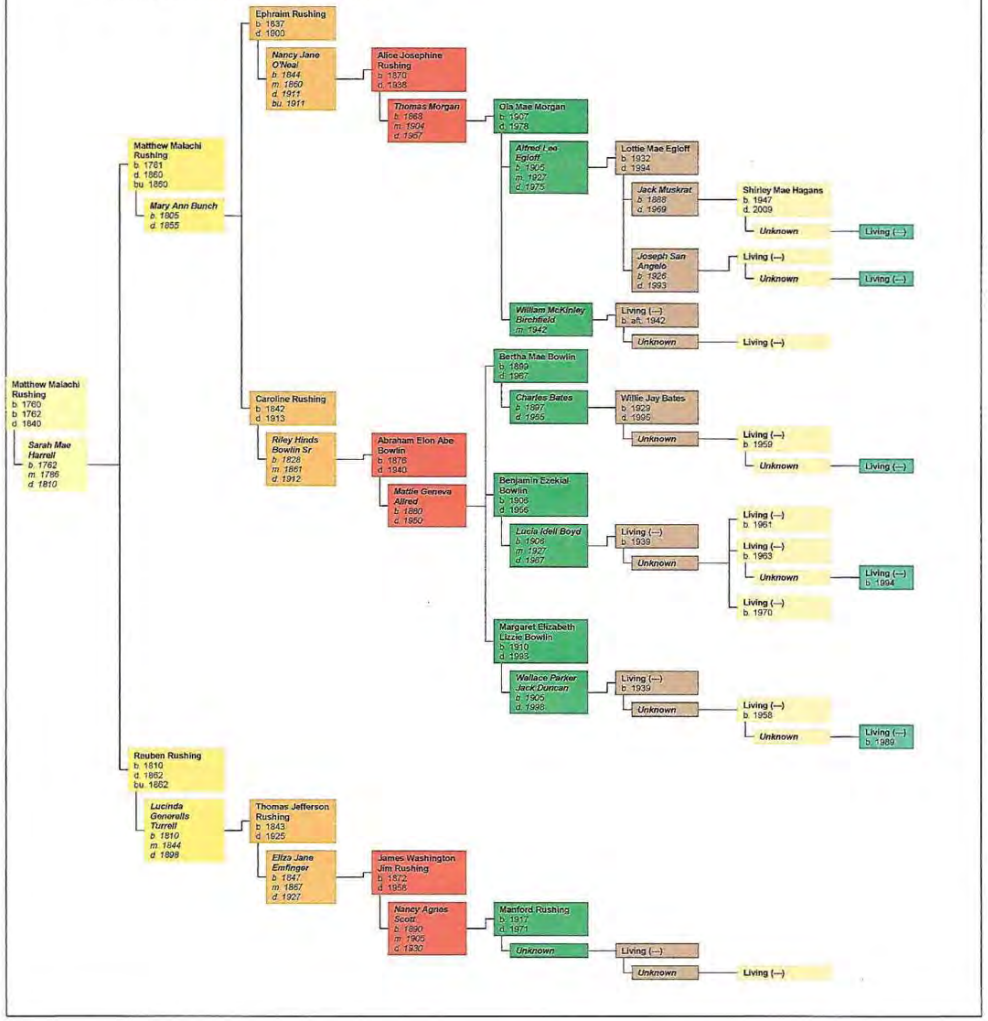
Reuben had at least one affected son, Thomas Jefferson Rushing.

Caroline, Ephraim, and Thomas Jefferson went on to have many descendants.

The 8th generation affected by the common deletion is now in their 20s.


Living 1961-
Living
Living 1994-
Living
Living 1939-
Living 1970-
Living
Living aft. 1942-
Willie Jay Bates 1929-1995
Charles Bates 1897-1965
Bertha Mae Bowlin 1899-1967
Lucia Idell Boyd 1906-1967
Benjamin Ezekial Bowlin 1906-1956
William McKinley Birchfield
Mattie Geneva Allred 1880-1950
Abraham Elon Abe Bowlin 1876-1940
Riley Hinds Bowlin Sr 1828-1912
Caroline Rushing 1842-1913
Mary Ann Bunch 1805-1855
Matthew Malachi Rushing 1781-1860
Sarah Mae Harrell 1762-1810
Matthew Malachi Rushing 1760-1840
Reuben Rushing 1810-1862
Turrell 1810-1898
Lucinda Generellis
Thomas Jefferson Rushing 1843-1925
Eliza Jane Emfinger 1847-1927
James Washington Jim Rushing 1872-1938
Nancy Agnes Scott 1890-1930
Manford Rushing 1917-1971
Wallace Parker Jack Duncan 1905-1998
Margaret Elizabeth Lizzie Bowlin 1910-1993
Living 1939-
Living 1989-
Living
Living
Living
Living
Joseph San Angelo 1926-1993
Lottie Mae Egloff 1932-1994
Alfred Lee Egloff 1905-1975
Ola Mae Morgan 1907-1978
Thomas Morgan 1868-1957
Alice Josephine Rushing 1870-1938
Nancy Jane O'Neal 1844-1911
Ephraim Rushing 1837-1900
Jack Muskrat 1888-1969
Living

Ancestors Descendants of Matthew Malachi Rushing



Tip of the Iceberg

- Matthew Malachi Rushing Sr. and Sarah Harrell had at least 12 children who lived to adulthood. Odds are good that Matthew Malachi Jr. and Reuben were not the only ones affected.
- Matthew Malachi Rushing Jr. had 8 children who lived into adulthood.

And so on…

Next Steps

Continue Genealogy

- Our pro bono genealogist will be spending 12 days in Salt Lake City in January devoted to this project. We hope to fund additional genealogical assistance as needed.

Increase Visibility

- Increase visibility of project through genetic testing labs, CCM Clinical Centers, regional providers.

Advocate

- Reach out to state level legislators in the Deep South/Texas/Oklahoma through Rare Action Network and to Senators to help raise visibility and government support.

Thank You!