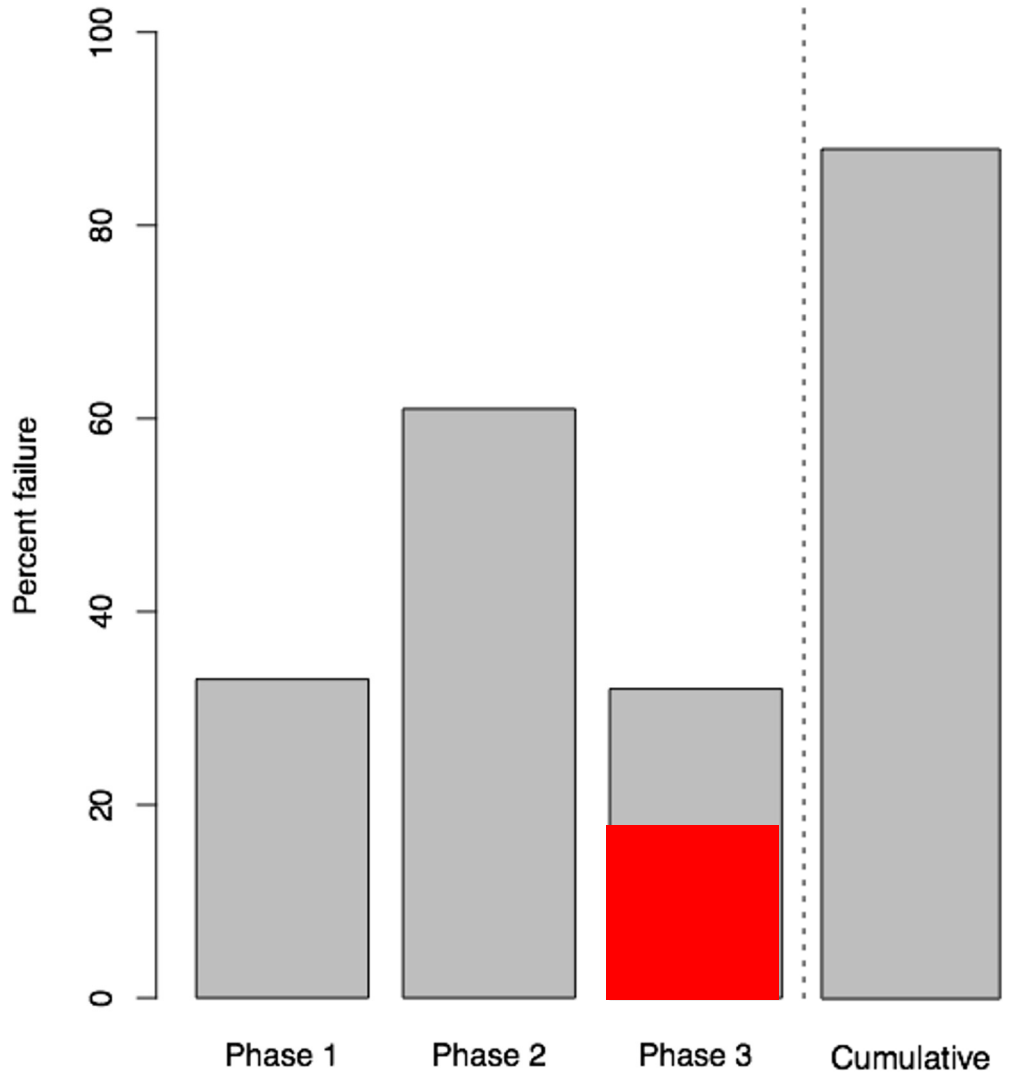
VariantSurvival: A tool to identify genotype-treatment response

The Team

Hiba


SLAYER

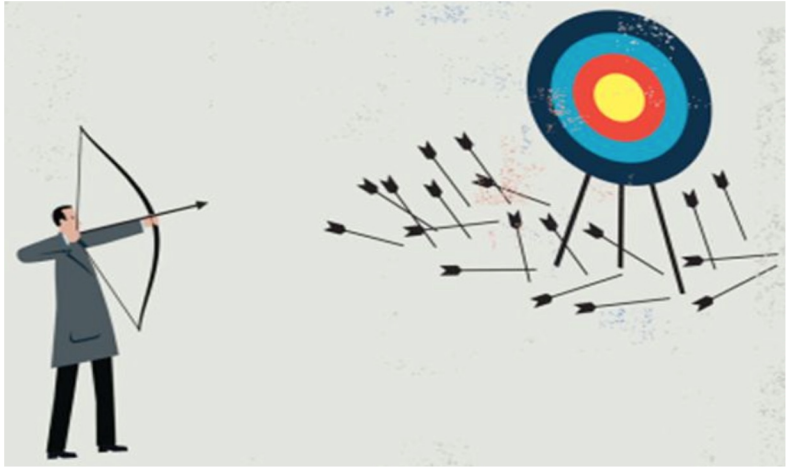
Drug development rarely succeeds…



- Nearly 85% of candidate drugs that enter clinical trials fail
- Failure happens often in late phase due to lack of efficacy

Hay *et al. Nature Biotechnology*. 2014.

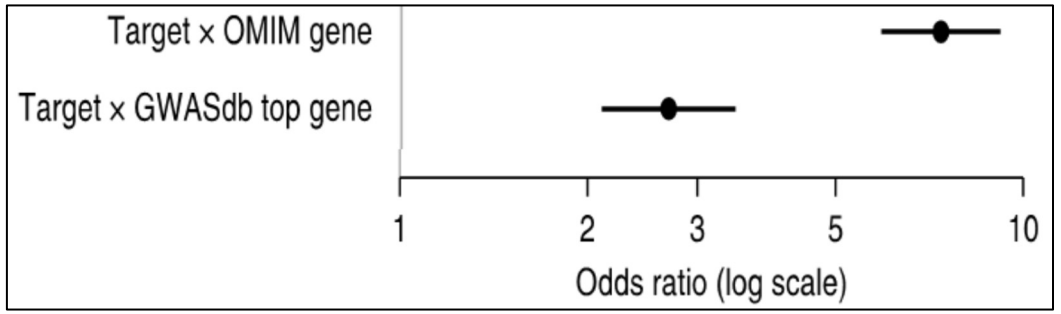
How can we reduce clinical trials failure?



Genetics increase chances of success

The support of human genetic evidence for approved drug indications

Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]



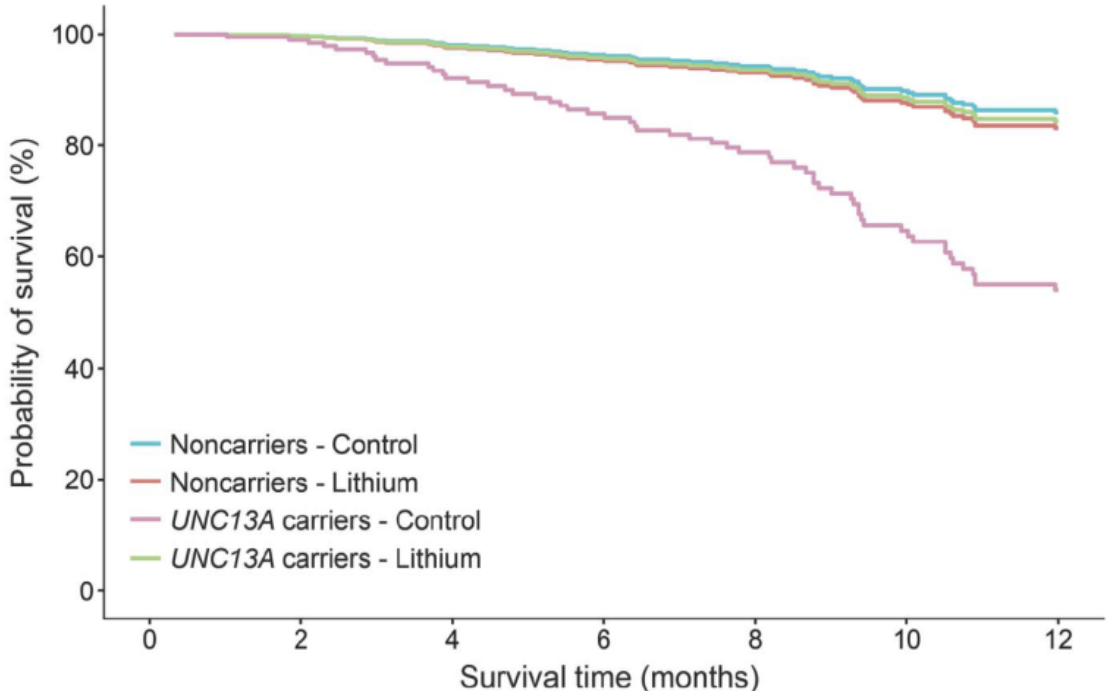
- Nelson *et al.* , Nature Genetics, 2015
- Drug is ~8x more likely to succeed if target identified in Mendelian genetic evidence
- Drug is >2x more likely to succeed if target is supported by GWAS evidence

Major challenge

Systematic strategy to integrate disease-associated variants with functional genomic and drug datasets to provide insight into disease pathogenesis and guide drug discovery and clinical trials for complex traits

PRELUDE trial of lithium in ALS

- Original lithium trials were all negative
- Combined results of 3 of these by genotype
  - Shows benefit of lithium in people with a specific genetic background



mnda
motor neurone disease association

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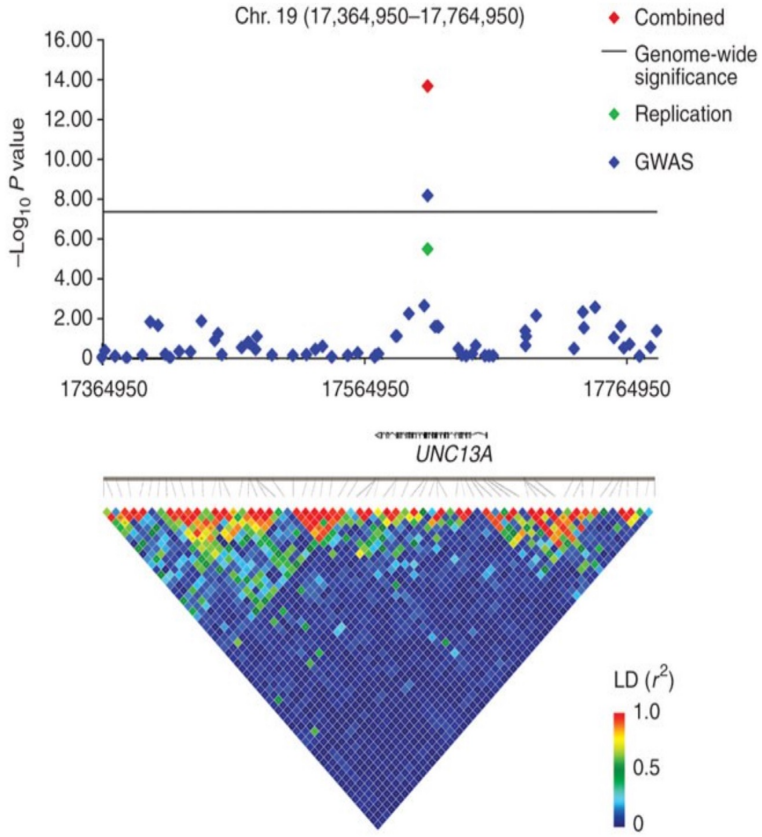
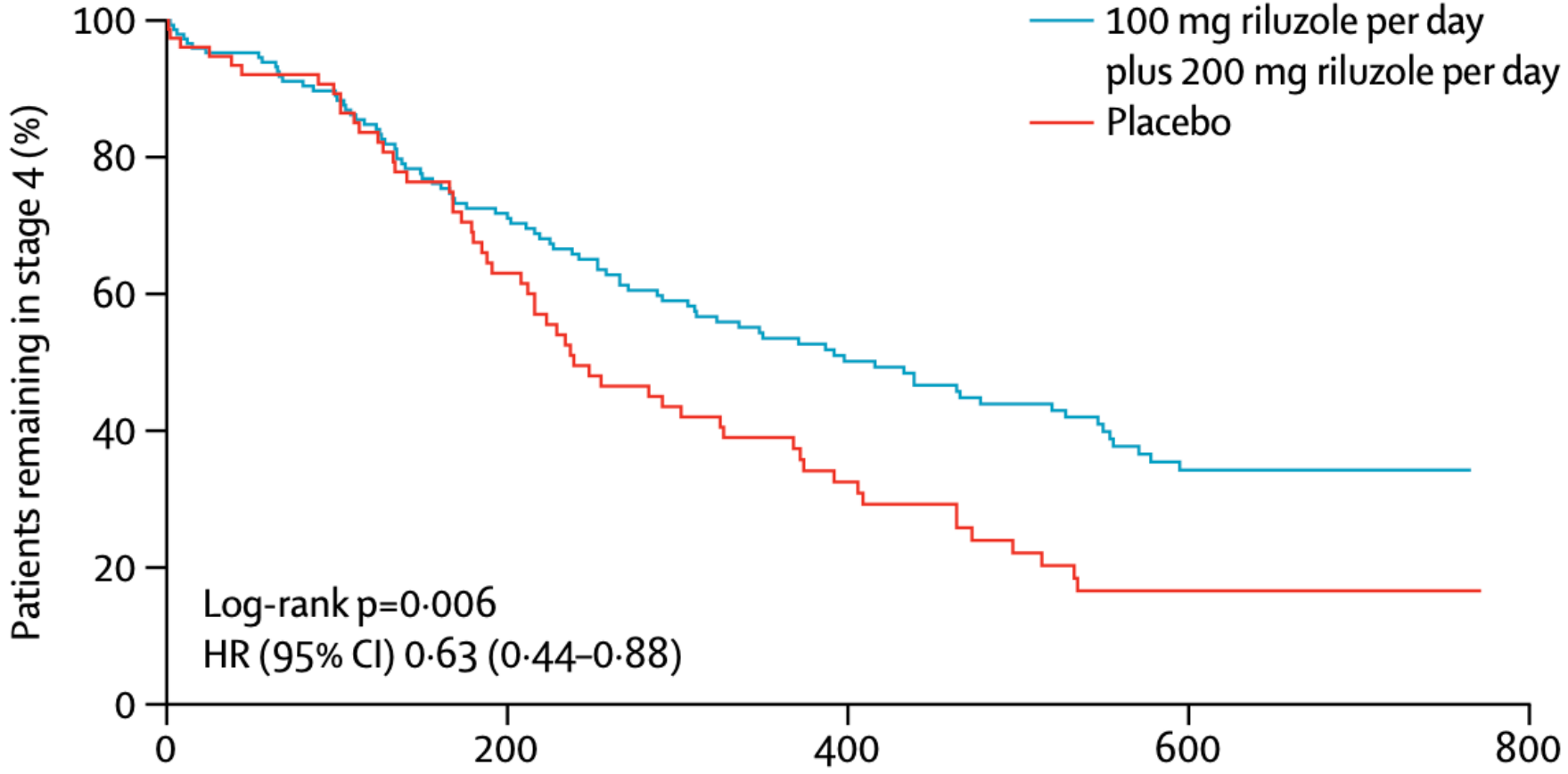


Stage 4 compared with placebo



Number at risk					
100 mg riluzole per day plus 200 mg riluzole per day	148	96	59	29	0
Placebo	77	42	20	7	0

Treatment with higher doses significantly prolonged time in stage 4 compared with placebo (p=0·006).

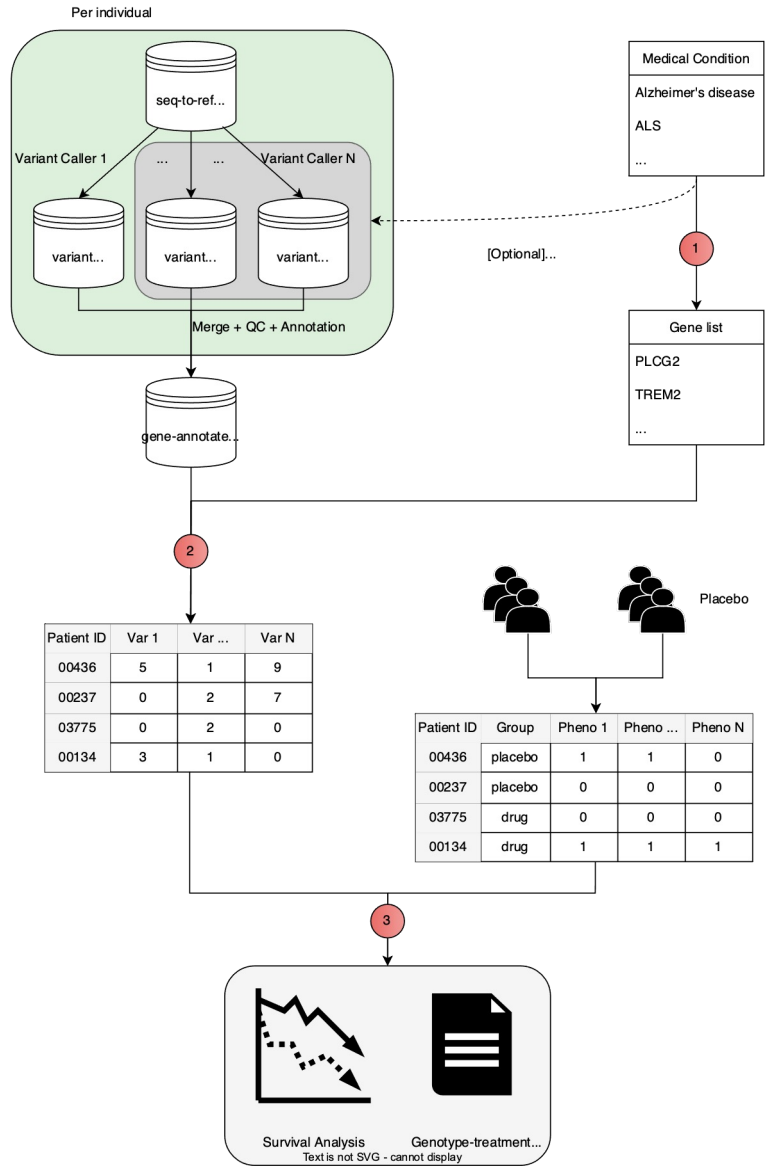
	50 mg/day riluzole	100 mg/day riluzole	200 mg/day riluzole	Placebo
Stage transition				
2–3	109 (99–118)	70 (60–81)	100 (89–110)	82 (72–91)
3–4	38 (29–48)	52 (43–61)	30 (23–37)	69 (61–78)
4–5	207 (195–219)	234 (222–246)	226 (215–237)	198 (186–209)

Data are the mean number of days (95% CI), presented by treatment group.

Table 3: **Multistate outcome analysis of treatment analysis of time to transition from one stage of amyotrophic lateral sclerosis to the next**

Better ways to measure outcomes

Fang T. Lancet Neurol 2018


Per individual
seq-to-ref...
Variant Caller 1
...
...
Variant Caller N
variant...
variant...
variant...
Merge + QC + Annotation
gene-annotate...
Medical Condition
Alzheimer's disease
ALS
...
[Optional]...
1
Gene list
PLCG2
TREM2
...
2
Patient ID | Var 1 | Var ... | Var N
00436 | 5 | 1 | 9
00237 | 0 | 2 | 7
03775 | 0 | 2 | 0
00134 | 3 | 1 | 0
Placebo
Patient ID | Group | Pheno 1 | Pheno ... | Pheno N
00436 | placebo | 1 | 1 | 0
00237 | placebo | 0 | 0 | 0
03775 | drug | 0 | 0 | 0
00134 | drug | 1 | 1 | 1
3
Survival Analysis
Genotype-treatment...
Text is not SVG - cannot display

VariantSurvival

Import Data

Survival Analysis

Import File

Import the variant data vcf file here

Upload vcf file

Browse... merged.filtered.vcf

Upload complete

Import File

Import the metadata file here

Upload metadata file

Browse... metadata.xlsx

Upload complete

Chose disease

Chose the disease from the list below

diseases

Amyotrophic lateral sclerosis

Genes

Note : It is recommended to use the Illumina ExpansionHunter tool for the SV calling.

Based on literature The following genes are associated with the disease mechanism

Show 10 entries Search:

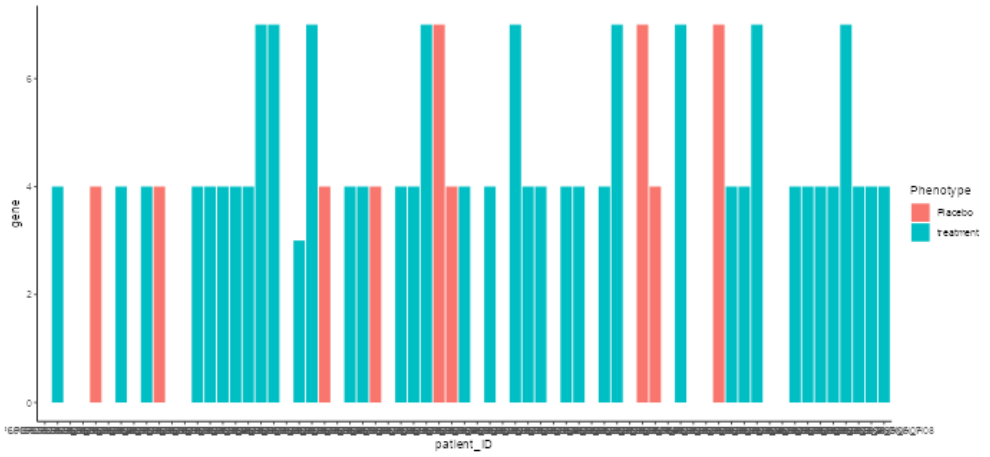
	gene
1	ALS2
2	ANG
3	CHMP2B
4	DAO
5	DCTN1
6	FIG4
7	FUS
8	NEFH
9	OPTN
10	PFN1

Showing 1 to 10 of 22 entries Previous 1 2 3 Next

Select your gene of interest

SETX

Structural Variant in selected gene

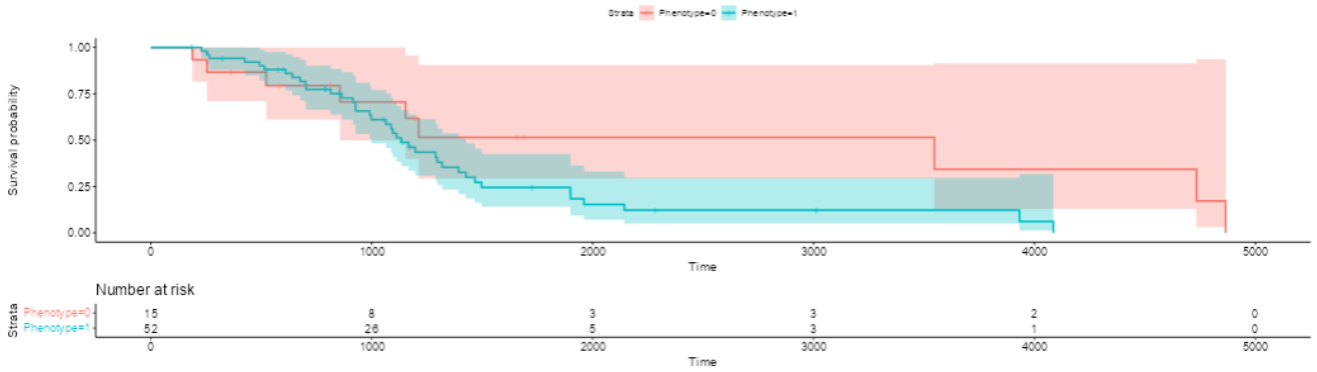


VariantSurvival ≡

Survival Analysis Results

Survival Plot according to existing or not of the SVs

Download the plot



Competing risks regression

Factor = Variant

Show 10 entries Search:

	Characteristic	**HR**	**95% CI**	**p-value**
1	variant	0.93	0.50, 1.72	0.8

Showing 1 to 1 of 1 entries Previous 1 Next

Competing risks regression

Factor = Phenotype

Show 10 entries Search:

	Characteristic	**HR**	**95% CI**	**p-value**
1	Phenotype	2.07	0.91, 4.72	0.084

Showing 1 to 1 of 1 entries Previous 1 Next

Survival Plot according to SV count