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Grid based genetic population analysis challenges for Genetics Linkage Analysis of SNPs.

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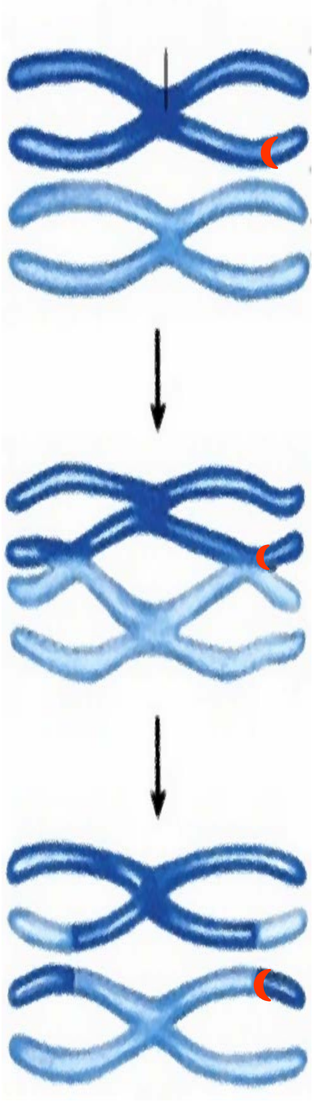
e-infrastructure

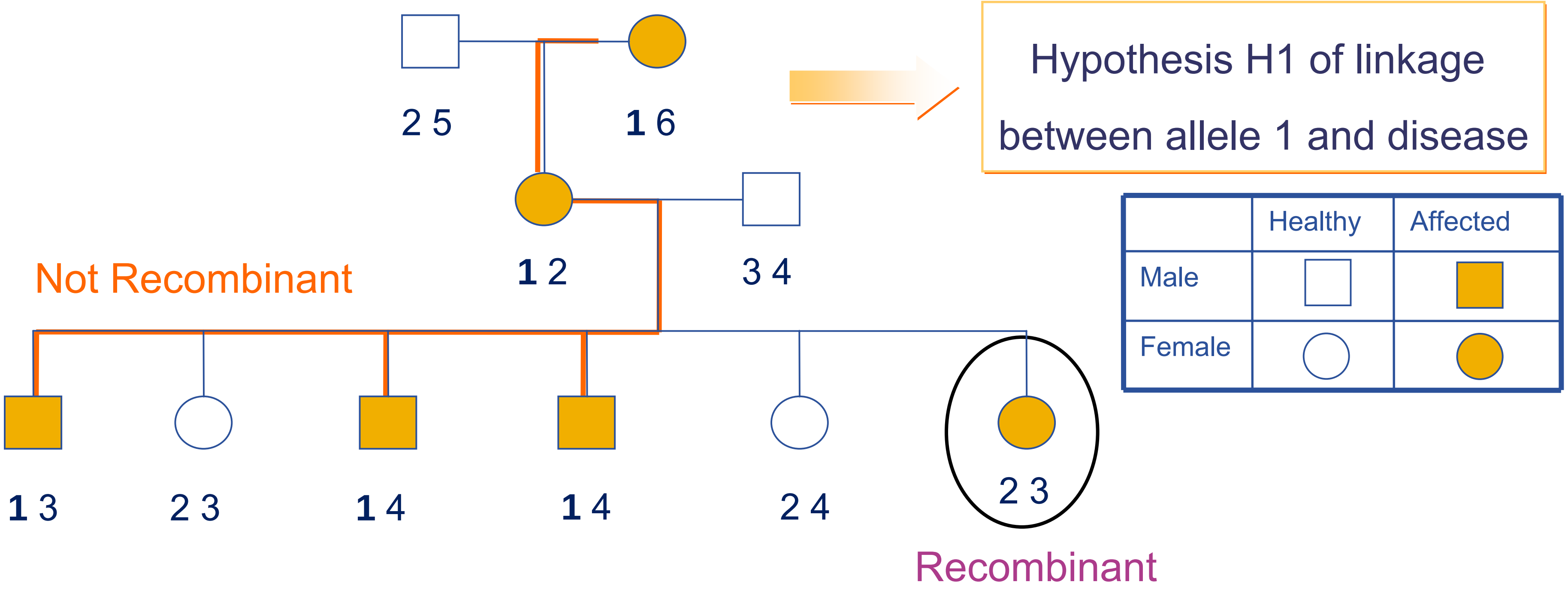
Introduction

- The human genome is very large and contains many thousands of genes.
- Traditionally, the search for a disease gene begins with Linkage Analysis that is a statistical method used to identify the location on a chromosome of a given gene involved in a disease relative to a known location of chromosome markers.
- Usually markers are Quantitative Traits Loci, Microsatellites, and their number is limited on the linkage analysis. Recently, also **SNPs** can be adopted as **biallelic markers**.
- New technologies on chips (for example Illumina) have developed SNP genotyping array, from 10000 SNPs to more than 1 million.



Introduction

- Genetic Linkage Analysis
  - Pedigree example of recombination vs non recombination



Hypothesis H1 of linkage between allele 1 and disease

	Healthy	Affected
Male	□	■
Female	○	●

  - LOD Score Estimate

Introduction

- The Linkage Analysis Problem is NP-hard

Algorithms (most important)	**Applications**	**Computational Bounds**
Elston-Stewart	Linkage, *SLink*, Fastlink, Vitesse, Mendel	n° loci: ~8 n° subjects: > 50
Lander-Green	*GeneHunter*, Allegro, Merlin	n° loci: > 20 n° subjects: ~20
Bayesian Networks	Superlink	n° loci: nr n° subjects: nr

Algorithms	**Increasing computational time by**		
	Individuals	**Loci**	**Time**
Elston-Stewart	Linear	Exponential	$O((m2^n)^p)$
Lander-Green	Exponential	Linear	$O(m2^{4p})$
Bayesian Networks	Linear	Linear	nr

Objectives

- Execute quantitative computation of Linkage analysis with SNPs (biallelic markers)
  - Actual technologies for Chips collect up to **1.000.000** SNPs (whole genome)
  - Pedigrees are often large (more then 30 individuals)
  - Linkage analysis software are mostly not MPI or distributed
- Computational time and space on single CPU is not enough with these preconditions
- Need for distributed and high performance infrastructure and a system that enables linkage analysis with SNPs
  - **Infrastructure**: **Grid Technology** can be a possible answare improve efficiency
  - **Application**: a system which performs runnig linkage analysis challanges in grid environment adopting customizable workflows and user friendly access

Methods

- **System's Design**
  - Our system relies on the grid middleware for low level interactions with the hardware resources
  - Logics to eneable distribution for grid environment
    - Choose linkage analysis software; ie: **GenHunter**
    - Split inputs (SNP or generic markers, and pedigree) into smaller sets having size smaller than bounds of the linkage analysis software chosen; ie: 370k SNP, 26 individuals → split SNP size into sets of 100, obtaining X jobs
    - Execute linkage analysis program N sets of the X jobs in parallel over Z working nodes
    - Monitor job's status, execution and outputs retrieving
  - Logics to ease access Grid technology
    - Create web access with standard technologies
    - Create a workflow for the linkage analysis steps

Methods

The system is designed in 3 different layers:

- **the presentation layer**

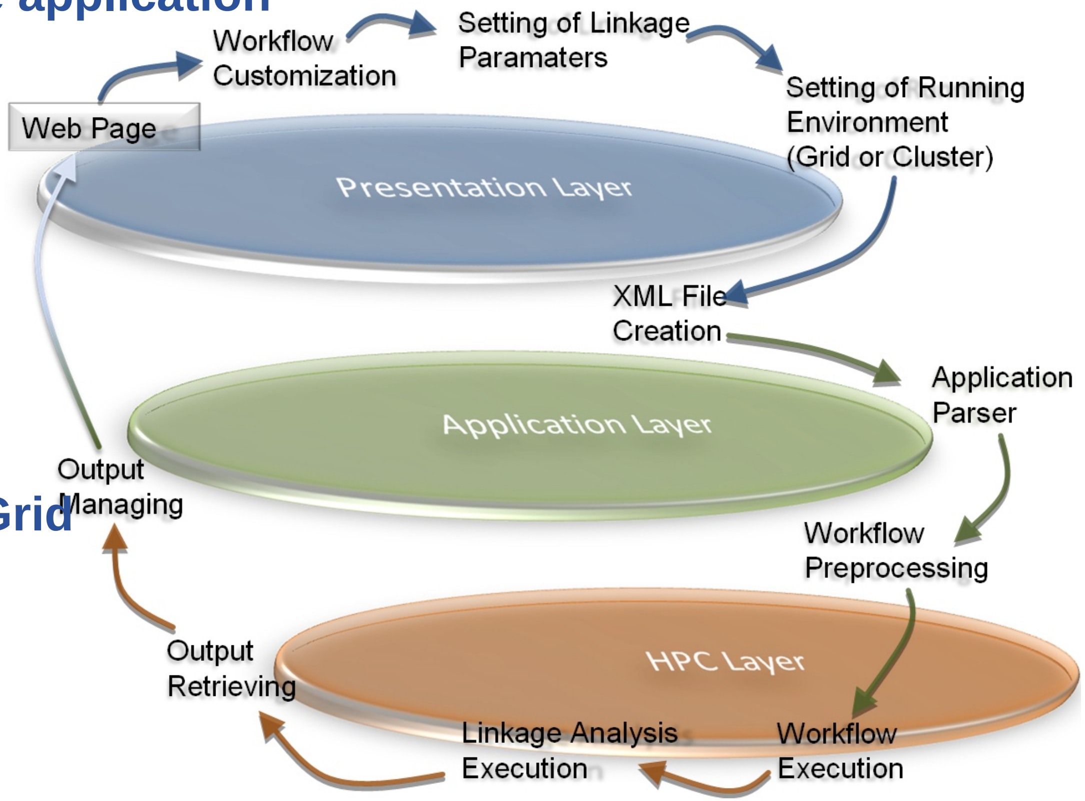
  where users interact with the application

- **the application layer**

  where are stored and run the logics of execution

- **the Grid layer**

  where interactions with the Grid middleware are managed



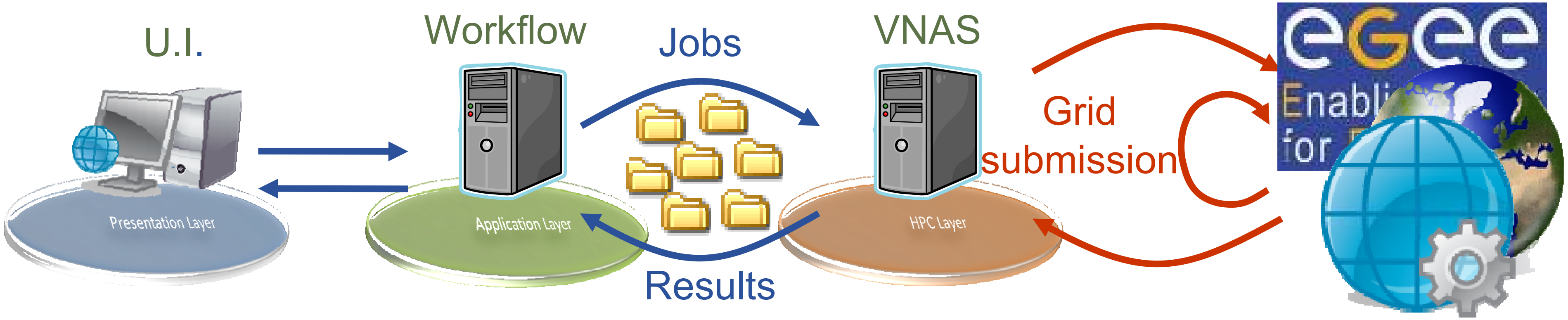
Methods

- **The Grid Layer**

The workflow engine splits the workload into small jobs and distributes analysis tasks over the available resources

This is achieved by a software layer, called VNAS, built on top of the grid middleware which monitors each single grid process and ensures its elaboration success by managing the resubmission of failed jobs automatically .

When all tasks are computed the results are retrieved, merged and made available for downloading through the web interface.

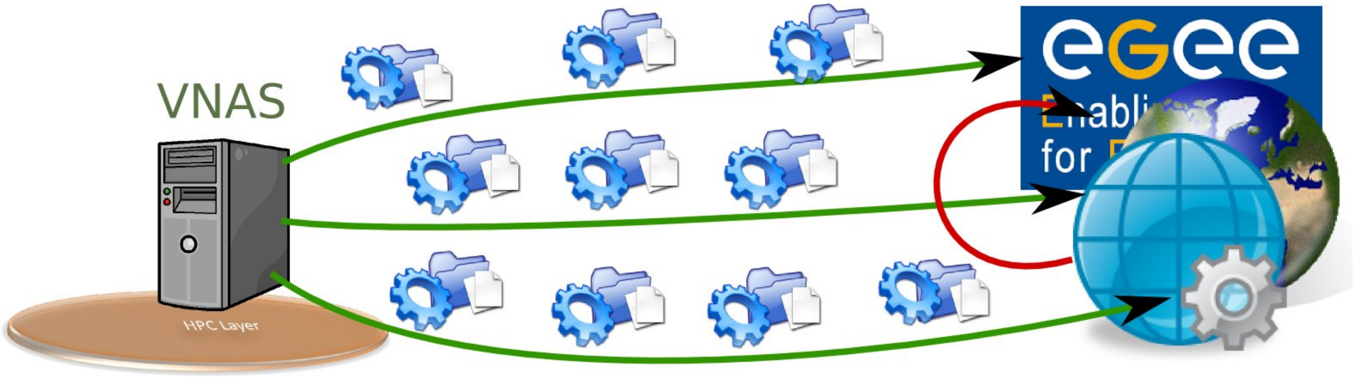


Methods

- **VNAS**

VNAS is an interface providing an abstraction over the Grid middleware

- **Vnas manages job submission over the Grid, monitoring of jobs, fetching of results.**
- **Reduces the complexity in writing Grid applications and pipelines**
- **Reduces Grid overhead, increases throughput**

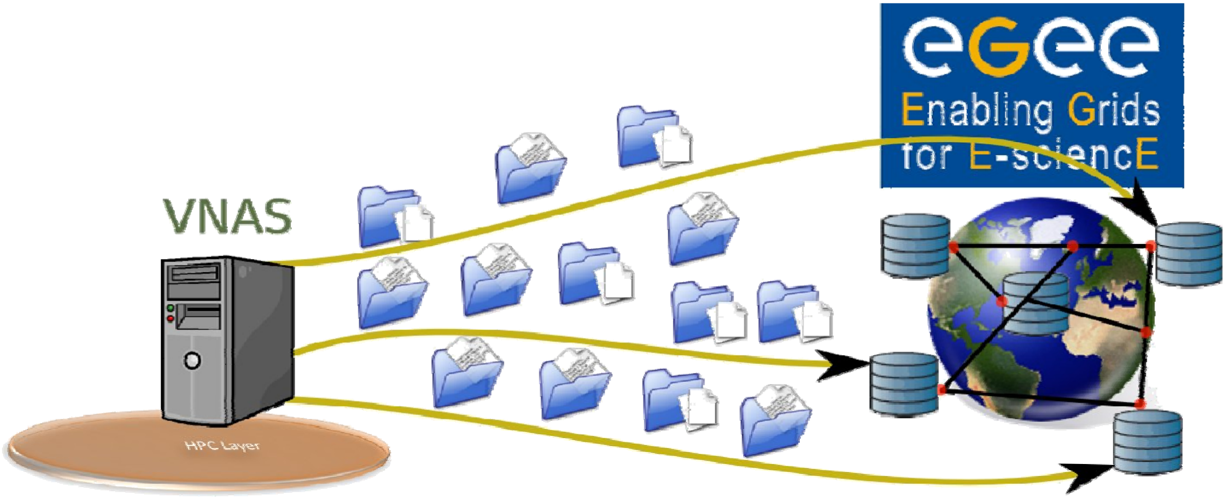


Methods

- **VNAS**

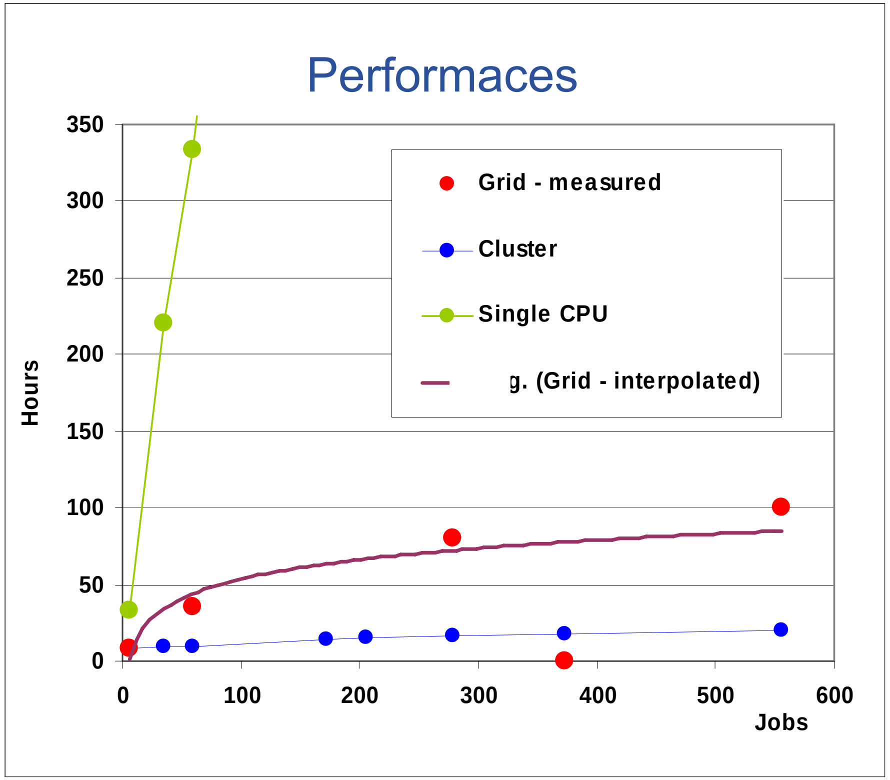
Provides abstraction of the Grid's storage system (Storage Elements)

- **identifies files needed for the job to run on the Grid WNs**
- **identifies files already uploaded to the Grid SEs and re-uses them**
- **reduces Grid bandwidth usage**
- **garbage-collects files from SEs after N days of no-use**
- **prevents user's leftovers on Storage Elements**



Results

Illumina Chip	# Runs [50 SNP]	# Jobs [6 h]	Comput. Cost (time)		
			Single CPU	Cluster (70 nodes) (280 CPUs)	Grid *interp.
10 k	200	6	33 h	8 h	8 h
66 k	1320	35	220 h	9.5 h	*30 h
100 k	2000	60	333 h	10 h	35 h
317 k	6340	172	1056 h	13 h	*72 h
370 k	7400	206	1233 h	15 h	*75 h
500 k	10000	278	1665 h	16 h	80 h
670 k	13400	373	2233 h	18 h	*87 h
1 M	20000	556	3332 h	20 h	100 h



- This approach is mostly useful in high-end challenges, where Grid overheads are less affecting overall execution times compared to single CPU performances. Only very small challenges may show higher efficiency when run in a single CPU workstation.

Results: Case Study 1

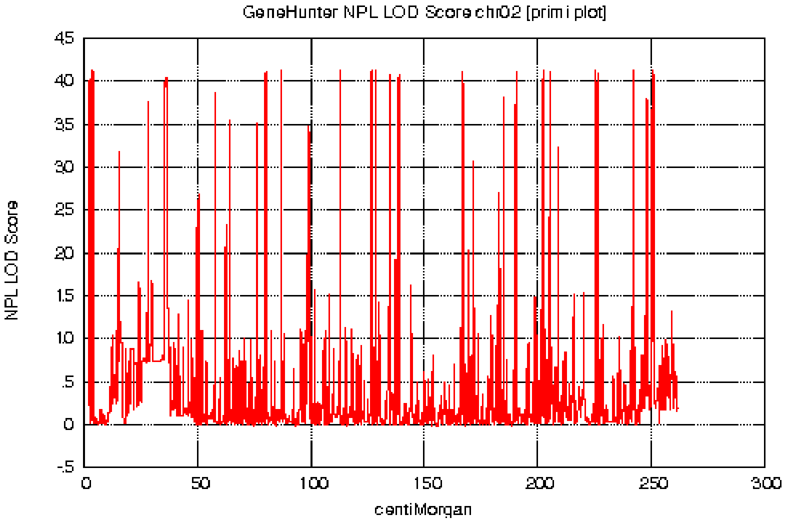
- Chip: Illumina 317.000 SNPs
- Analysis: whole genome (23 chromosomes)
- Software: Genehunter (patients: 32)
- Run time per job: 10 mins
- SNPs per job: 80
- Total jobs:
  - number of runs of Genehunter: 3962
  - number of hours each Computing Element: 6 hours -> 36 runs each Grid Job execution
  - number of Grid Jobs: 111

- Results are presented joined per chromosome

Results: Case Study 1

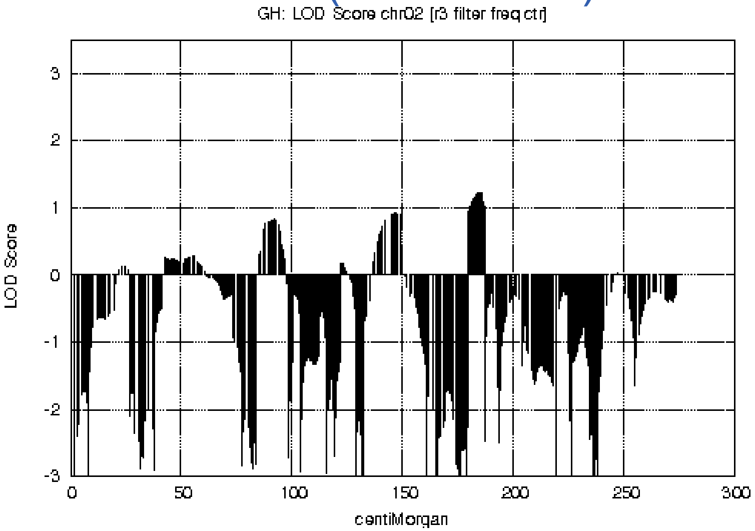
LOD score function for whole Chromosomes 2 and 6 (317k SNPs)

Chrom. 2



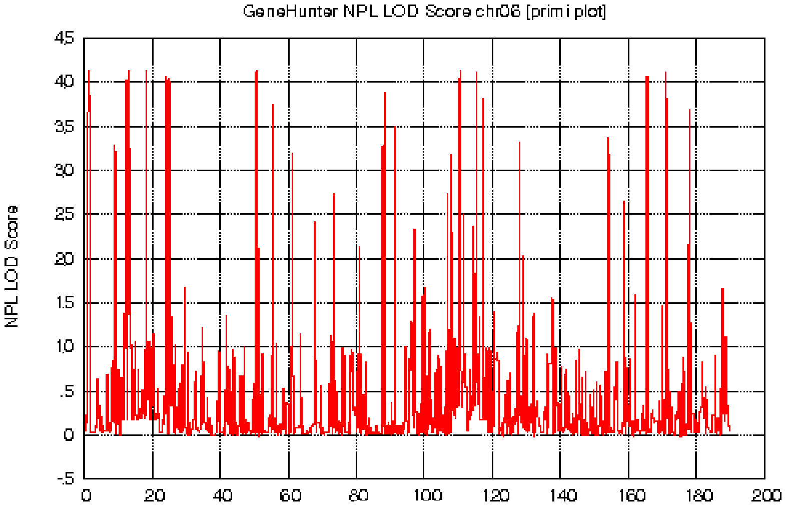
Non Parametric Linkage Analysis

Chrom. 2



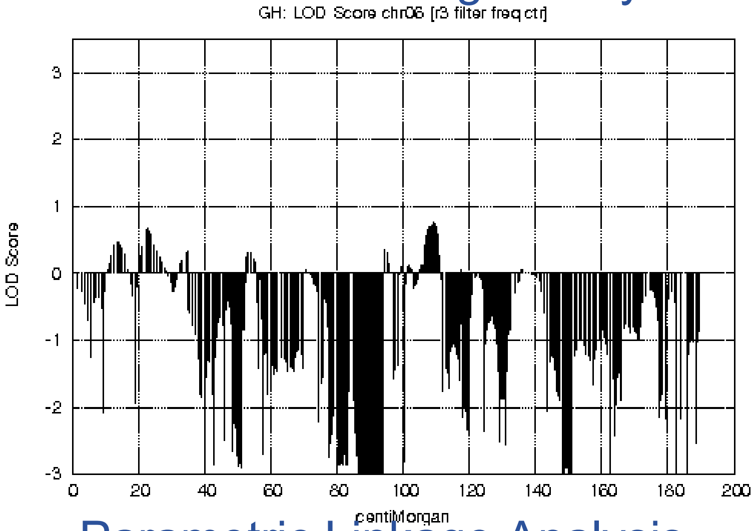
Parametric Linkage Analysis

Chrom. 6



Non Parametric Linkage Analysis

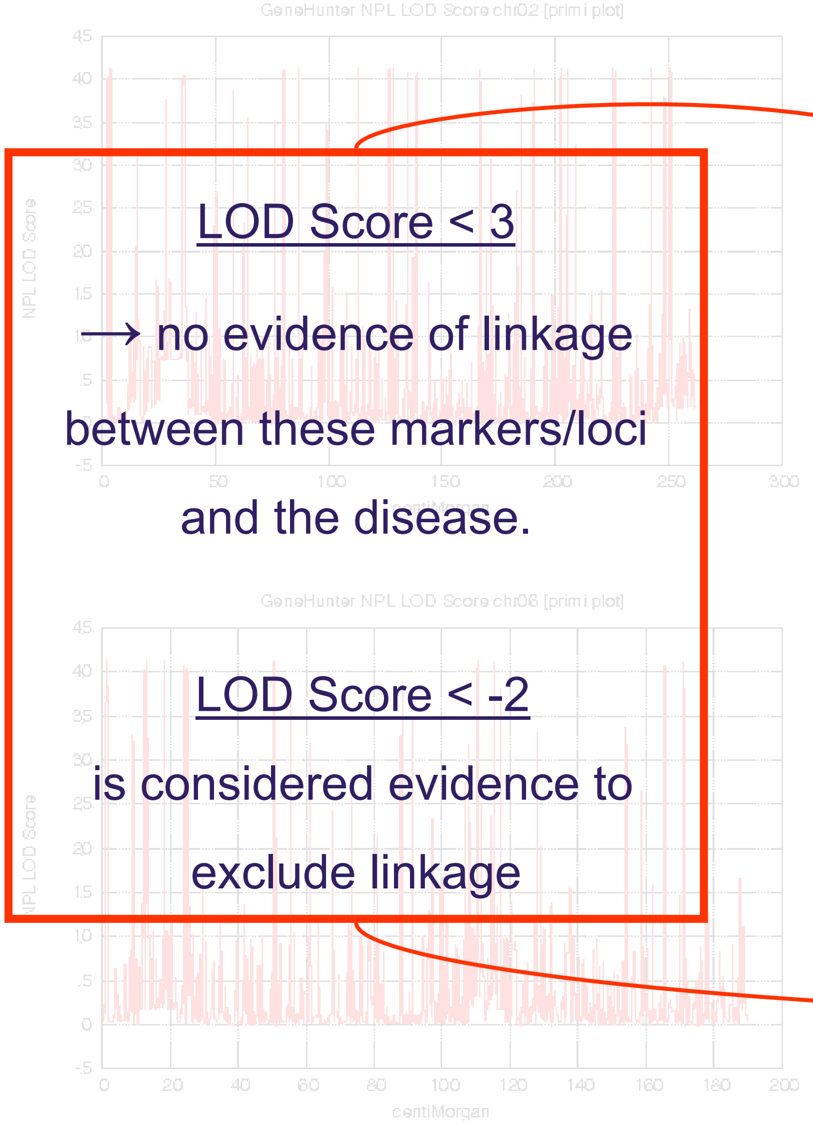
Chrom. 6



Parametric Linkage Analysis

Results: Case Study 1

LOD score function for whole Chromosomes 2 and 6 (317k SNPs)

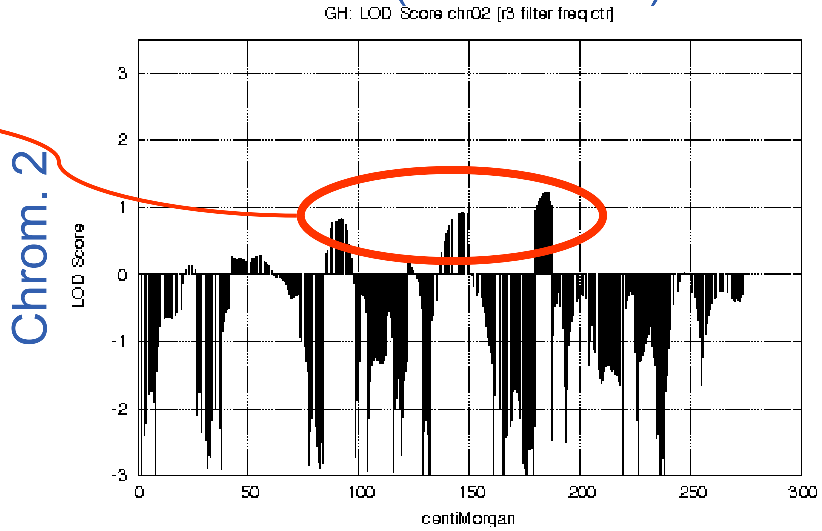


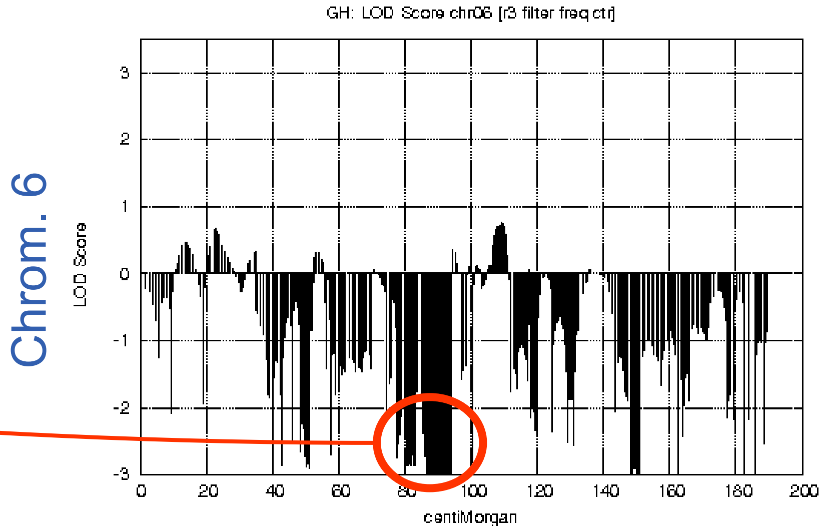
LOD Score < 3

→ no evidence of linkage between these markers/loci and the disease.

LOD Score < -2

is considered evidence to exclude linkage





Results: Case Study 2

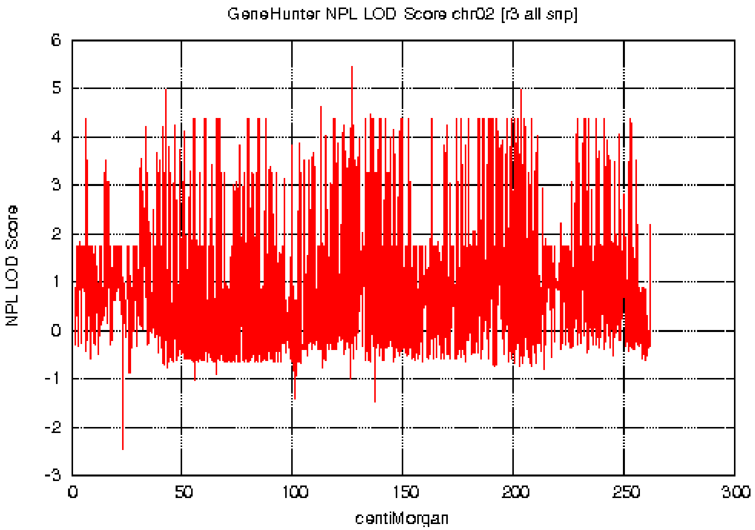
- Chip: Illumina 1 Million SNPs
- Analysis: whole genome (23 chromosomes)
- Software: Genehunter (patients: 24)
- Run time per job: 13 mins
- SNPs per job: 80
- Total jobs:
  - number of runs of Genehunter: 12500
  - number of hours each Computing Element: 6 hours -> 36 runs each Grid Job execution
  - number of Grid Jobs: 348

- Results are presented joined per chromosome

Results: Case Study 2

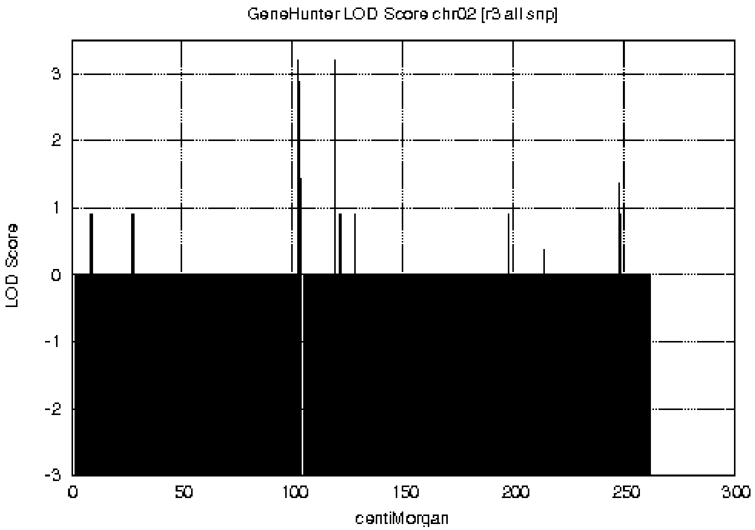
LOD score function for whole Chromosomes 2 and 17 (1M SNPs)

Chrom. 2



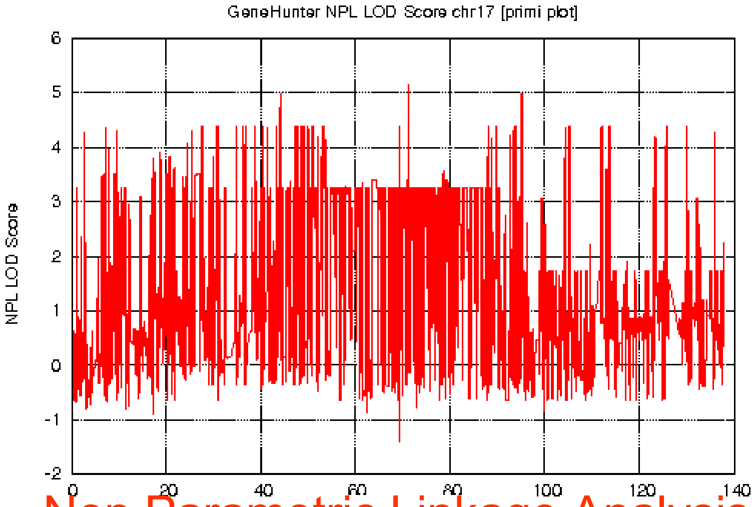
Non Parametric Linkage Analysis

Chrom. 2



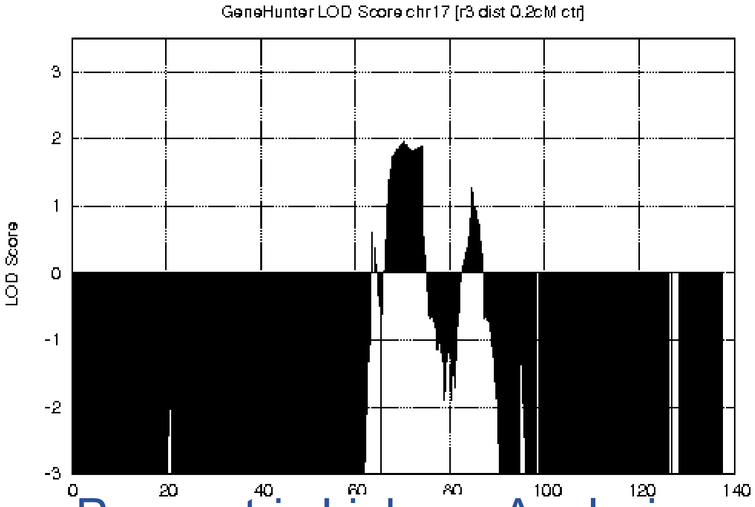
Parametric Linkage Analysis

Chrom. 17



Non Parametric Linkage Analysis

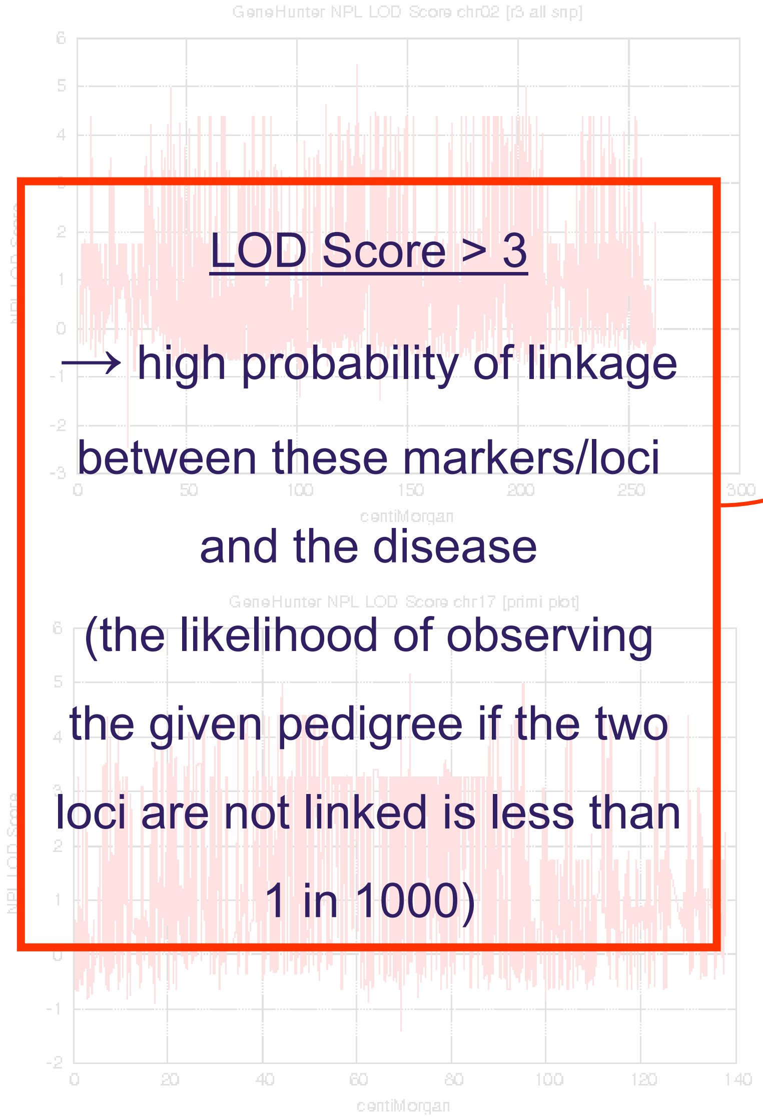
Chrom. 17



Parametric Linkage Analysis

Results: Case Study 2

LOD score function for whole Chromosomes 2 and 17 (1M SNPs)

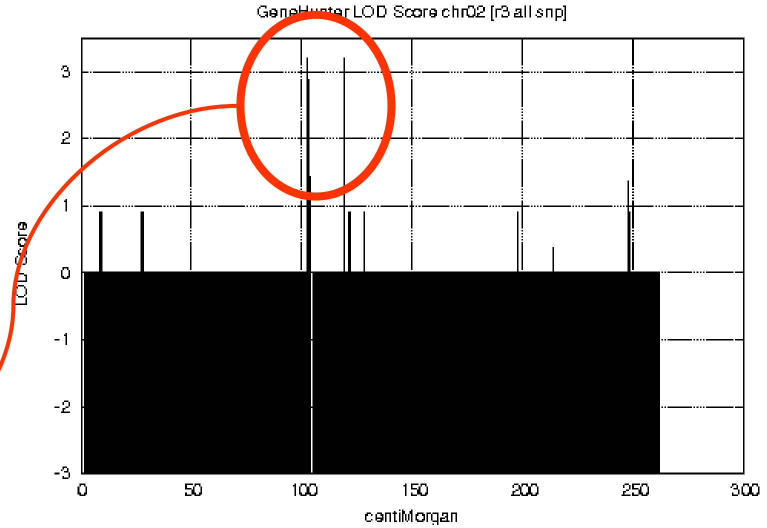


LOD Score > 3

→ high probability of linkage between these markers/loci and the disease

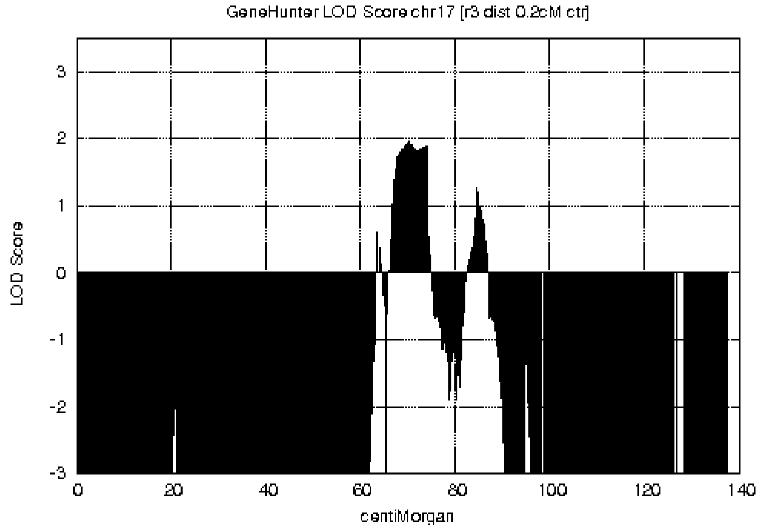
(the likelihood of observing the given pedigree if the two loci are not linked is less than 1 in 1000)

Chrom. 2



Parametric Linkage Analysis

Chrom. 17



Summary

- **This application enables the user to launch genetic linkage analysis calculations for medium to large challenges over a distributed computational infrastructure like the EGEE Grid. It offers:**
  - a parallel processing of the pipeline tasks;
  - A user interface that provides an easier approach to linkage analysis software;
  - A reliable software layer that manages low-level interactions with the distributed computing elements.

Acknowledgments

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