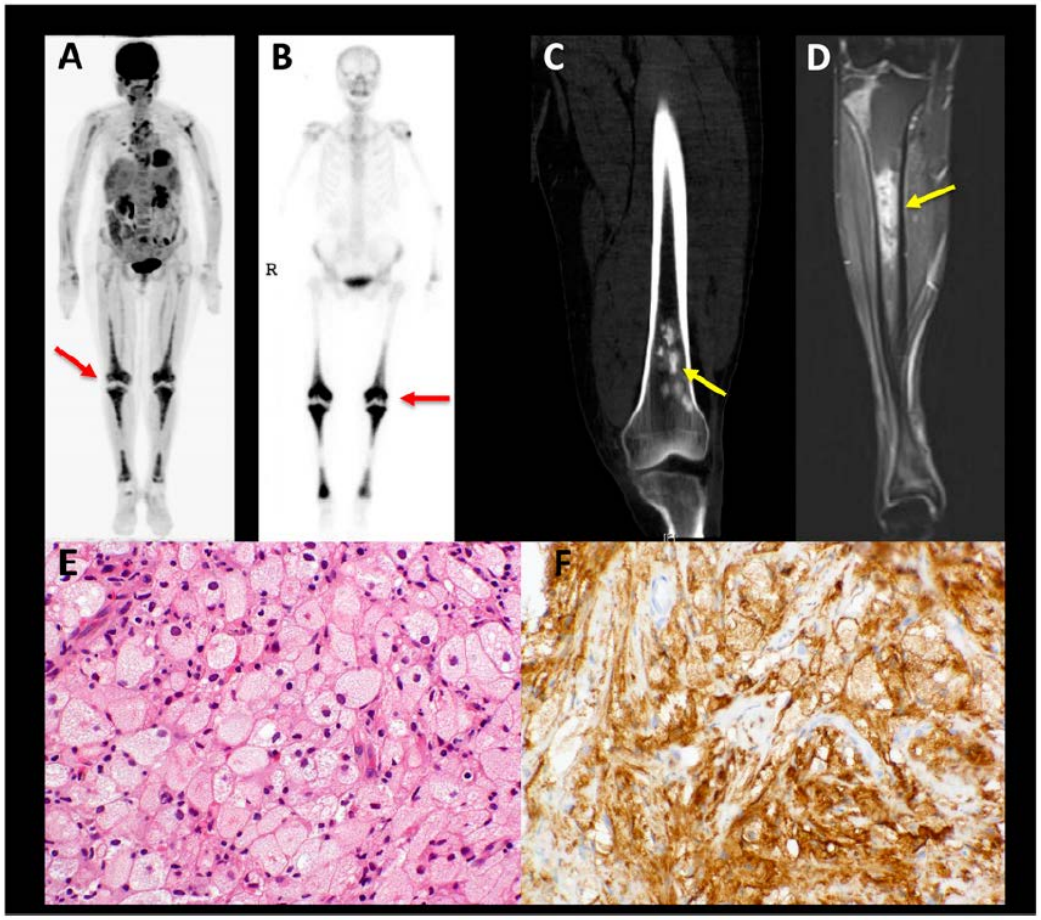
Future genetic studies in Erdheim-Chester disease

Javier Martín MD, PhD



Diamond EL et al, Blood, 2014

Genetic studies in Erdheim-Chester disease

The Challenges of Rare-Disease Research

With few resources and hesitant investors, basic scientists must rely on clinicians, patient advocates, and their own keen eye for biological connections.

By Jyoti Madhusoodanan | The Scientist, September 1, 2016

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In the next few years, there will be hundreds if not thousands of rare diseases that will be identified based on genomic data and exome sequencing.—Hudson Freeze
Sanford Burnham Prebys
Medical Discovery Institut

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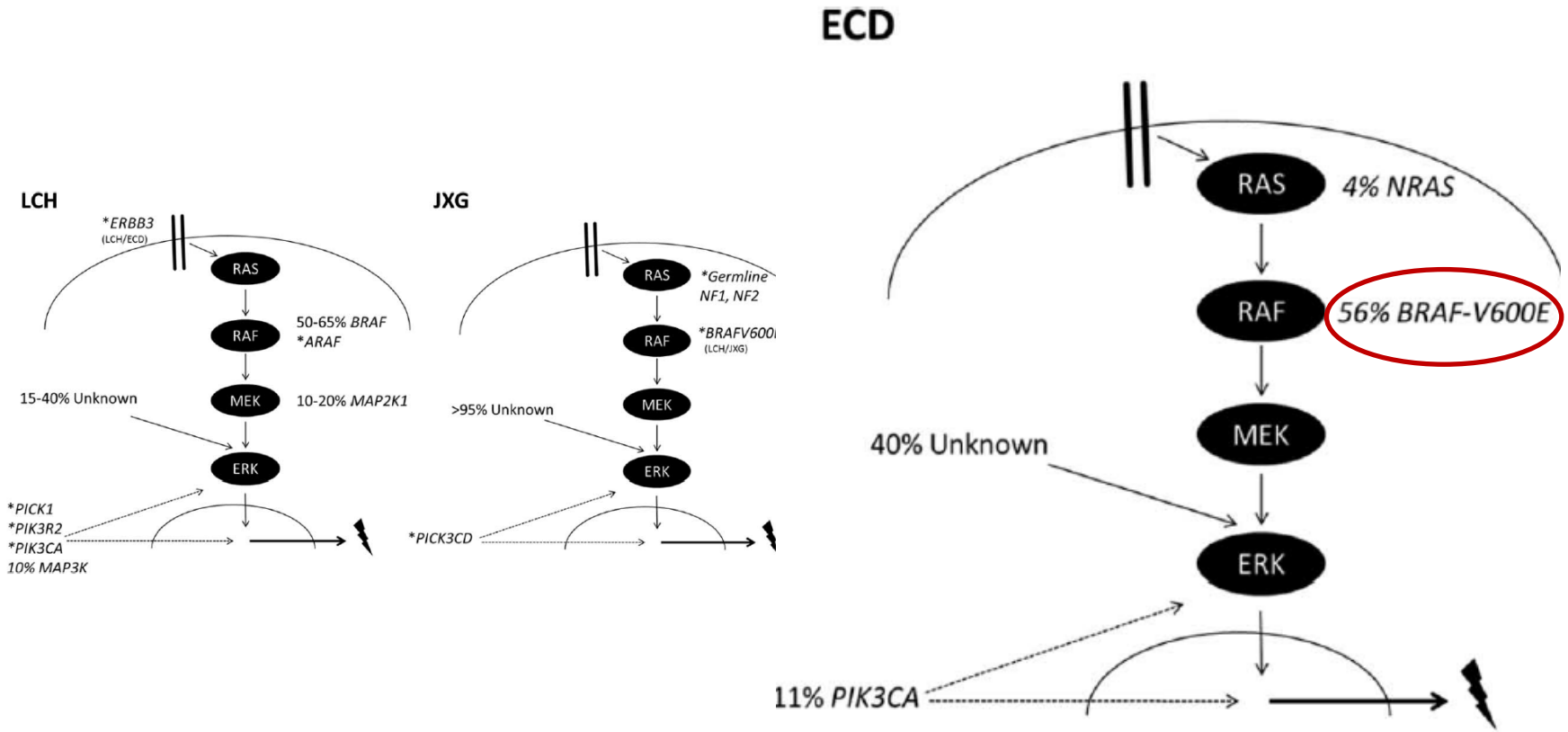
Genomic landscape of histiocytic neoplasias.



Allen & Parsons, Hematology 2015

Somatic mutations ¡¡

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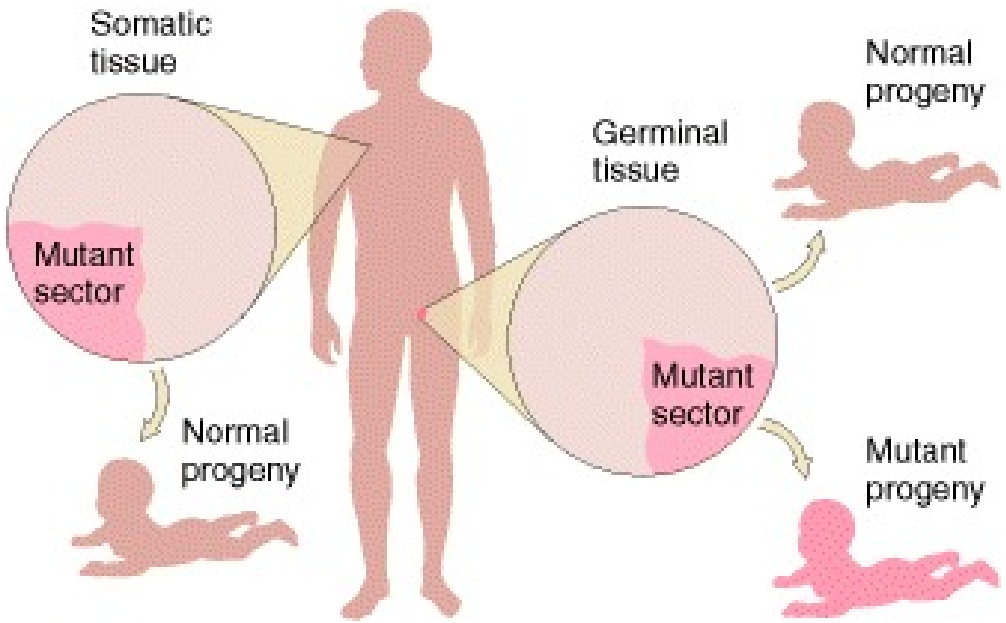

Somatic mutations are not transmitted to progeny, but **germinal mutations** may be transmitted to some or all progeny.

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Germline Mutations for Cancer Predisposition

Germline mutations, also called hereditary mutations, are passed on from parents to offspring. Inherited germline mutations play an important role in cancer risk and susceptibility. Knowledge of these heritable mutations can lead to the development of preventive measures to reduce the likelihood of developing cancer.

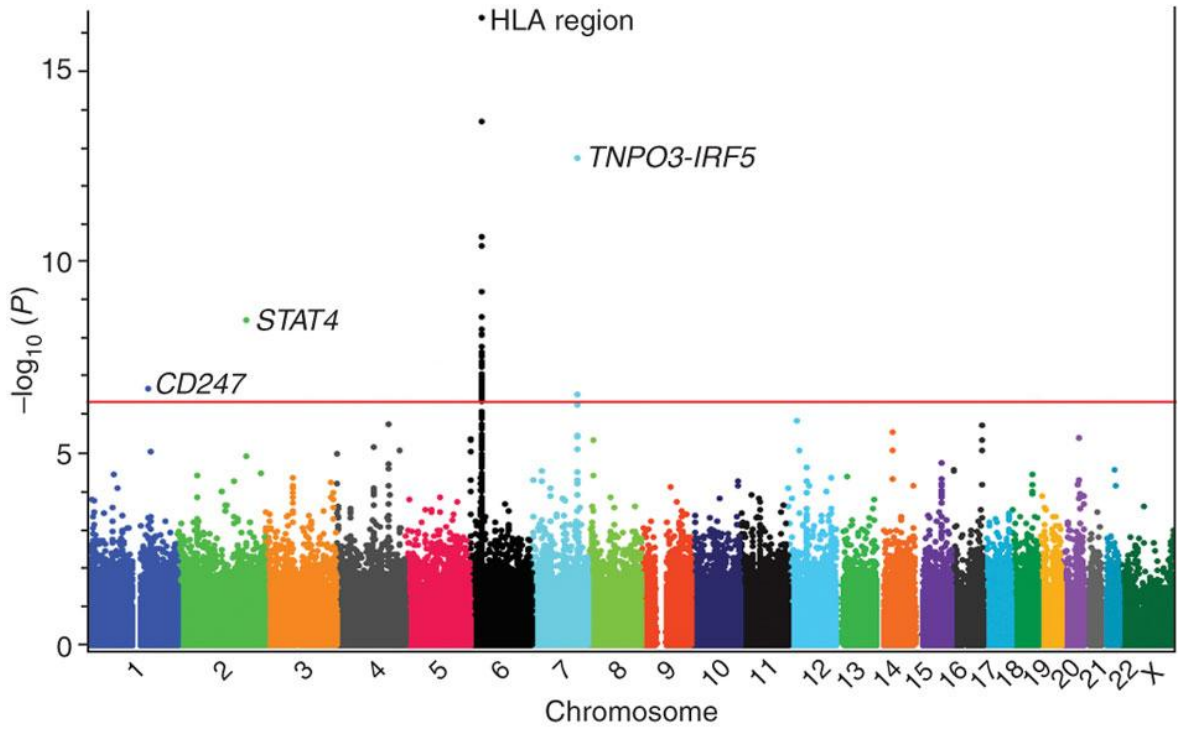
Inherited mutations associated with cancer predisposition and risk can be analyzed through various approaches, including microarrays and next-generation sequencing (NGS).

Sequencing to Identify Common Germline Mutations

NGS can be used to sequence many samples for germline mutations. Whole-genome sequencing provides a complete picture of germline mutations across the cancer genome. Targeted sequencing studies assess only the genes that have known associations with cancer predisposition, reducing sequencing costs and data analysis burdens.

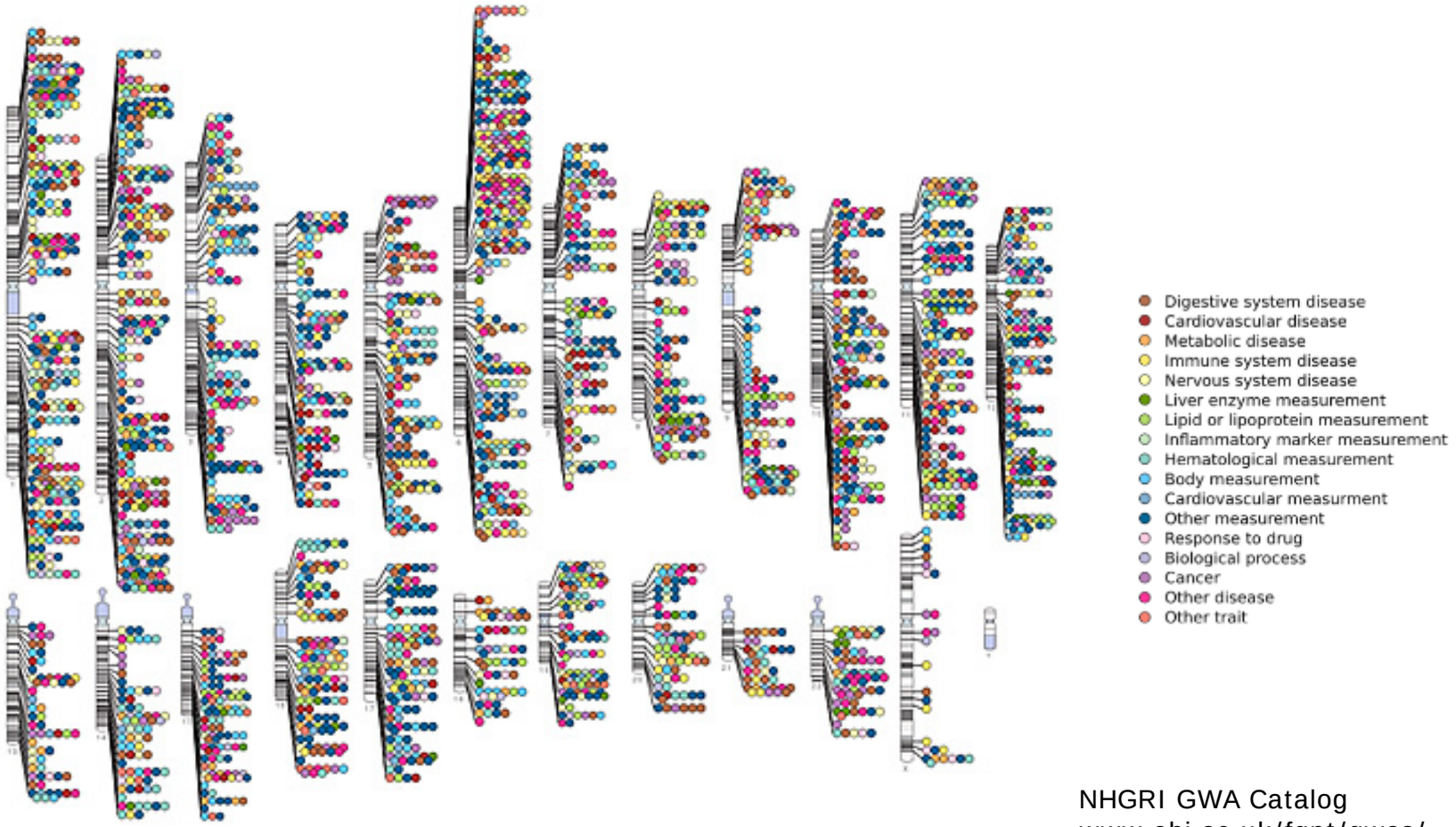
GWAS strategy

- Case/control studies
- Non-hypothesis-driven analysis / Hypothesis generating
- Common variants (frequency >5%) across the whole genome (from 300.000 to 4 million SNPs)



Radstake Tr et al. Nat Genet . 2010

GWAS contribution



NHGRI GWA Catalog
www.ebi.ac.uk/fgpt/gwas/

Missing heritability

Non-additivity genes effects, epigenetics, disease heterogenety, rare variants, structural variants

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MYELOID NEOPLASIA

BLOOD, 25 AUGUST 2016 • VOLUME 128, NUMBER 8

Germ line variants predispose to both *JAK2* V617F clonal hematopoiesis and myeloproliferative neoplasms

David A. Hinds,[1] Kimberly E. Barnholt,[1] Ruben A. Mesa,[2] Amy K. Kiefer,[1] Chuong B. Do,[1] Nicholas Eriksson,[1] Joanna L. Mountain,[1] Uta Francke,[1] Joyce Y. Tung,[1] Huong (Marie) Nguyen,[3] Haiyu Zhang,[4] Linda Gojenola,[4] James L. Zehnder,[4,5] and Jason Gotlib[5]

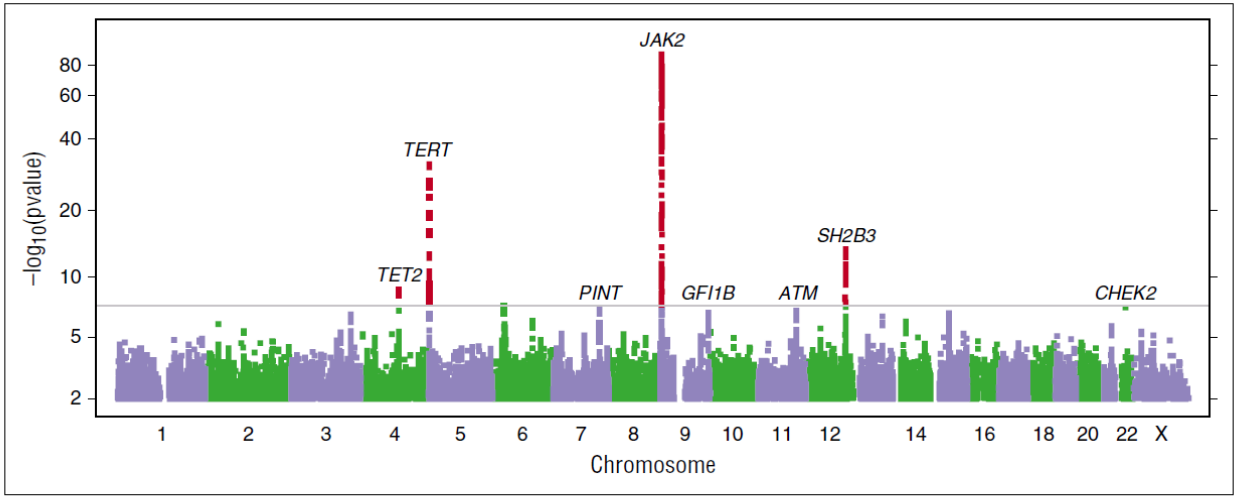


Figure 2. Manhattan plot of the combined GWAS of MPN cases and V617F carriers. Results with $P < 5 \times 10^{-8}$ (conventional threshold for genome-wide significance) are shown in red. We have also labeled suggestive results ($P < 1 \times 10^{-6}$) discussed in the text. Gene labels are provided for cross referencing with other results and are not intended to suggest a causal basis for the observed associations.

Key Points

- Germ line variants in *TERT*, *SH2B3*, *TET2*, *ATM*, *CHEK2*, *PINT*, and *GFI1B* are associated with *JAK2* V617F clonal hematopoiesis and MPNs.

Genetic studies in Erdheim-Chester disease

Comment on Hinds et al, page 1121

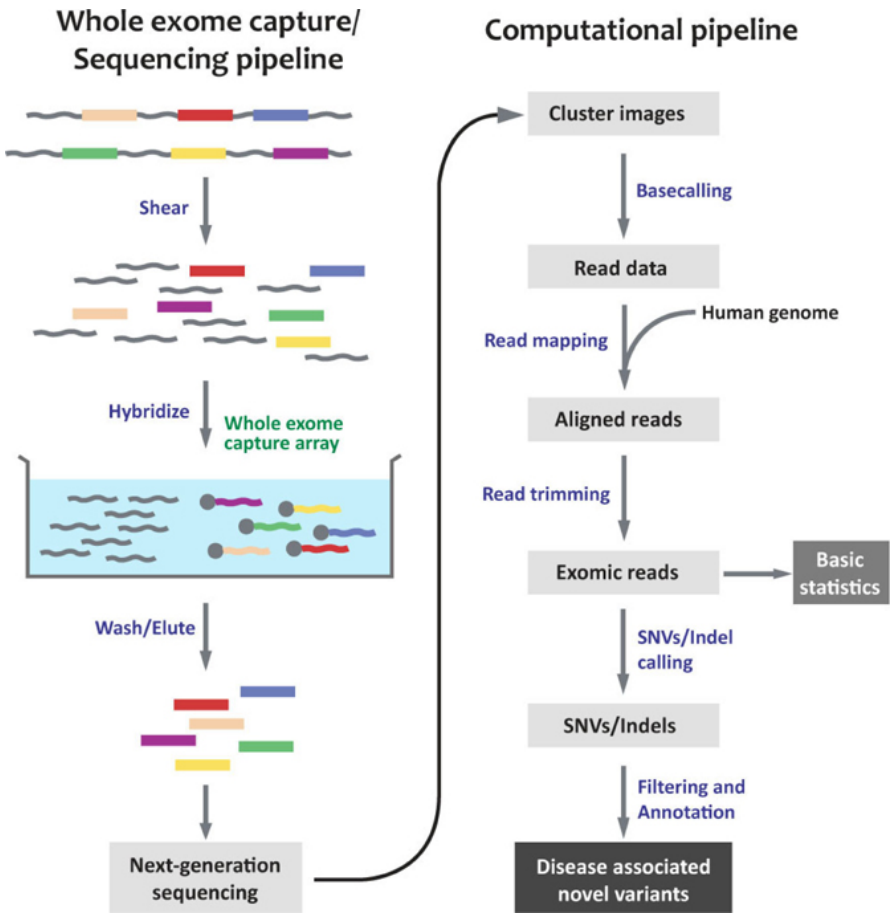
JAK2 V617F clonal disorders: fate or chance?

George S. Vassiliou WELLCOME TRUST SANGER INSTITUTE

Their findings affirm the notion that, although the acquisition of somatic mutations in hematopoietic stem cell (HSC) genomes is an infrequent and apparently stochastic process, the fate of mutant cells and their clonal progeny is profoundly influenced by heritable genetic polymorphisms present in the host's genome.

Next Generation Sequencing (NGS)

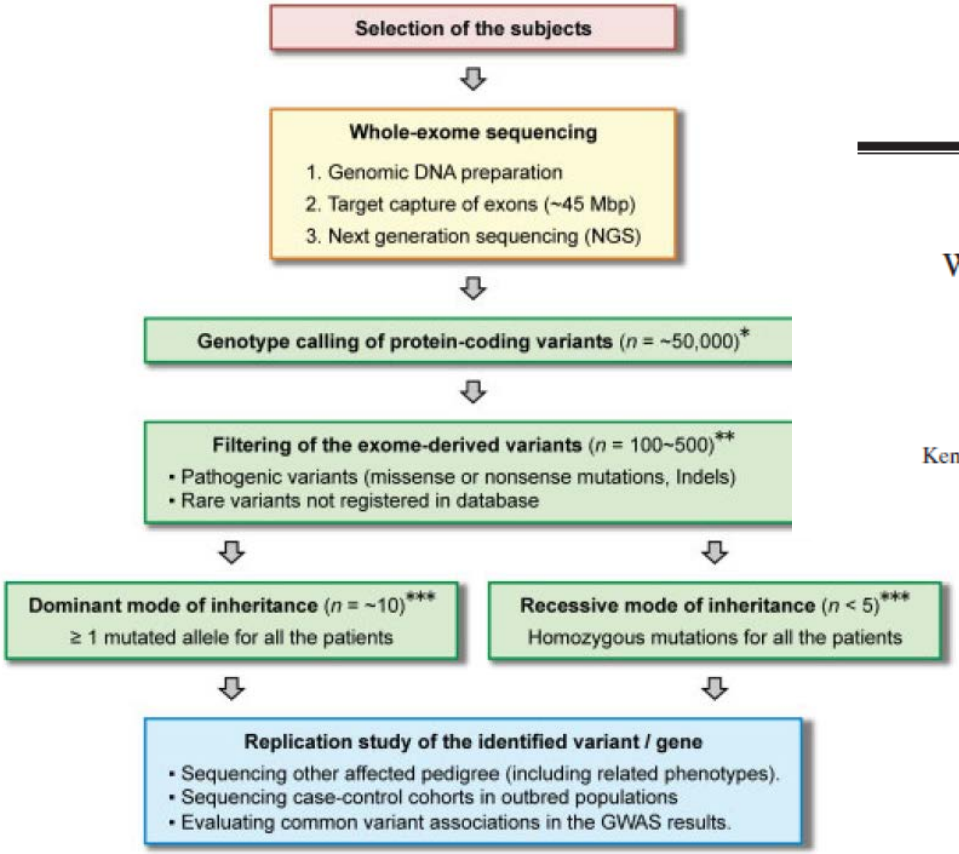
Whole **Genome** Sequencing (**WGS**) / Whole **Exome** Sequencing (**WES**)



- Rare variants
- Structural variants
  - Copy Number variants (CNV)
  - Deletions/Insertions
  - Duplications
  - Inversions

Goh G et al. Genomics Inform. 2012

Next Generation Sequencing (NGS)



ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 12, December 2014, pp 3486–3495
DOI 10.1002/art.38793

Whole-Exome Sequencing Reveals Overlap Between Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis and Familial Hemophagocytic Lymphohistiocytosis

Kenneth M. Kaufman,[1] Bolan Linghu,[2] Joseph D. Szustakowski,[2] Ammar Husami,[3] Fan Yang,[2] Kejian Zhang,[3] Alexandra H. Filipovich,[3] Ndate Fall,[3] John B. Harley,[1] N. R. Nirmala,[2] and Alexei A. Grom[3]

Conclusion. **Whole-exome sequencing performed in patients with systemic JIA and MAS identified rare protein-altering variants in known HLH-associated genes as well as in new candidate genes.**

Okada Y & Plenge R, Arthritis Rheum 2013

GWAS vs WGS / WES

	GWAS	WGS /WES
Study desing	Case/Control	Case/Control and Family studies
Free –hypothesis	Yes	Yes
Genetic markers	• Described SNPs • Common variants (>5%) • Across all genome	• SNPs and structural variants • Common and rare variants • All genome / Only exome
Limitations	• Detects only common SNPs • **Large case/control cohorts** • Fine-mapping studies to identify casual variants	• **High cost** • It requires large computational resources for the analysis and for the data storage

Genetic studies in Erdheim-Chester disease

PROPOSAL

Two steps study:

1. ***- GWAS (including patients collection)***

2. ***- WES (family studies, targeted sequencing, severe cases)***

Javier Martín MD, PhD

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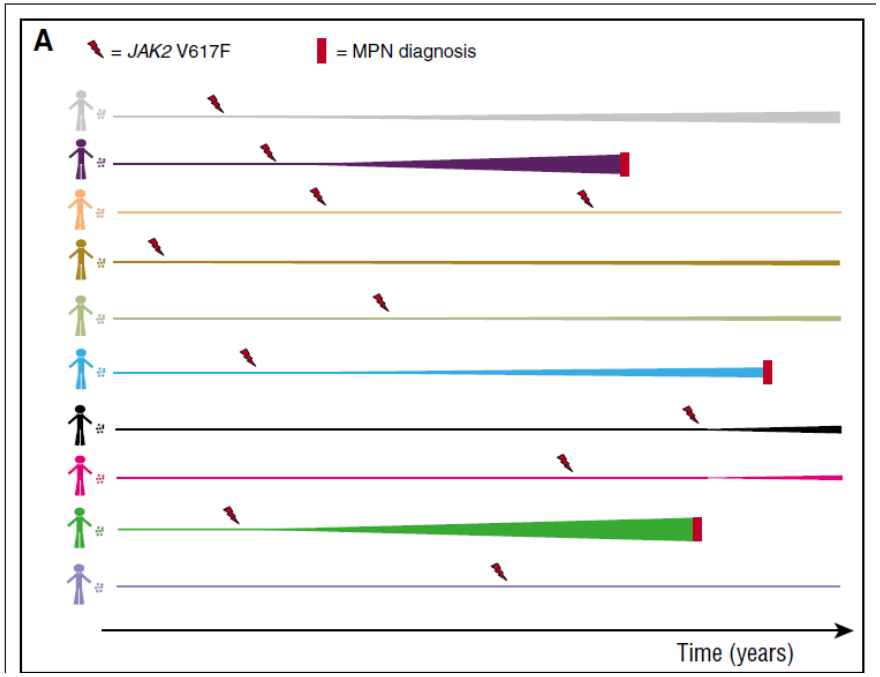
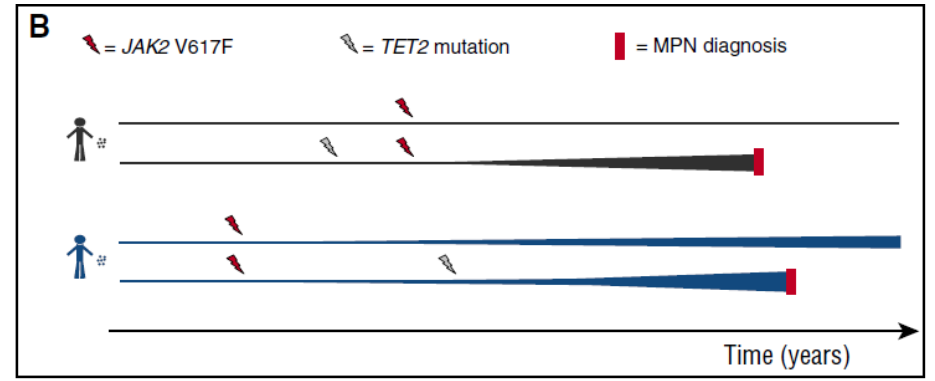
Genetic studies in Erdheim-Chester disease

Impact of the inherited genome on the fate of *JAK2* V617F mutant hematopoietic stem cells. (A) After the acquisition of the *JAK2* V617F mutation, the fate of HSCs and their progeny is markedly influenced by heritable polymorphisms in the host genome. In many instances, expansion of *JAK2* V617F–positive clones (depicted as expanding lines) leads to the development of detectable clonal hematopoiesis, and in some of these, the clones enlarge sufficiently to produce an MPN phenotype. It is also probable that, in many instances, clones remain very small and below the detection limits of conventional approaches. It should be noted that, although many genetic polymorphisms are likely to operate in a cell autonomous manner, others may influence the growth of mutant HSCs through non–cell autonomous effects. Also, the clonal size required to produce a clinical phenotype varies significantly between individuals, and this is also likely to be influenced by genetics. (B) Although most cases of *JAK2* V617F–positive MPNs do not harbor any additional identifiable somatic driver mutations, some cases do have such mutations and they most commonly affect the *TET2* gene. Hypothetically prior acquisition of a mutation in *TET2* may be able to convert an unfavorable genome into a favorable one for *JAK2* V617F to drive clonal expansion and MPN development (this is depicted in the fates of 2 distinct HSCs from the same individual). Alternatively, acquisition of *TET2* mutations after *JAK2* can accelerate clonal growth.





Vassiliou G, Blood, 2016

Genetic studies in Erdheim-Chester disease

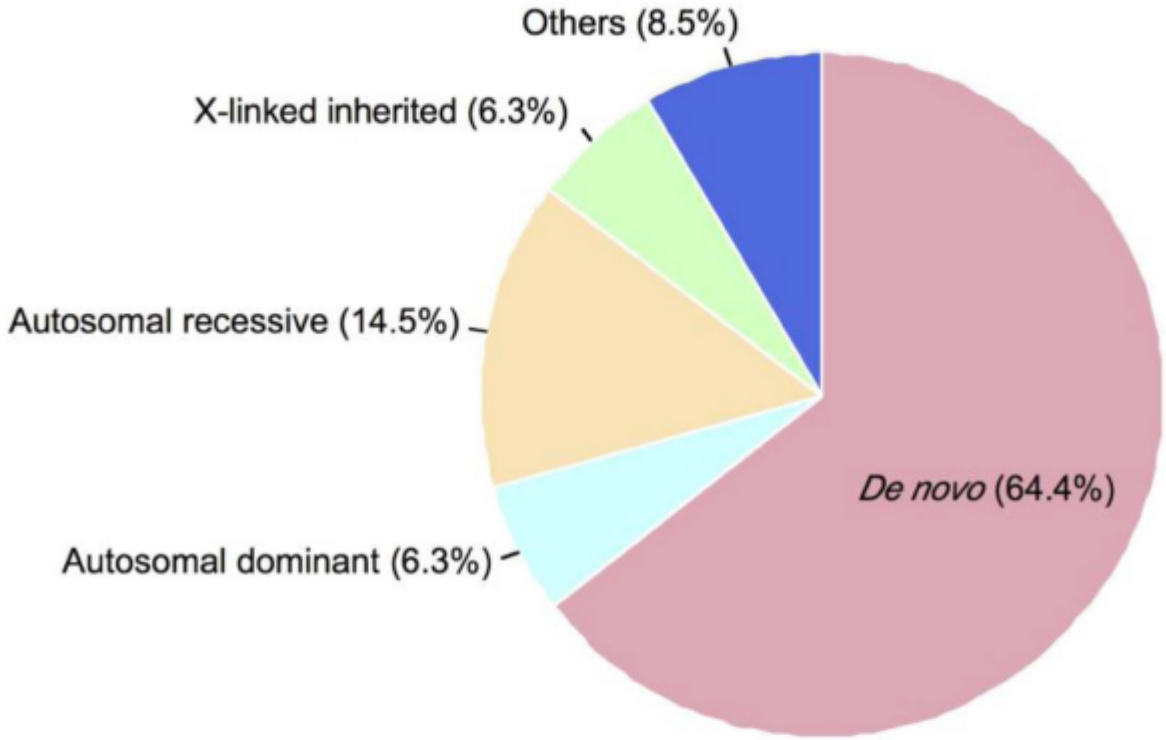


Fig. 1. Mode of inheritance of rare genetic diseases that were definitively diagnosed in a cohort of developmental disorders. Drawn with data adopted from Deciphering Developmental Disorders Study. *Nature* 2015;519:223-228 [9].