Genetics of Familial WM

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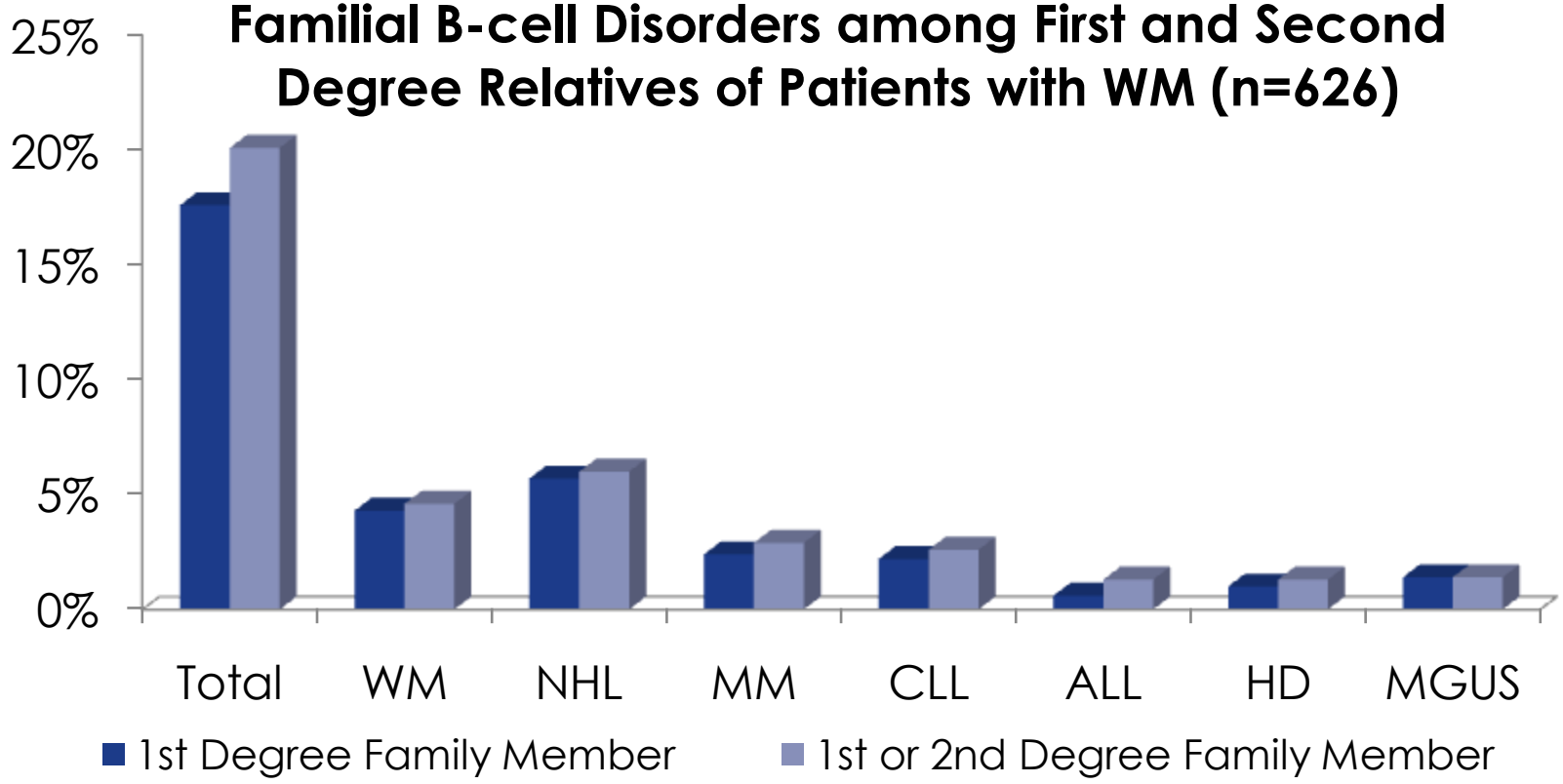
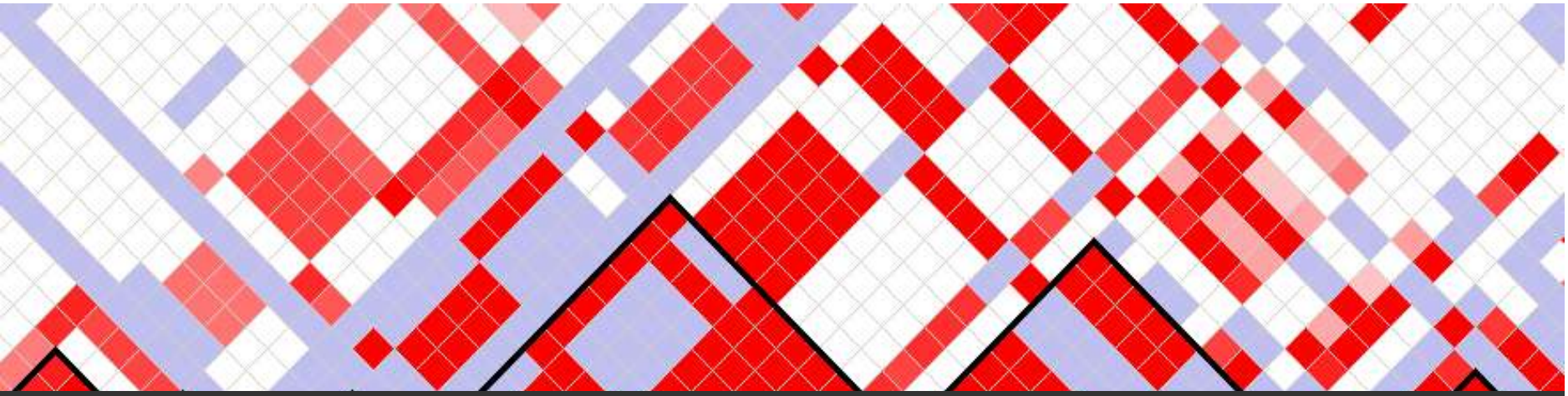
Family History & WM



Overview – Three Easy Pieces

- Part 1: Understanding Genetics and Familial Disease
  - Overview of genetics and genetic terminology
  - What is known about the genetics of WM
  - Why this research is important to all WM patients
- Part 2: Clinical Findings
  - Working definitions of family history in WM
  - Differences in inheritance patterns
  - Clinical differences by family type
- Part 3: Genetics
  - Genetic associations based on genotyping
  - Current projects including whole genome sequencing



Part 1

Understanding Genetics and Familial Disease

Quick Review - Genetics

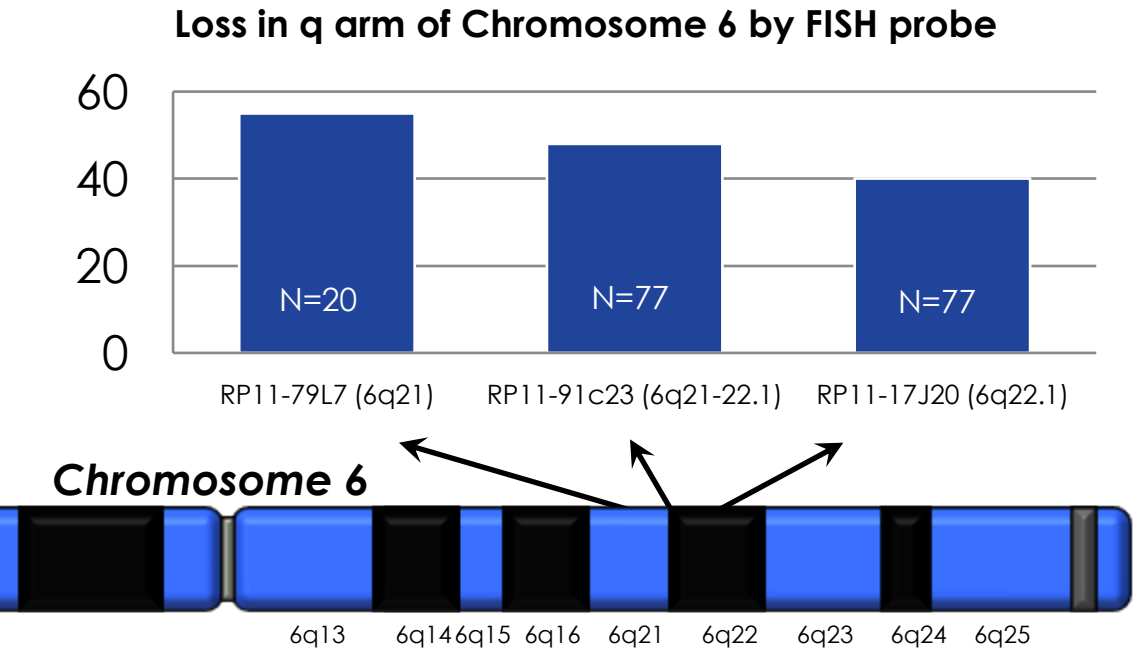
We inherit traits from our parents through DNA.

DNA is organized into 23 chromosomes.

Each person as two copies of each chromosome, one from each parent.

DNA encodes instructions the regulate cell function. Differences in these instructions account for most inheritable traits.

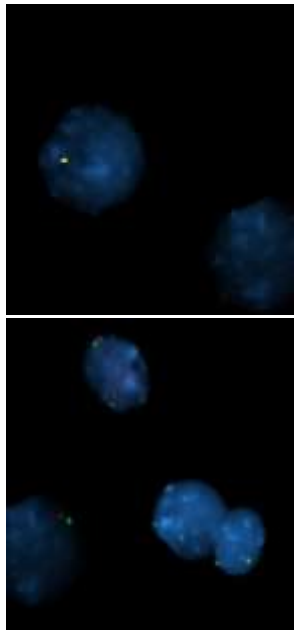
DNA damage can alter these instructions causing the effected cells to change their behavior. These changes in behavior can result in disease, including cancer.



Loss of 6q as demonstrated by Florescent in Situ Hybridization (FISH).

Right: Overall study results by location.

Left: Florescent probes visible in WM cell samples



WM Genetics: What is Known

- Loss of a portion of the long arm (also known as the q arm) of chromosome 6 has been associated with WM and other lymphomas
- Gaines in 6p (the short arm) have been seen to in a subset of patients with 6q loss (Braggio et al, Cancer Research 2009).
- Mutations effecting MIRN15A, MIN16-1, TRAF3 and TNFAIP3 in less than 10% of patients (ibid)

Why Study Families?

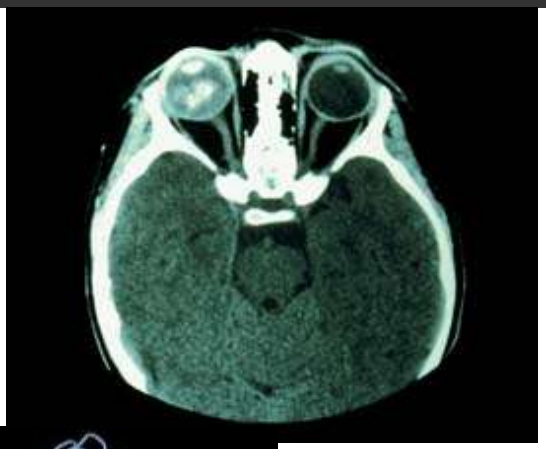
There are more than 3 billion base pairs in the human genome.

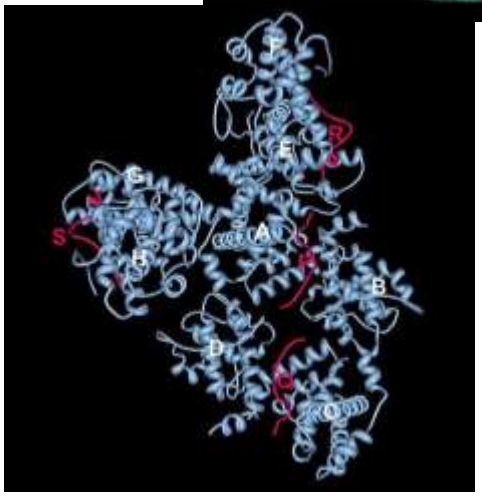
With familial diseases we can combine genetic tests with inheritance patterns to narrow our search considerably.

The genetic predisposition often located in the same gene or pathway of genes that is mutated in non familial cases

This technique has been used successfully to identify the root cause of several diseases including the cancer retinoblastoma

Once a gene or pathway is identified, we can design new drugs to target tailored to correct the problem





Above: CT scan of a patient with retinoblastoma

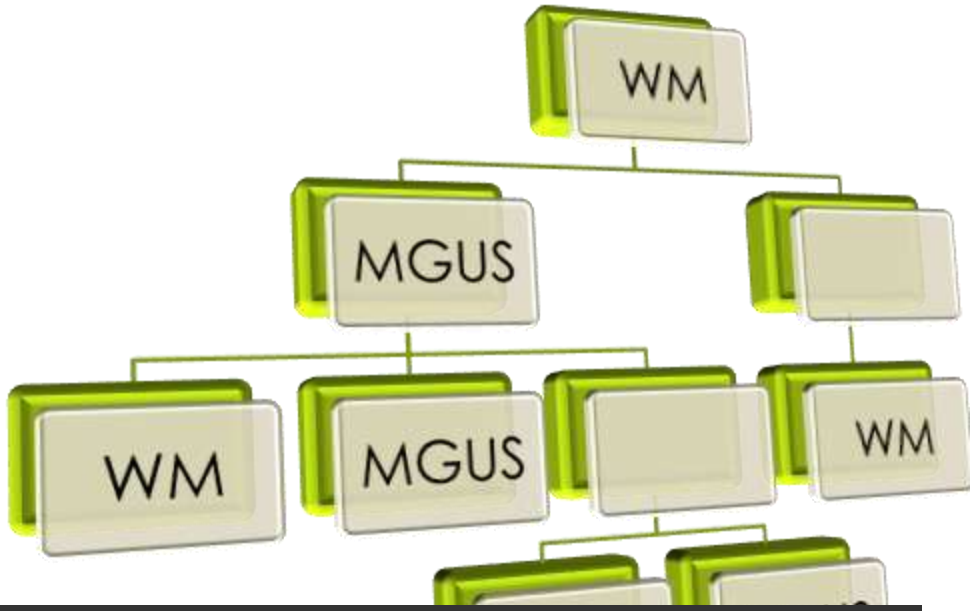
Left: The mutated RB protein found to be the cause of the disease

What not to worry about…

Familial disease accounts for only 20% of WM patients.

There are approximately 3,000 new cases of WM in the US per year.

Genetic associations do not predict the future and are not the only factor in the development of cancer.



Part 2

Clinical Findings

The Bing Center Family Study

Started in 2006 we have enrolled more then 800 individuals from over 190 families.

Any WM patient or family member with a first or second degree relative with WM is encouraged to participate

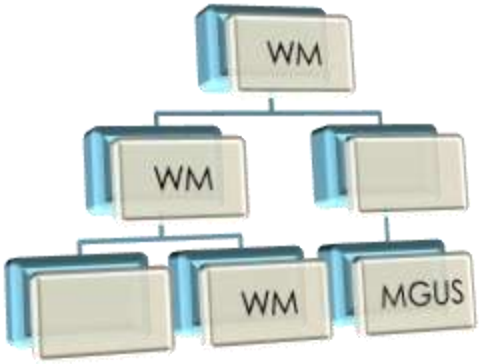
DNA, survey data, serum samples and clinical laboratory tests are conducted for all participants

All participants must be at least 18 years old.

Definitions of Family History

While reviewing the family trees from participants in this study we noticed three broad categories could be used to classify the families.

1. **Familial WM**: Multiple cases of WM were observed
2. **Mixed B-Cell**: Multiple B-Cell Cancers were observed but only one case of WM
3. **Sporadic WM**: No other B-Cell cancers were observed



Familial WM

Mixed B-Cell

Sporadic

Interim Study Results for Family Members

Sporadic	Mixed B-Cell	WM History
74 Families *170 Participants*	*77 Families* *212 Participants*	*38 Families* *171 Participants*
❑ 9.3% of those with no monoclonal protein had low IgA or IgG. ❑ 9.3% had IgM abnormalities.*	❑ 10.9% of those with no monoclonal protein had low IgA or IgG. ❑ 16.2% had IgM abnormalities.* ❑ 11% had MGUS	❑ 9.8% of those with no monoclonal protein had low IgA or IgG. ❑ 20.6% had IgM abnormalities.* ❑ 22.1% had MGUS

** IgM abnormalities include IgM MGUS and serum IgM levels outside the normal range*

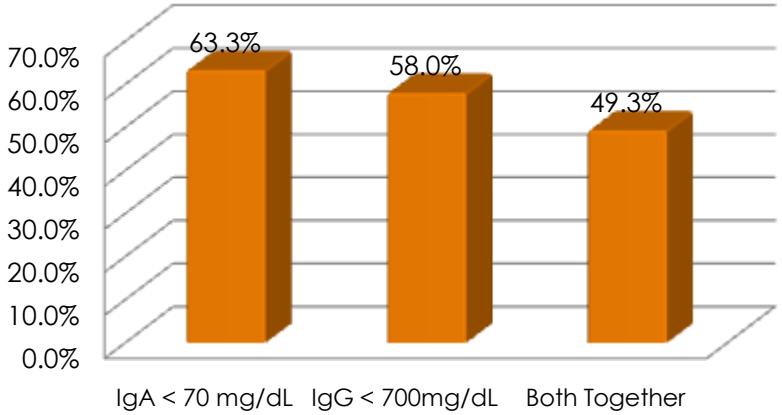
Hypogammaglobulinemia in WM

Abnormally low levels of normal IgG and IgA are frequently observed in WM

This does not improve with therapy, regardless of clinical response

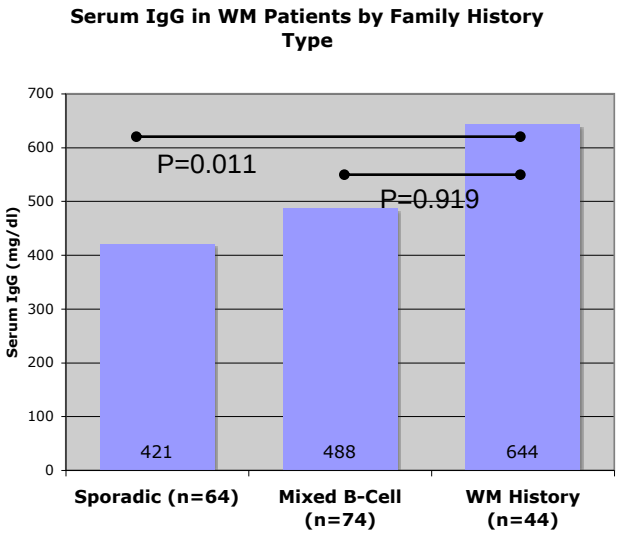
This finding does not seem to be directly related to the recurrent infections experienced by many WM patients

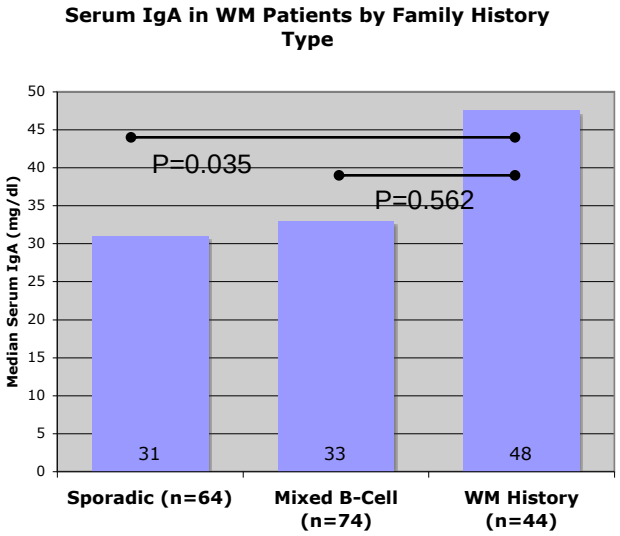
IgG and IgA Hypogammaglobulinemia in WM

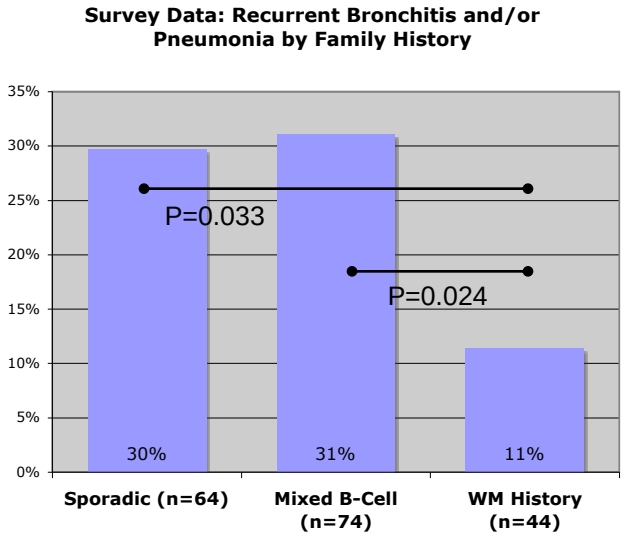


mg/dL	With recurring infections (n=75)	Without recurring infections (n=130)	P
IgA <70	52	77	0.1492
IgA <30	21	25	0.1473
IgG <700	45	74	0.6714
IgG <300	10	11	0.2674
IgA <70, IgG <700	41	60	0.2401
IgA <30, IgG <300	9	7	0.0891
Median IgA	51 (range, 9-266)	51 (range, 7-597)	0.3536
Median IgG	658 (range, 127-1450)	642 (range, 175-3130)	0.7002

Clinical Differences by Family Type

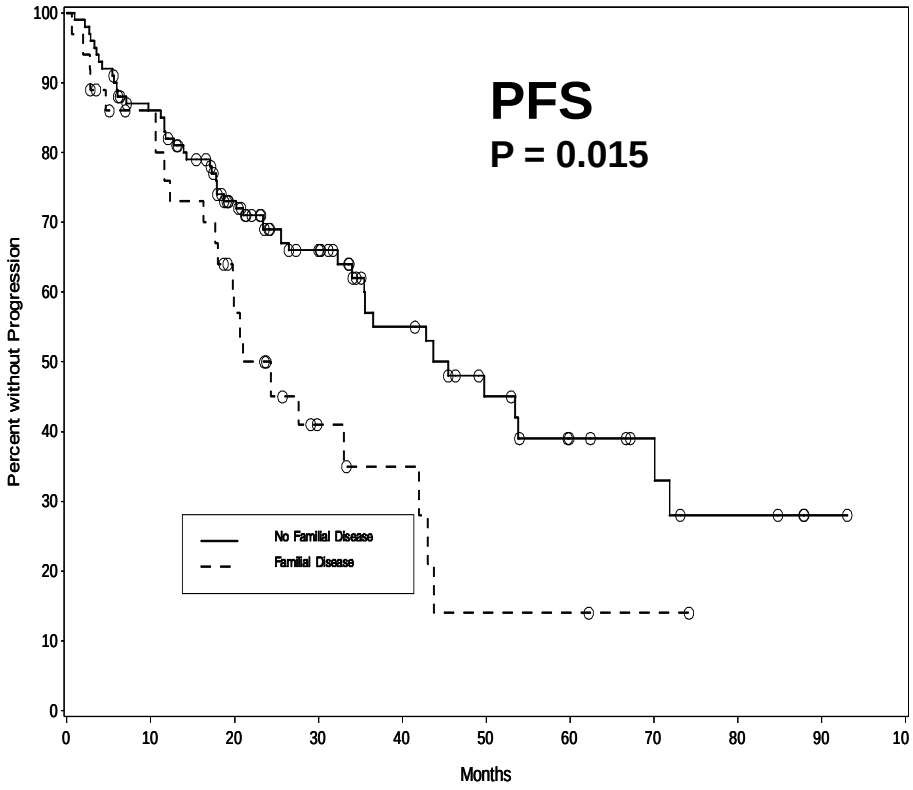


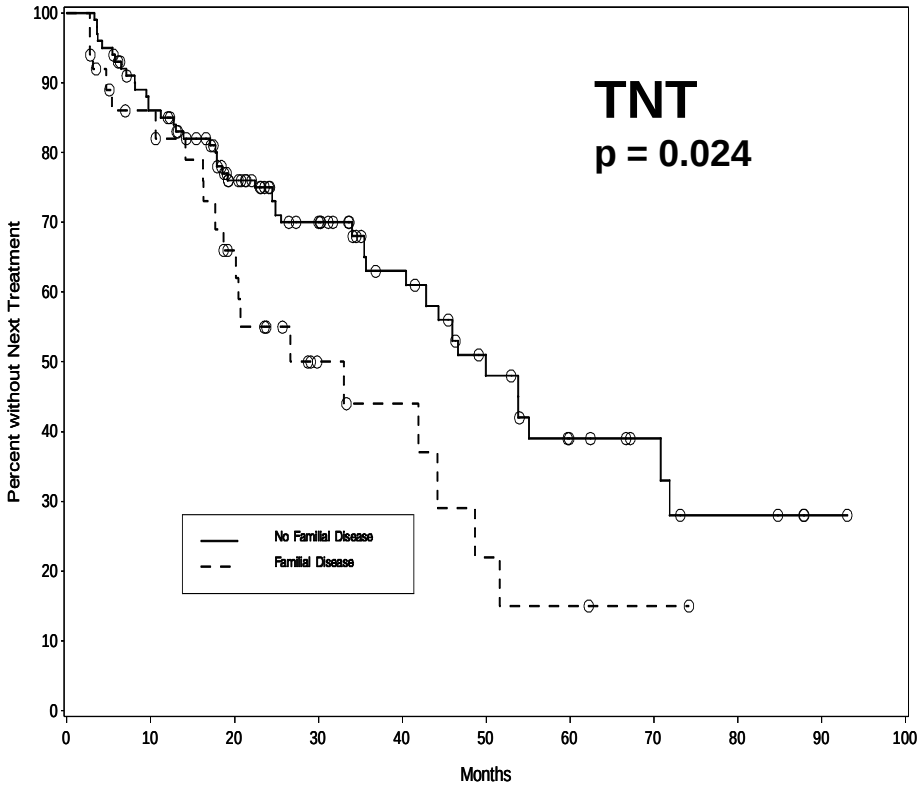




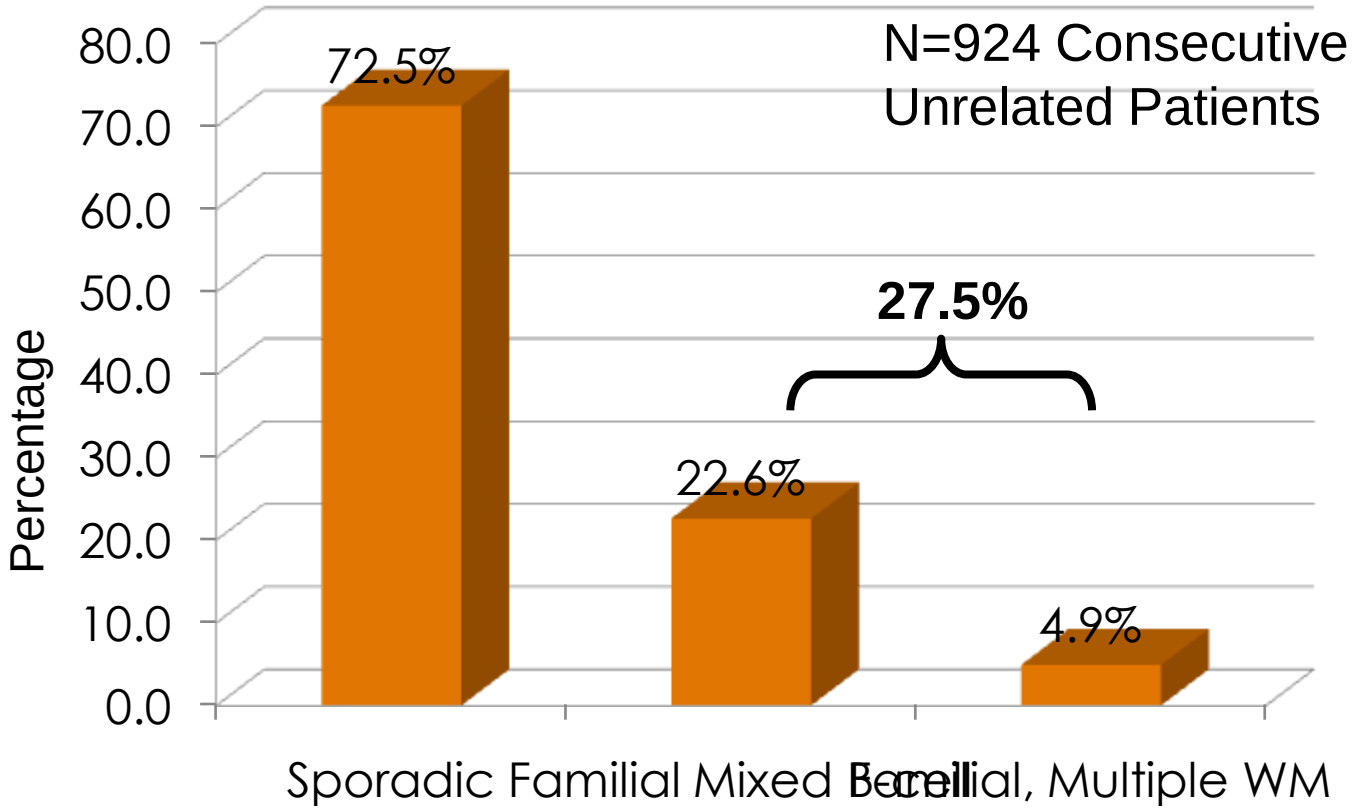
Progression Free Survival and Time to Next Therapy is Associated with Familial Disease Status

PFS and TNT data from 159 patients who received rituximab-based therapy and stratified based on the presence of having a 1st or 2nd degree relative with a related B-cell disorder.

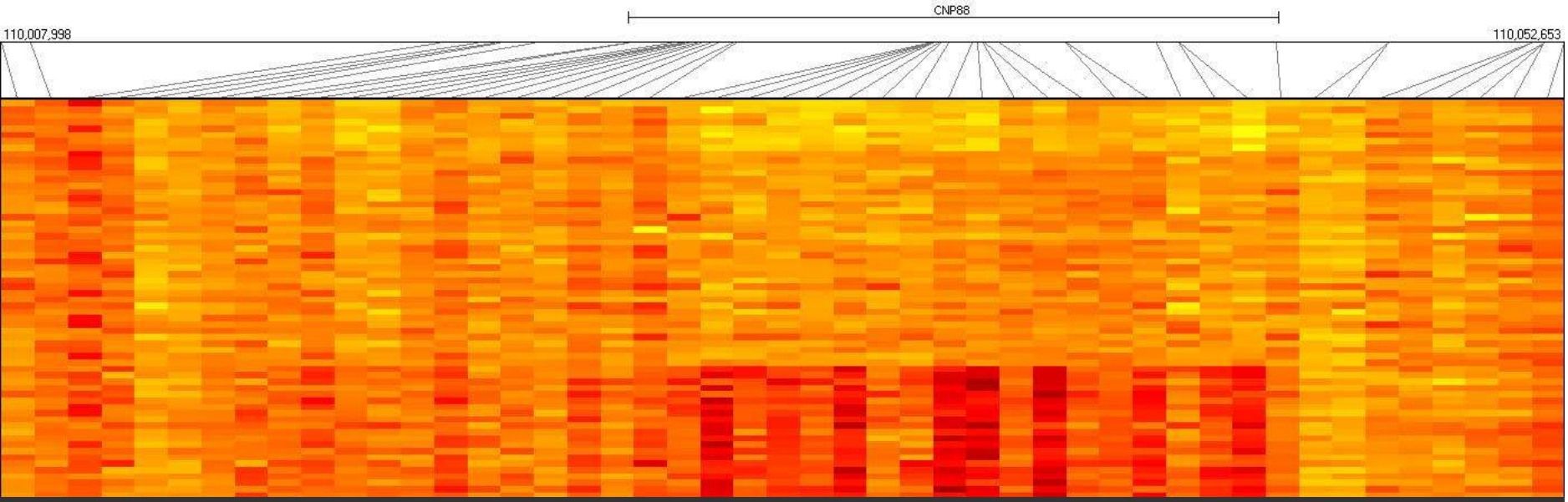




Familial Distribution in WM



Hanzis et al, ASCO 2011 Submitted



Part 3

Genetics

How Genetic Associations Work

Small differences in our DNA are quite common and are part of what make us unique. These differences can be as small as a single base pair of DNA.

These are known as single nucleotide polymorphisms (SNPs)

While we received one copy of each chromosome from each parent, the chromosome we receive is actually a blend of the two belonging to that parent.

If a SNP is near a WM related region it is unlikely to be separated from that region during this blending process and will track with the predisposition through multiple generations

In this study we examined over 900 thousand known SNPs in 273 WM patients and family members

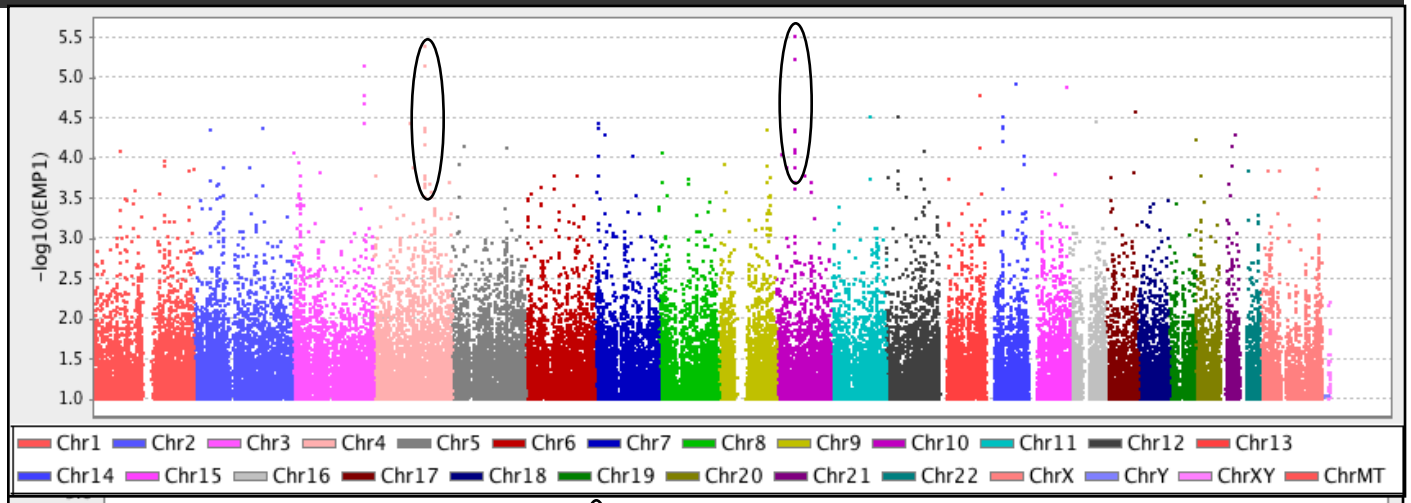
Genetic Associations by Family History Type

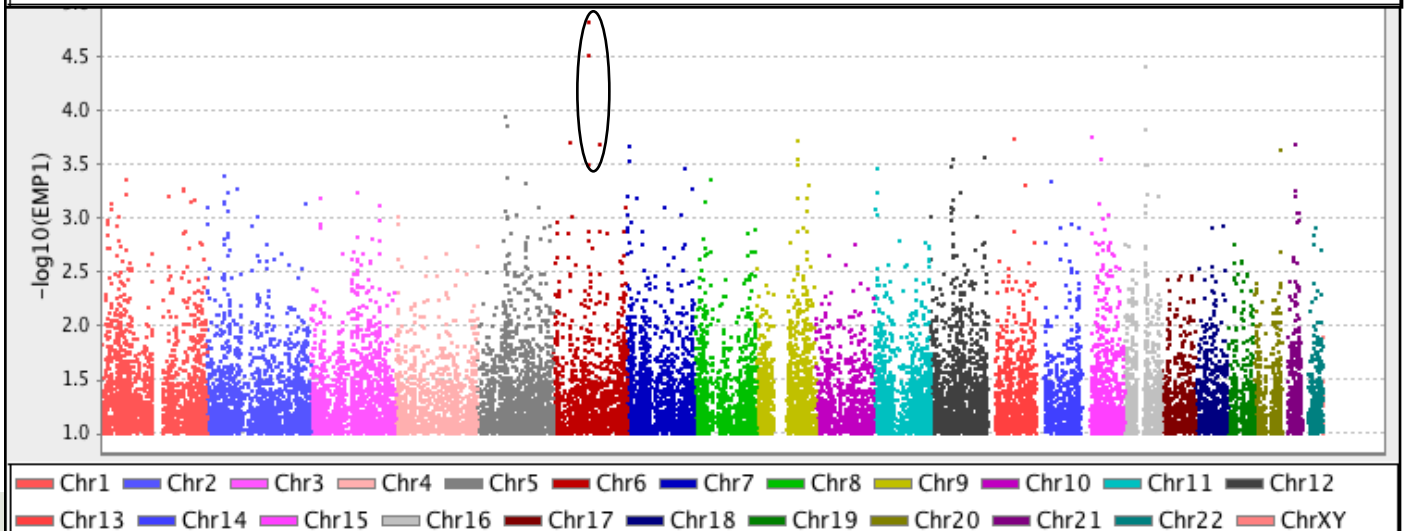
Mixed B-Cell

50 Families
112participants
Affected status includes only subjects with WM, MGUS, or related B-Cell Disorder.

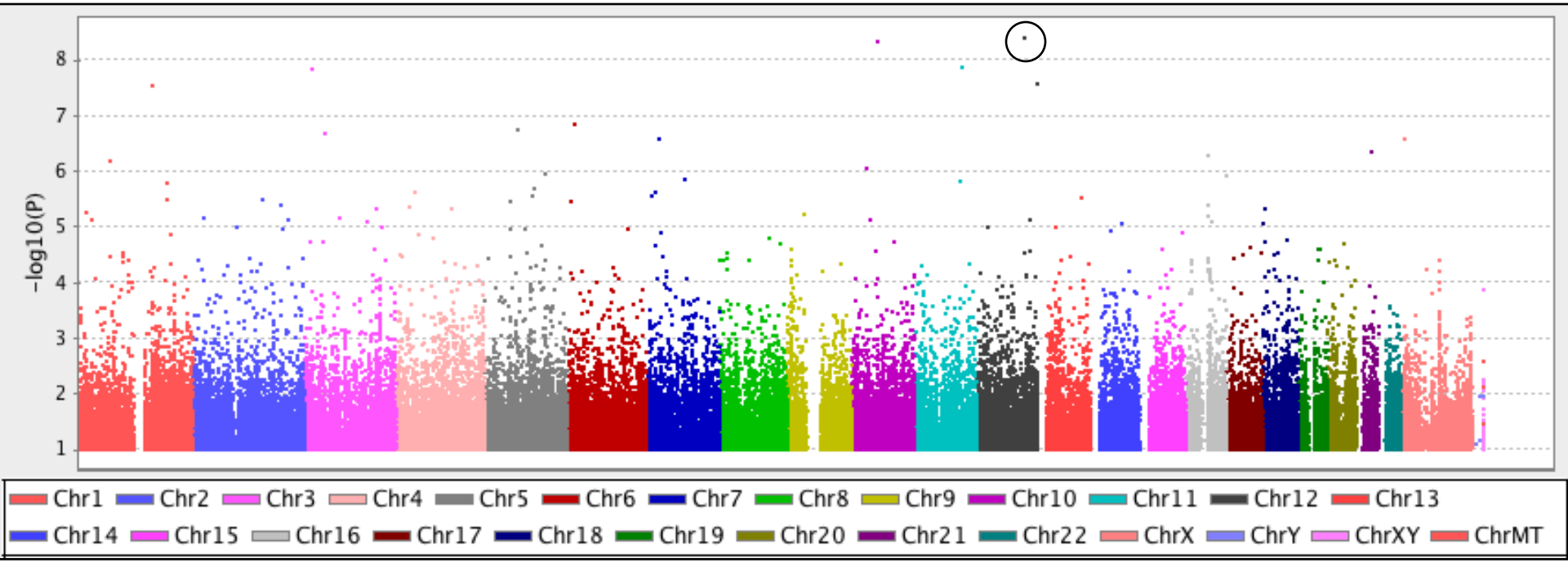
WM History

31 Families
101 participants
Affected status includes only subjects with WM, or IgM MGUS.





Whole Population Analysis



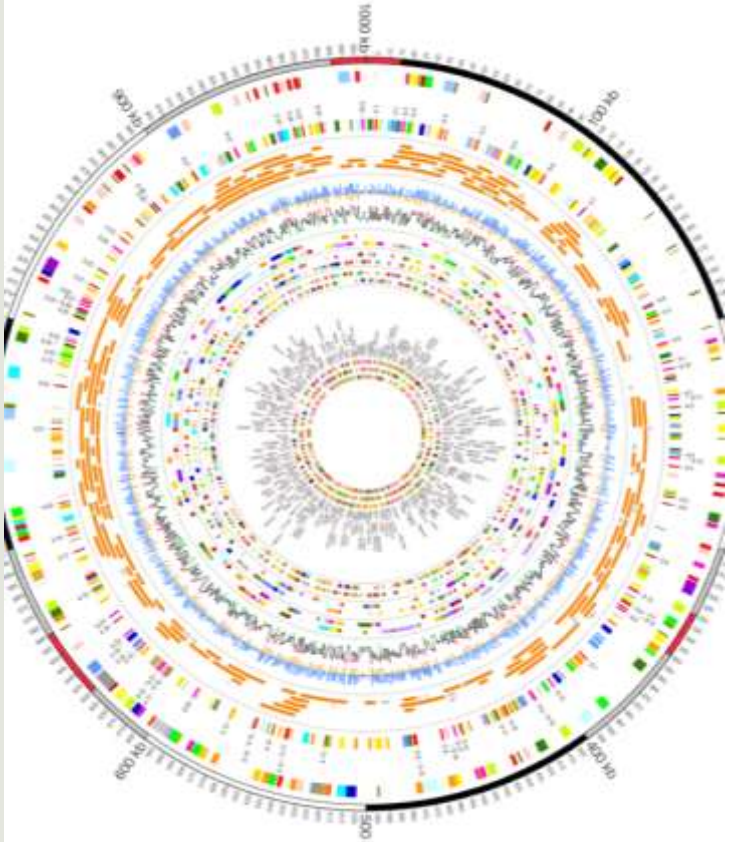
Next Steps: Whole Genome Sequencing

It took 13 years and massive collective effort to complete the human genome project.

We sequenced 30 patients in 50 days.

We plan to use this technology to investigate WM hotspots and learn more of the genetic basis of both familial and sporadic disease.

By identifying the genes and pathways that are altered in WM we can develop new and more targeted therapeutics.



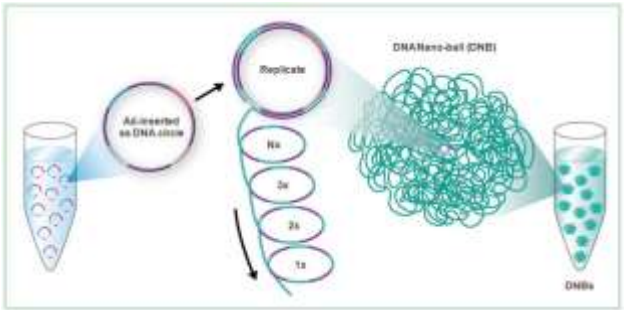
Circos diagram depicting characteristics of a bacterial genome

Whole Genome Sequencing With Complete Genomics

Complete Genomics Inc. sequencing technology produces billions of short sequences from DNA samples.

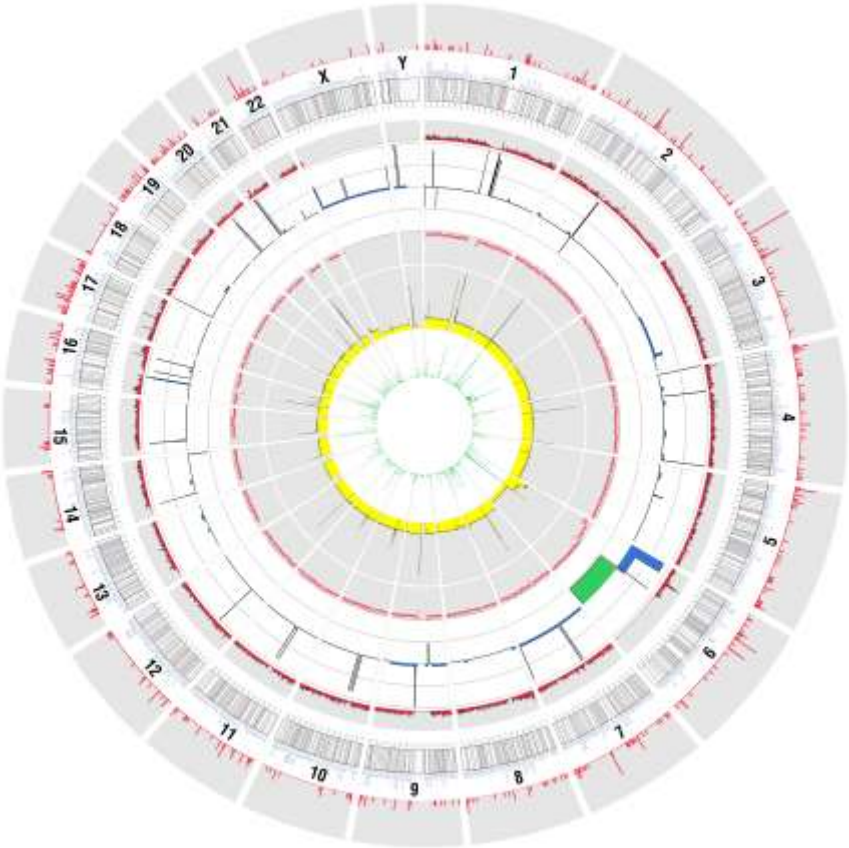
These short reads are then stacked together to reconstruct the genome.

We are now comparing the sequences from B-cell depleted peripheral blood and WM tumor cells from the same patient to find the tumor specific mutations that underlie this disease.



Complete genomics

The Waldenström's Genome



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Cartoons by Sidney Harris. www.sciencecartoonsplus.com