PAE
Projeto Atenção Especializada

CEHMOB·MG WORKSHOP:
Projeto Atenção Especializada
para Doença Falciforme

Update on Pulmonary Complications of Sickle Cell Disease

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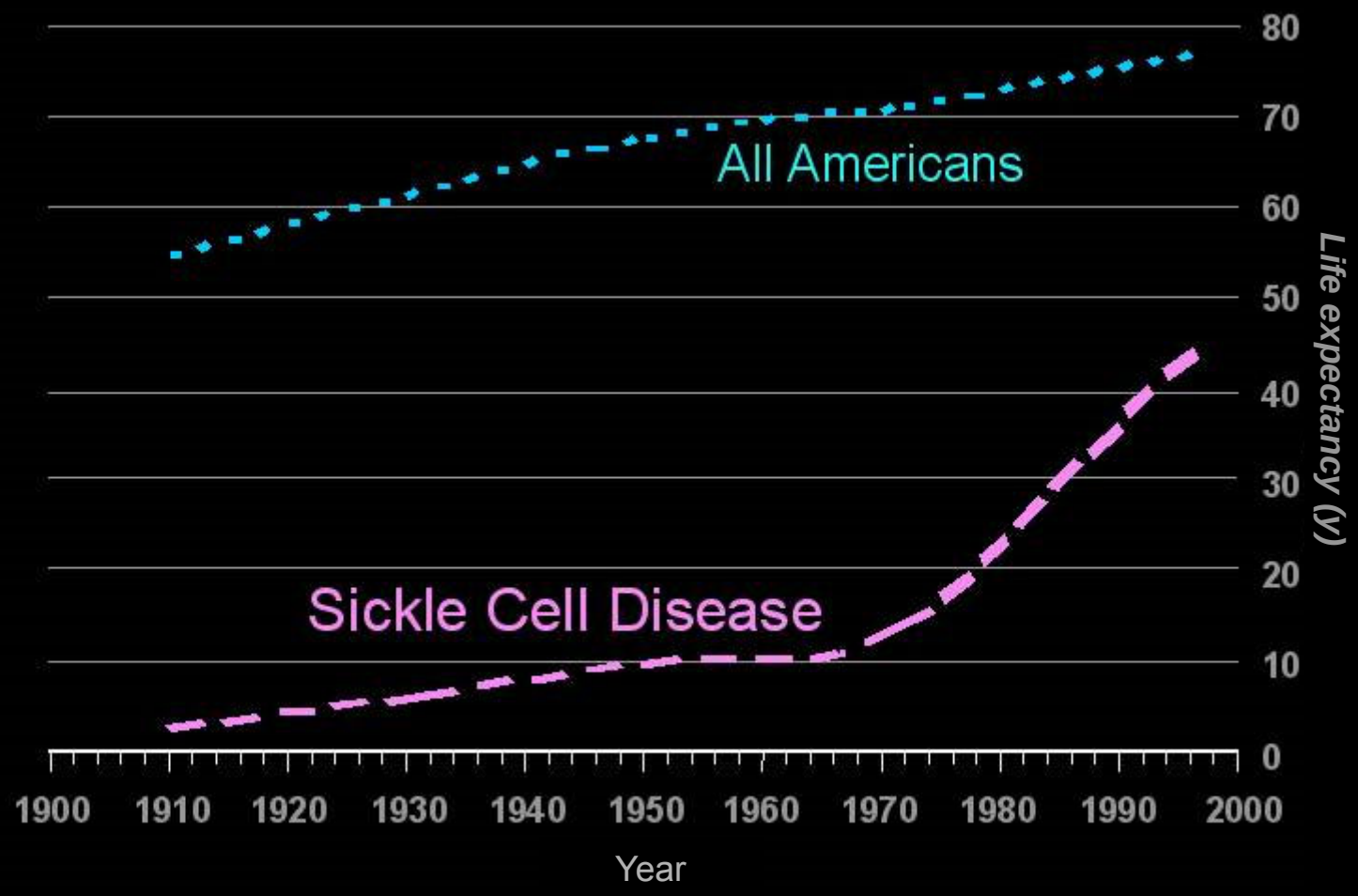
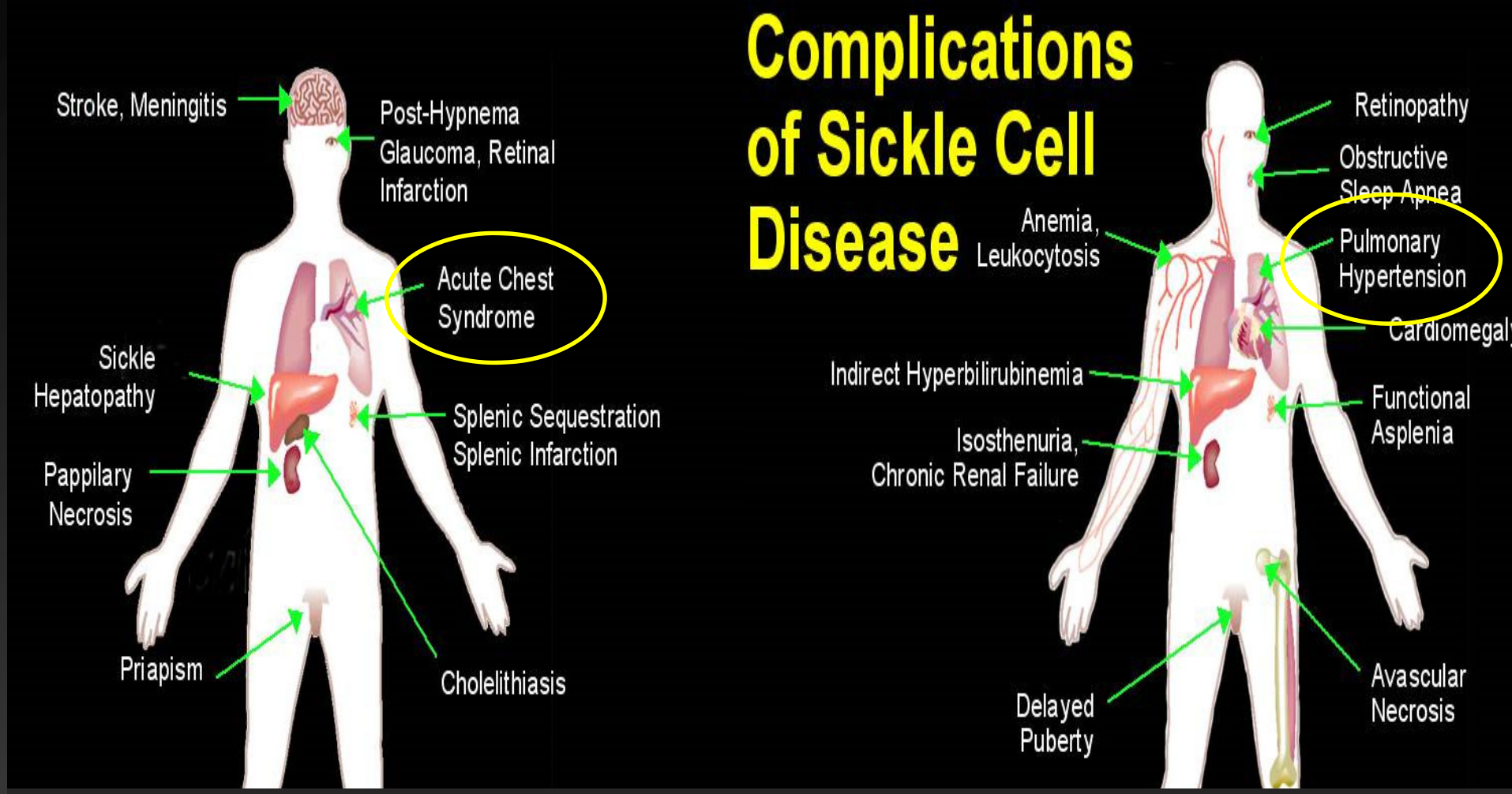
Hospital & Health Sciences System
Changing medicine. For good.

Increases in Life Expectancies of Patients With Sickle Cell Disease



Source: National Heart, Lung, and Blood Institute.



- Pulmonary complications account for a large proportion of deaths in adults with SCD
- 20% of adults in the CSSCD had fatal pulmonary complications
- In the MSH long-term follow up study lung disease was the most common cause of mortality accounting for 28% of all deaths

What is Chronic Lung Disease in SCD ?

?

Chronic Lung Disease

- Waste basket term
- Should be replaced by specific diagnostic classification e.g.:
  - Pulmonary fibrosis
  - Asthma
  - Pulmonary hypertension

Pulmonary Fibrosis/Restrictive Lung Disease

- Repetitive episodes of ACS result in parenchymal damage and is the major risk factor for the development of pulmonary fibrosis
- Abnormal PFTs observed in 90% of 310 HbSS patients: FVC 84 ± 16%, FEV_1 83 ± 16%, TLC 70 ± 15%, $DL_{CO(c)}$ 65 ± 20%
- Restriction 74%
- Isolated low DL_{CO} 13%
- Obstruction (simple or combined) 3%
- Patients with h/o ACS tend to have lower TLC and DL_{CO}
- Presence of restrictive lung disease associated with markers of severity of SCD: low Hb, high WBC

Powars et al. *Medicine.* 1998;67:66, Klings et al. AJRCCM. 2006;173:1264

Airway Hyper-reactivity/Asthma

- Airway hyper-reactivity occurs in at least 30% of children with SCD
- Very little formal data characterizing the asthma phenotype in adults with SCD
- Airflow obstruction appears to be rare in adults with SCD
- Hyper-reactivity by methacholine demonstrated in 20-30% of adults based on two small studies
- Children with SCD and asthma experience almost twice as many episodes of ACS than their counterparts without asthma
- Asthma is an independent risk factor for mortality in children with SCD, conferring a two-fold higher risk of death
- In adults self-reported severe and recurrent wheezing is associated with increased rates of pain, ACS, and risk of death, the study did not find a relationship between a physician diagnosis of asthma and these complications

Acute Chest Syndrome

- Acute lung injury syndrome
- Second most common cause of hospital admission in patients with sickle cell disease
- Leading cause of premature death (25% of cases)
- Prospective Cooperative Study of Sickle Cell Disease in 3,751 subjects with sickle cell anemia 29% incidence of ACS over a 2-yr period
- Attack rate of 12.8 episodes/100 patient years for homozygous sickle cell disease
- Most common cause of ICU admission in patients with sickle cell disease

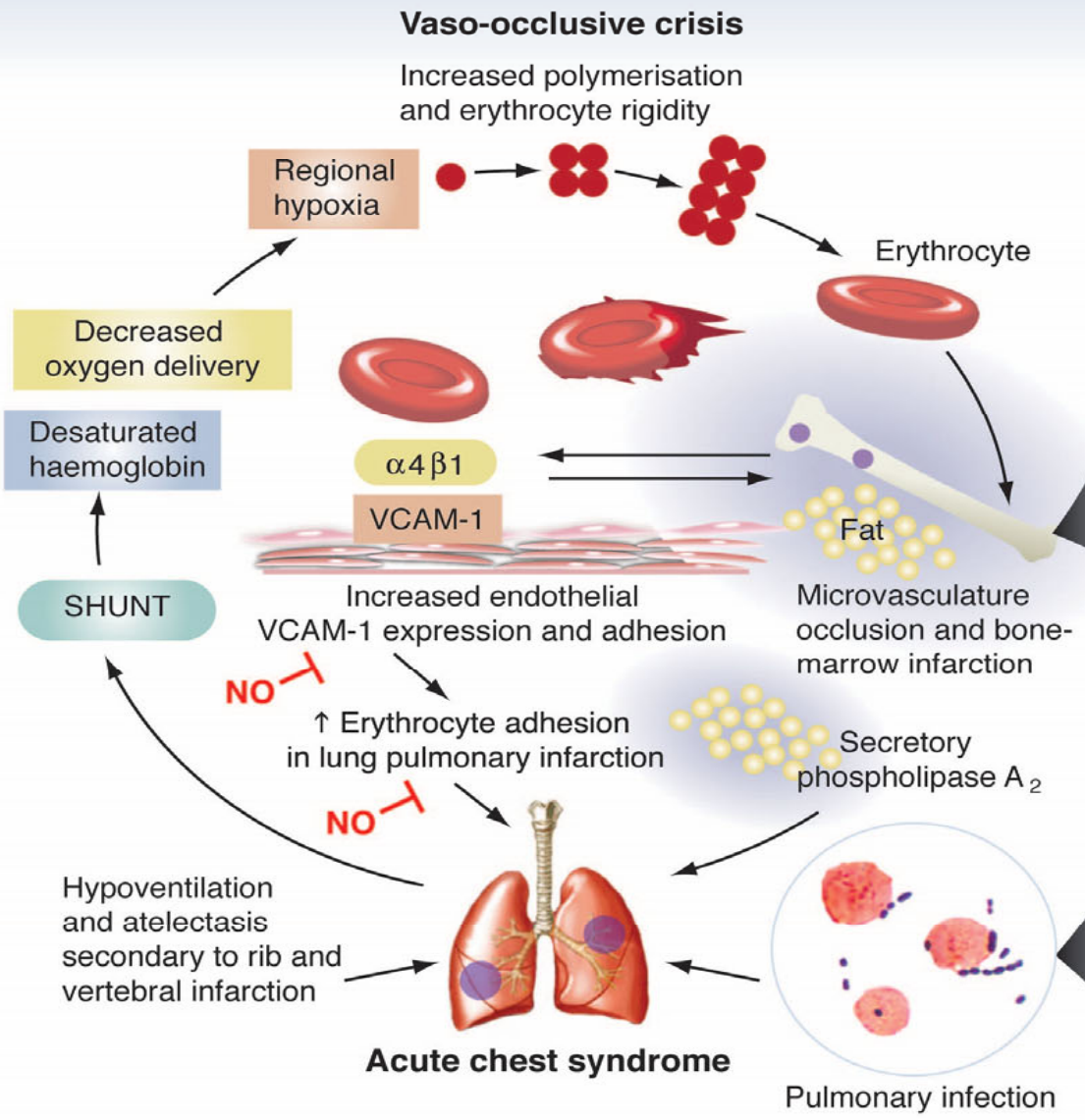
Definition

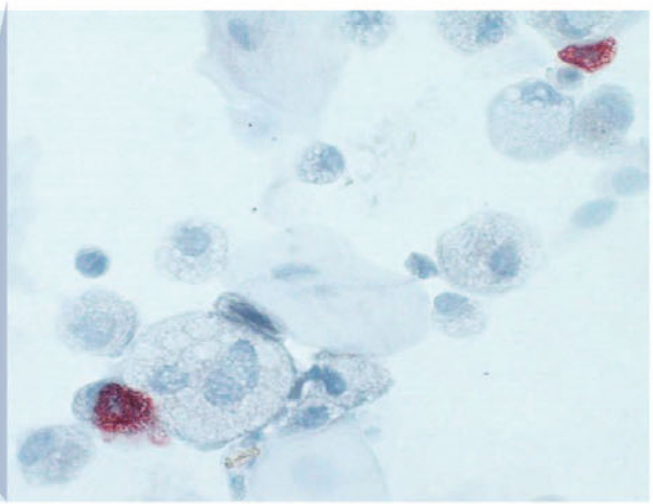
- New pulmonary infiltrate involving at least one complete lung segment, consistent with the presence of alveolar consolidation (excluding atelectasis), plus one of the following:
  - Chest pain
  - Temperature greater than 38.5 C
  - Tachypnea
  - Wheezing
  - Cough

Vichinsky et al N Engl J Med 342:1855-1865, 2000

Pathogenesis

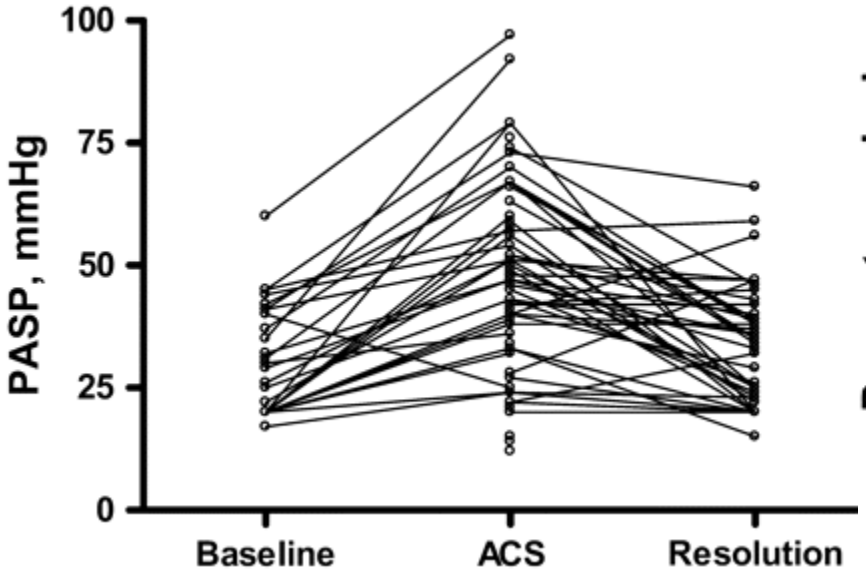
Vicious cycle of vaso-occlusive crisis and acute chest syndrome

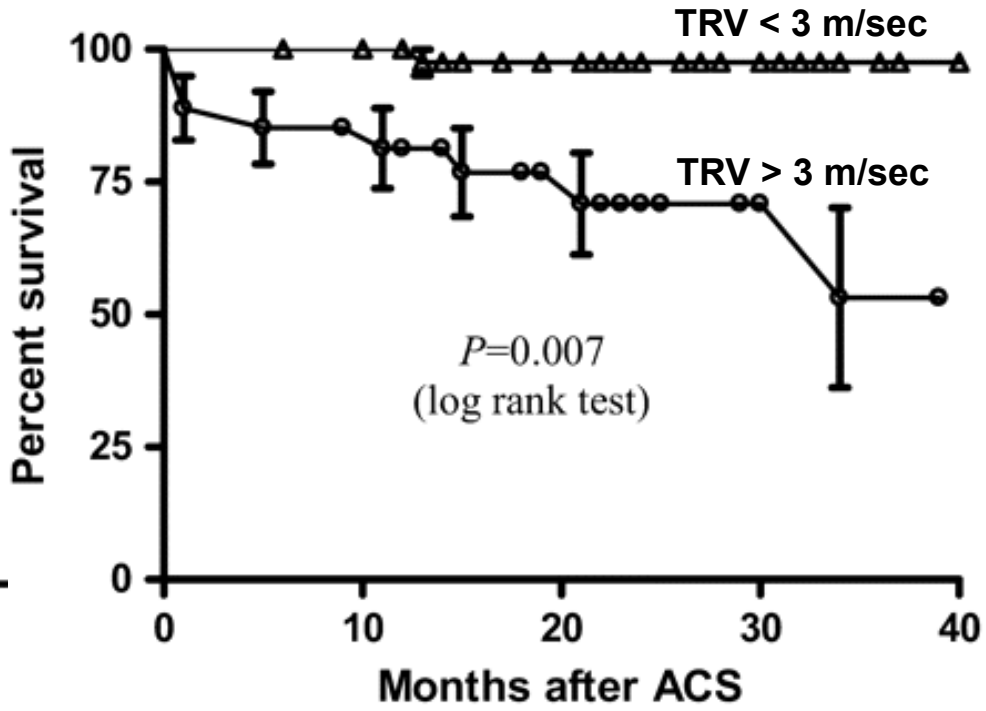




- 29% *Chlamydia pneumonia*
- 20% *Mycoplasma pneumonia*
- 2 % *Legionella pneumonia*
- 10% respiratory syncytial virus
- 4% parvovirus, 3% rhinovirus,
  2% parainfluenza virus,
  2% influenza A virus,
  2% cytomegalovirus,
  1% ebstein barr virus,
  1% herpes simplex virus
- *Staphylococcus aureus* was isolated in 5% of cases and *Streptococcus pneumonia* in only 4% of cases

ACS Increases PASP and PH Worsens Prognosis After ACS

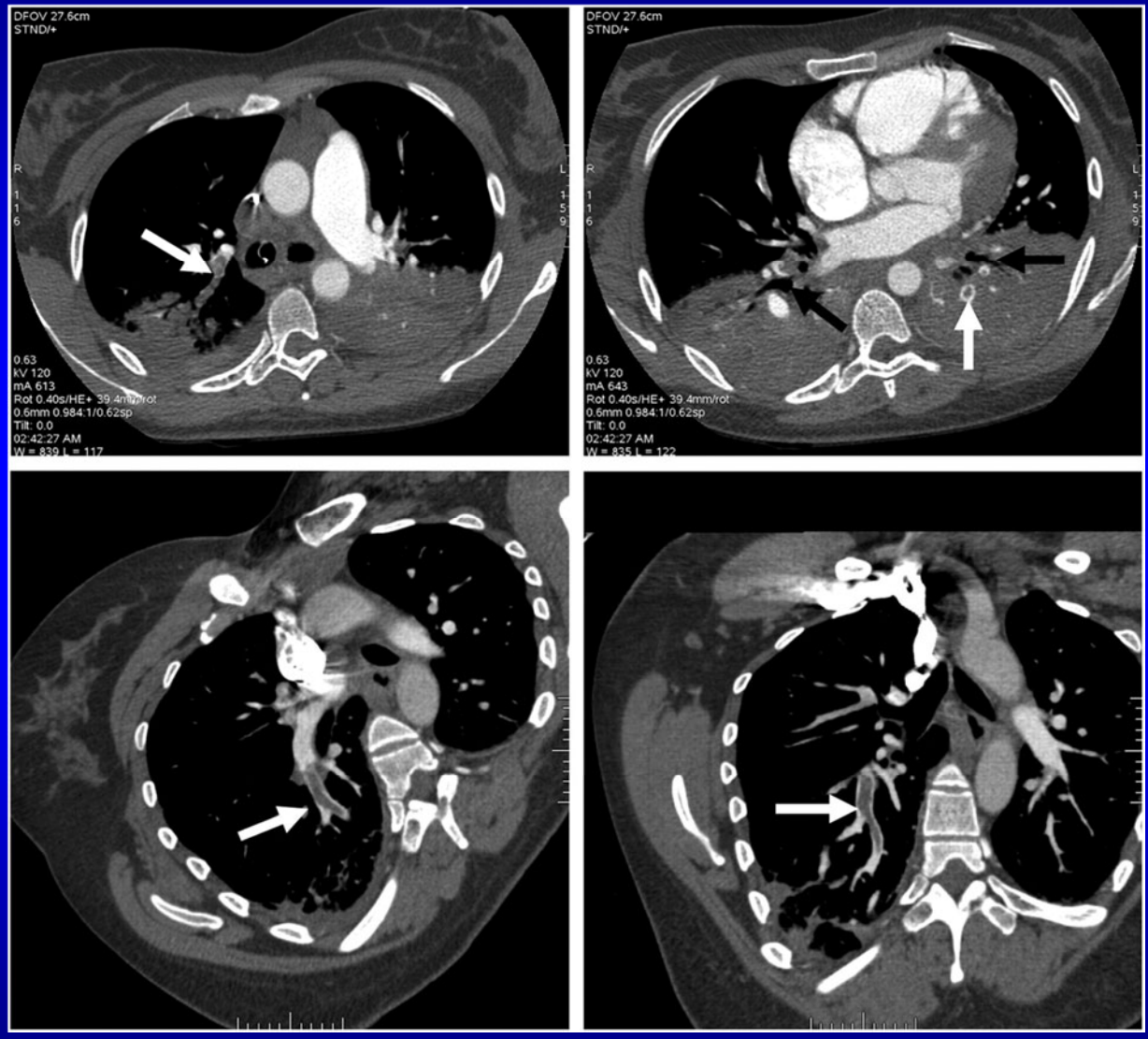




Dessap, A et al.Am J Resp. Crit. Care Med., 2008

Pulmonary Artery Thrombosis

- Cohort of 126 patients with SCD (144 episodes)
- 121 underwent CT angiogram
- D-dimer positive in 95%
- 17% had PA thrombus, no DVTs
- More likely in patients with higher platelet counts and lower hemolytic rate during ACS.



Dessap, A et al.Am J Resp. Crit. Care Med., 2011 Nov 1;184(9):1022-9

Chest CT in ACS

- Cohort of 127 patients with SCD and ACS (166 episodes)
- 145 underwent CT scans
- New opacity in 96%, 84% at one complete segment
- Patients with a new complete lung segment consolidation had a more severe presentation and course
- The sensitivity of bedside CR for the diagnosis of ACS using CT as a reference was good (>85%), whereas the specificity was weak (<60%)

Dessap, A et al. Thorax 2013 doi: 10.1136/thoraxjnl-2013-203775

Systemic Fat Embolization Syndrome

- Part of the spectrum of ACS due to fat embolism
- Should be suspected in patients with ACS with
  - Alterations in mental status
  - Multiorgan failure
  - Thrombocytopenia, coagulopathy
- Diagnosis is difficult
  - Upper body petechiae
  - Fat droplets in retinal vessels, urine, alveolar macrophages

Treatment

- General
  - Judicious hydration
  - Oxygen for hypoxemia
  - Pain control
  - Incentive spirometry
- Empiric antibiotics for “typical” and “atypical” pathogens
  - Consider bronchoscopy in patients not responding
  - Remember S. aureus
- Consider bronchodilators
  - High incidence of airway hyper reactivity in children
  - Mean FEV_1 53 % predicted in ACS
- Transfusion
- Steroids ?
- Nitric Oxide
  - Case reports of successful treatment
  - Rationale similar to ARDS

Summary: ACS

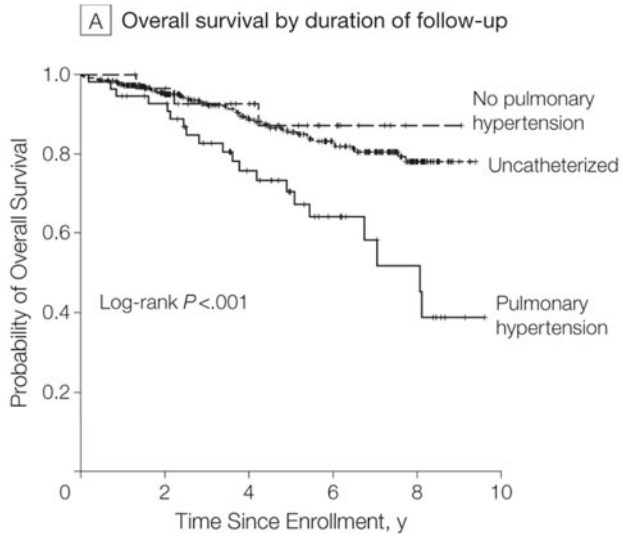
- Acute lung injury syndrome of several etiologies
- Common cause of morbidity and mortality in the sickle cell disease population
- Infectious etiologies cannot be completely ruled out and should be trated in all patients
- Fat embolization syndrome is part of the spectrum of ACS and seems to be associated with greater severity of illness
- Red blood cell transfusion seems to have a positive impact on the course of ACS and should be considered in most patients

Prevalence of PH in SCD: Screening Studies

- French screening study (N Engl J Med. 2011;365(1):44-53)
  - 398 patients
  - RHC for TRV ≥ 2.5 m/s
  - mPAP ≥ 25 mmHg = 6%
  - Excluded patients with renal failure, low TLC and liver disease
- Brazilian screening study (Eur Respir J. 2012;39(1):112-118)
  - 80 patients
  - RHC for TRV ≥ 2.5 m/s
  - mPAP ≥ 25 mmHg = 10 %
- NIH screening study (JAMA. 2012;307(12):1254-1256)
  - 531 patients
  - RHC for TRV ≥ 2.8 m/s
  - mPAP ≥ 25 mmHg = 11 %

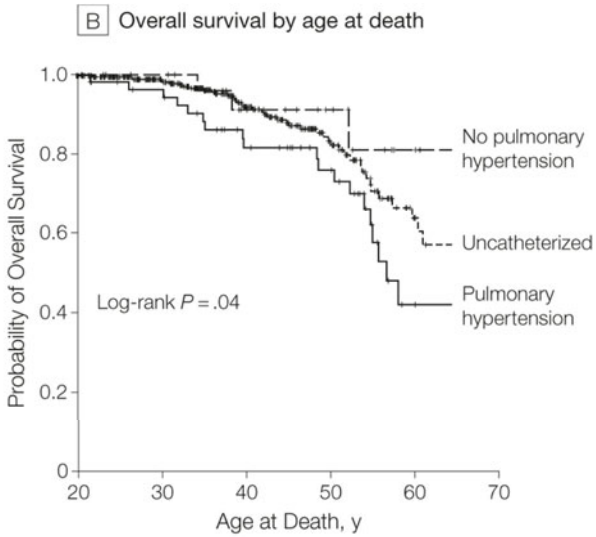
Pulmonary Hypertension and Survival

- French screening study (N Engl J Med. 2011;365(1):44-53)
  - Mortality rate was significantly higher in patients with PH than in patients without clinical and echocardiographic evidence of PH (12.5 percent versus 0.3 percent, P=0.002).
- Brazilian screening study (Eur Respir J. 2012;39(1):112-118)
  - Patients with PH confirmed by RHC had worse survival compared with the remaining patients (P=0.0005)
- NIH screening study (JAMA. 2012;307(12):1254-1256)
  - HR for death was 3.43 (95% CI, 1.02-11.55; P = 0.047) for patients with PH vs. no PH and 2.14 (95% CI, 1.25-3.67; P = 0.006) for patients with PH vs those who did not undergo RHC (uncatheterized)



No. at risk

No pulmonary hypertension	29	25	20	8	1
Uncatheterized	381	284	187	128	37
Pulmonary hypertension	55	48	30	15	8

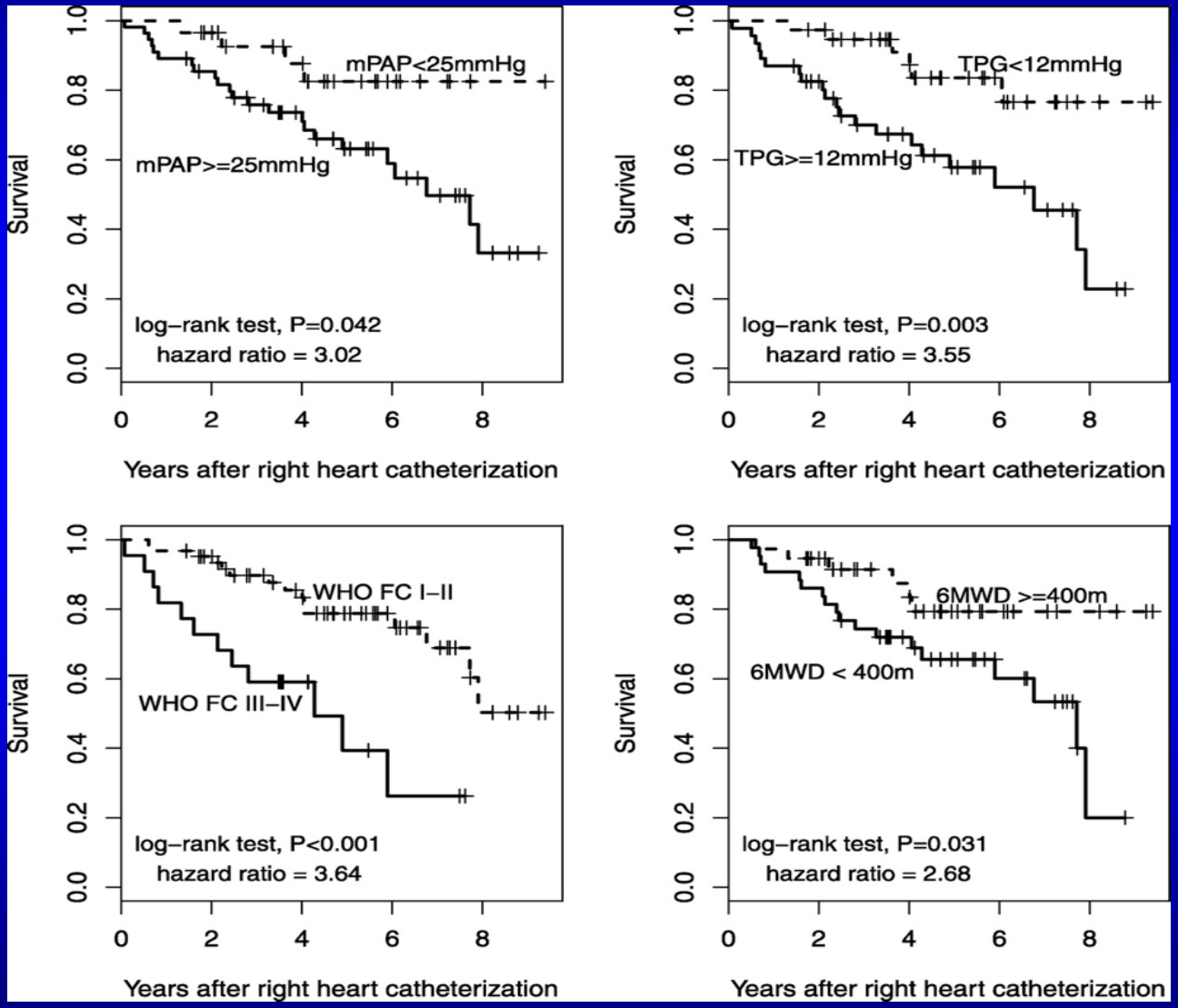


No. at risk

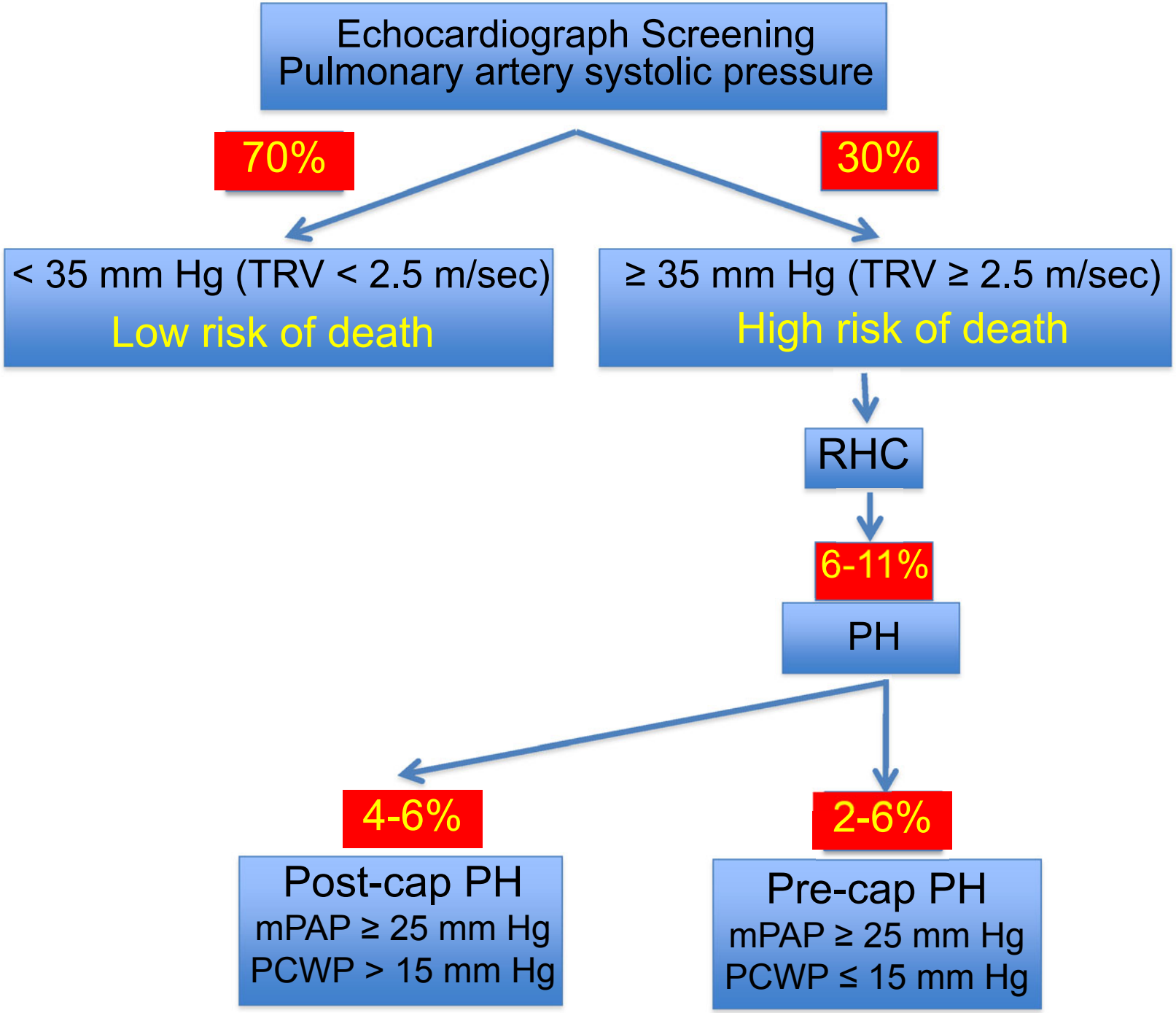
No pulmonary hypertension	29	26	16	11	4
Uncatheterized	376	276	157	79	22
Pulmonary hypertension	55	48	35	26	6

JAMA. 2012;307(12):1254-1256

Hemodynamics, Functional Capacity, and Survival



Mehari, A et al . *Am J Respir Crit Care Med.* 2013:187:840-847


Echocardiograph Screening
Pulmonary artery systolic pressure
70%
30%
< 35 mm Hg (TRV < 2.5 m/sec)
Low risk of death
≥ 35 mm Hg (TRV ≥ 2.5 m/sec)
High risk of death
RHC
6-11%
PH
4-6%
2-6%
Post-cap PH
mPAP ≥ 25 mm Hg
PCWP > 15 mm Hg
Pre-cap PH
mPAP ≥ 25 mm Hg
PCWP ≤ 15 mm Hg

Treatment of PH in SCD

- Very little disease specific data
  - Borrowed evidence from other diseases associated with PAH
- Overall approach:
  - Treat SCD aggressively
  - Treat associated conditions
  - Consider specific therapy in symptomatic patients with PAH

CME article

Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity

Roberto F. Machado,[1] Robyn J. Barst,[2] Nancy A. Yovetich,[3] Kathryn L. Hassell,[4] Gregory J. Kato,[5] Victor R. Gordeuk,[6] J. Simon R. Gibbs,[7] Jane A. Little,[8] Dean E. Schraufnagel,[1] Lakshmanan Krishnamurti,[9] Reda E. Girgis,[10] Claudia R. Morris,[11] Erika B. Rosenzweig,[2] David B. Badesch,[4] Sophie Lanzkron,[10] Onyinye Onyekwere,[6] Oswaldo L. Castro,[6] Vandana Sachdev,[5] Myron A. Waclawiw,[12] Rob Woolson,[3] Jonathan C. Goldsmith,[13] and Mark T. Gladwin,[14,15] on behalf of the walk-PHaSST Investigators and Patients

- Stopped early due to safety concerns in sildenafil treated vs. placebo subjects
- Higher number of SAEs in the sildenafil group (46% of sildenafil, 22% of placebo, P = 0.022)
- Patients on sildenafil had higher incidence of pain crises requiring hospitalization than placebo (35% with sildenafil vs.14% with placebo, P = 0.029)
- There was no evidence of a treatment effect on 6MWD, TRV, or N-terminal pro-brain natriuretic peptide levels

Machado, RF et al Blood. 2011 Jul 28;118(4):855-64

Summary: PH

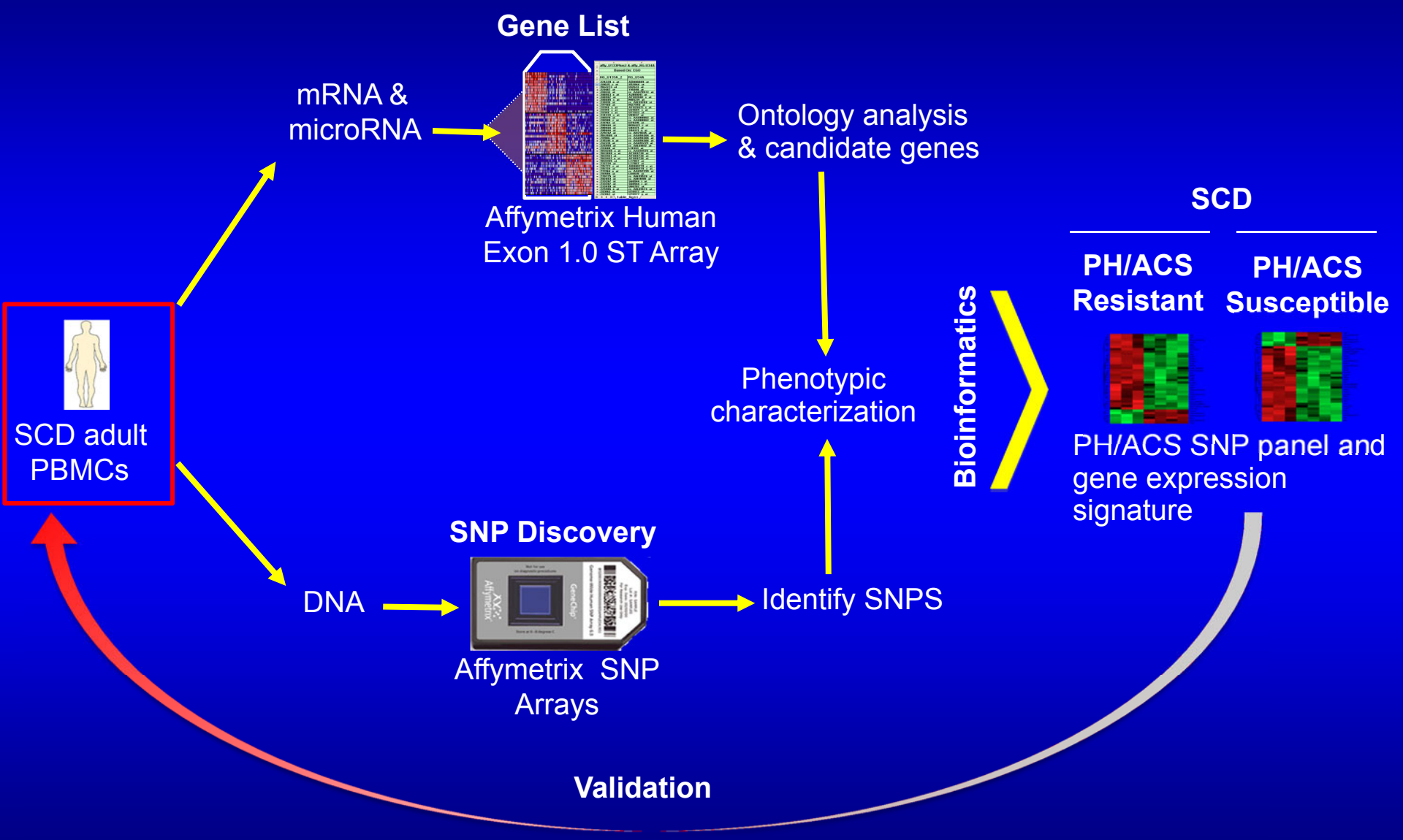
- Pulmonary hypertension is a major risk factor for death in patients with SCD
- Etiology of pulmonary hypertension is multifactorial
- Treatment of PH in SCD should include maximization of hemoglobinopathy therapy, treatment of associated conditions and PAH specific therapy in selected cases
- High quality data specific for patients with SCD is lacking
- Uncontrolled data suggest that treatment of pulmonary hypertension may may be beneficial in this patient population
- Sildenafil was not well tolerated due to increase in VOC in a RCT of patients not maximized on SCD therapy
- Effects of PAH therapy in more selected populations should be explored
- Further studies are needed

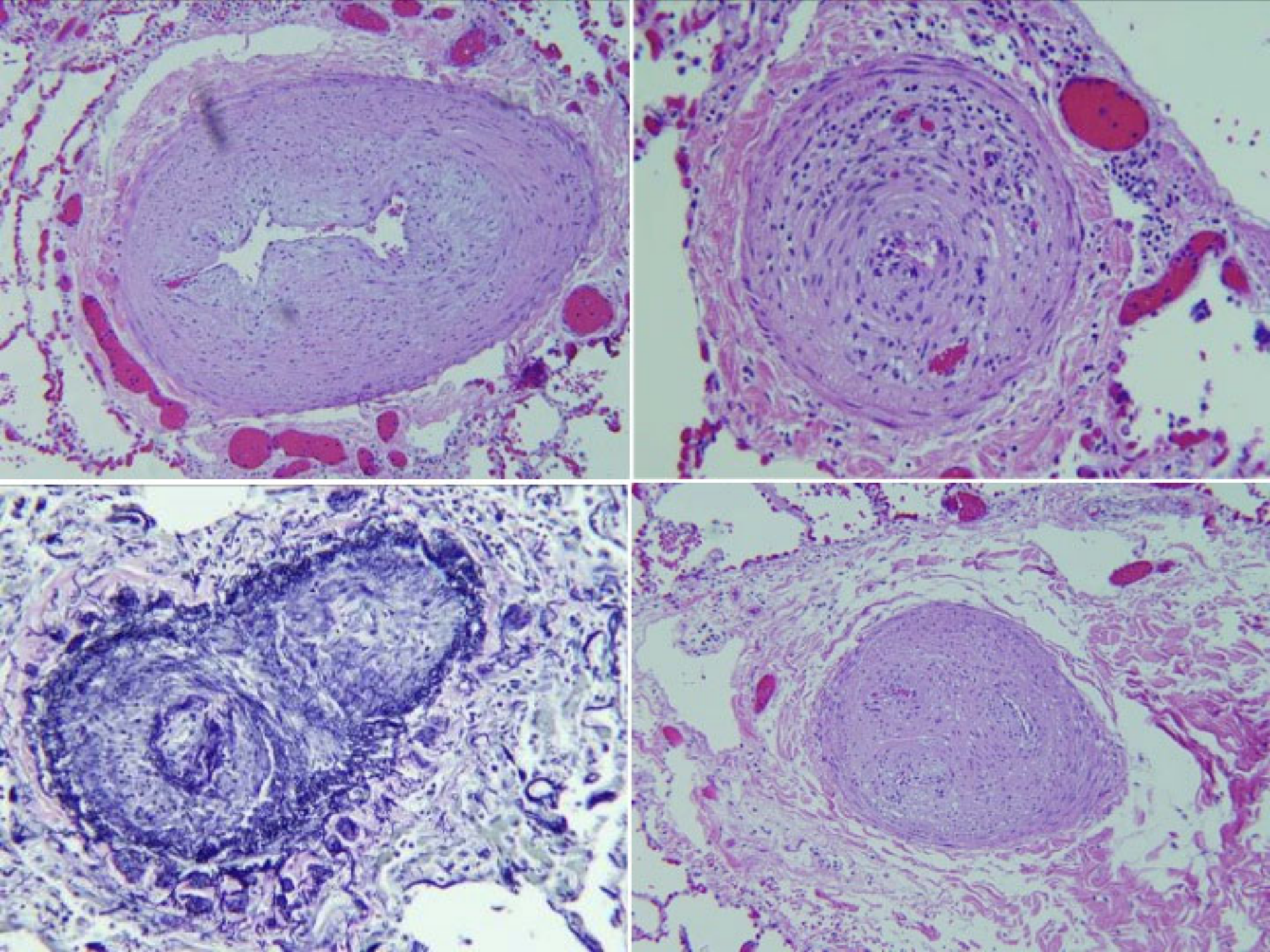
Modifiers of Sickle Cell Disease Pulmonary Complications

- The SCD population has a predictable prevalence and risk from pulmonary complications and represents a group that may benefit from early diagnosis and treatment.

- Despite harboring the identical genetic mutation (val6glu), there is extensive heterogeneity in the development of pulmnary complications implicating the contribution of modifier genes (SNPs & miRNAs).

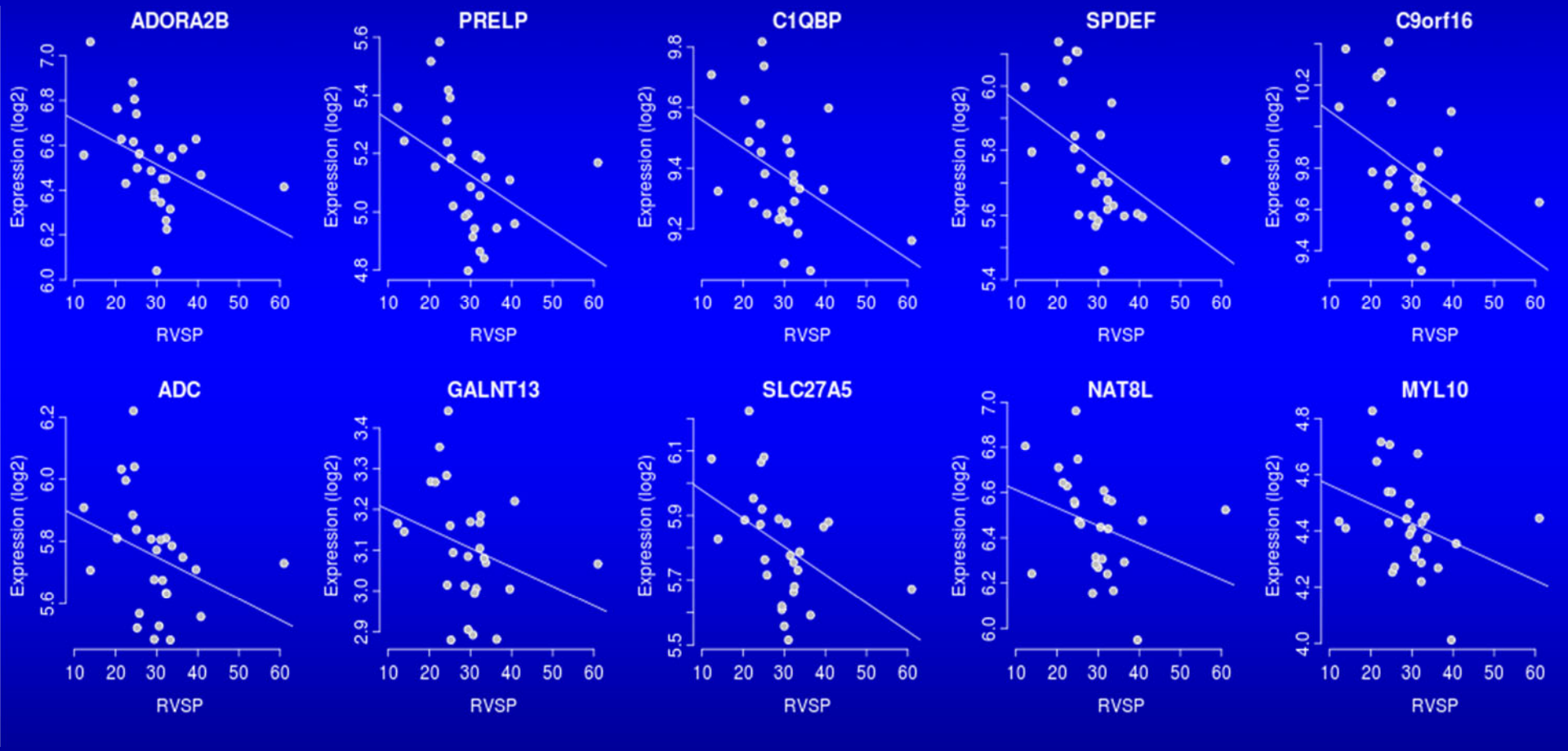
Methods- Schematic of the Investigations





Gene Signature for Elevated RVSP

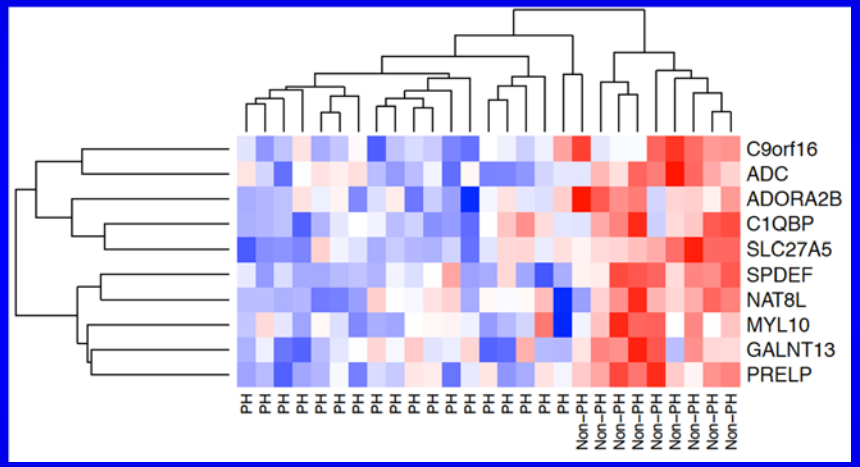
- 631 transcripts correlating with RVSP were subjected to an SVM analysis to generate a signature for elevated RVSP



Desai, AA, Am J Respir Crit Care Med. 2012;186(4):359-68

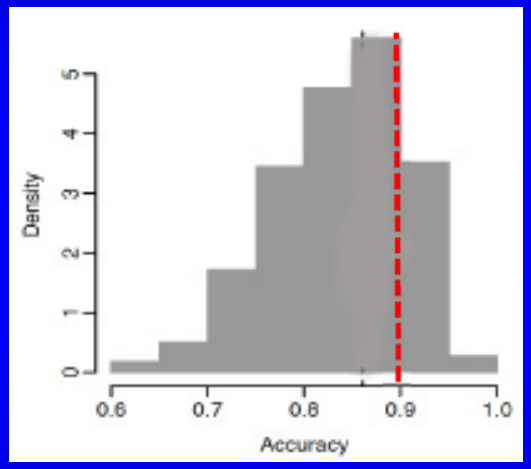
Validation of the gene signature in PH

- RVSP gene signature was tested against a validation cohort of patients with SCD and RHC-proven PH using an SVM analysis:



<u>To Predict PH in SCD</u>

- 90% Sensitivity
- 90% Specificity



Desai, AA, Am J Respir Crit Care Med. 2012;186(4):359-68

Candidate Gene Approach in SCD and Elevated RVSP

- 112 SCD patients with elevated RVSP (n=49) and normal RVSP (n=63)
- Of the 10 PH-associated signature genes, a total of 412 SNPs were represented on the Affymetrix 6.0 platform.
- Among these SNPs, 6 significant SNPs were identified within 2 signature genes associated with elevated RVSP (P<0.005) with 5 of 6 SNPs residing within GALNT13

SNP	PH Signature Gene	Minor allele	P value	P value *	OR	Frequency-SCD elevated RVSP cases	Frequency-SCD controls	Position
rs799813	**GALNT13**	**G**	**0.001**	**0.002**	**0.28**	**0.09375**	**0.2705**	**intronic**
rs2794452	PRELP	C	0.001	0.013	0.42	0.3367	0.5492	upstream
rs10497120	GALNT13	C	0.001	0.001	2.76	0.3333	0.1532	upstream
rs13407922	GALNT13	A	0.002	0.003	3.08	0.2449	0.09524	Intronic
rs16833378	GALNT13	G	0.003	0.003	0.26	0.06122	0.1984	upstream
rs9808145	GALNT13	A	0.004	0.006	2.97	0.2245	0.08871	intronic

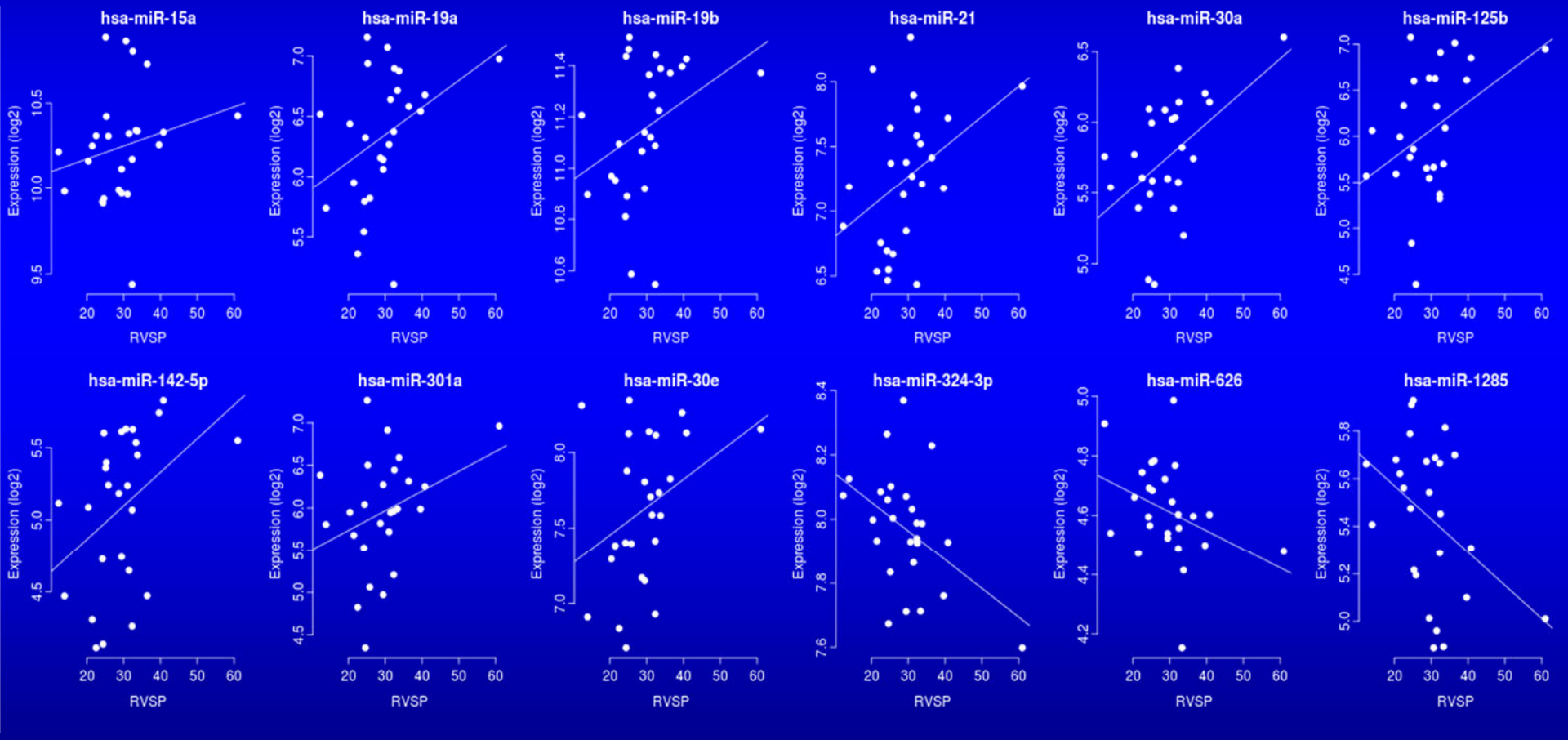
MAF= Minor allele Frequency; OR= Odds Ratio, * = adjusted for cohort

- Genetic studies also highlight GALNT13 as a potential candidate gene associated with elevated RVSP in SCD and further strengthen the specificity of the biomarker for elevated RVSP.

Desai, AA, Am J Respir Crit Care Med. 2012;186(4):359-68

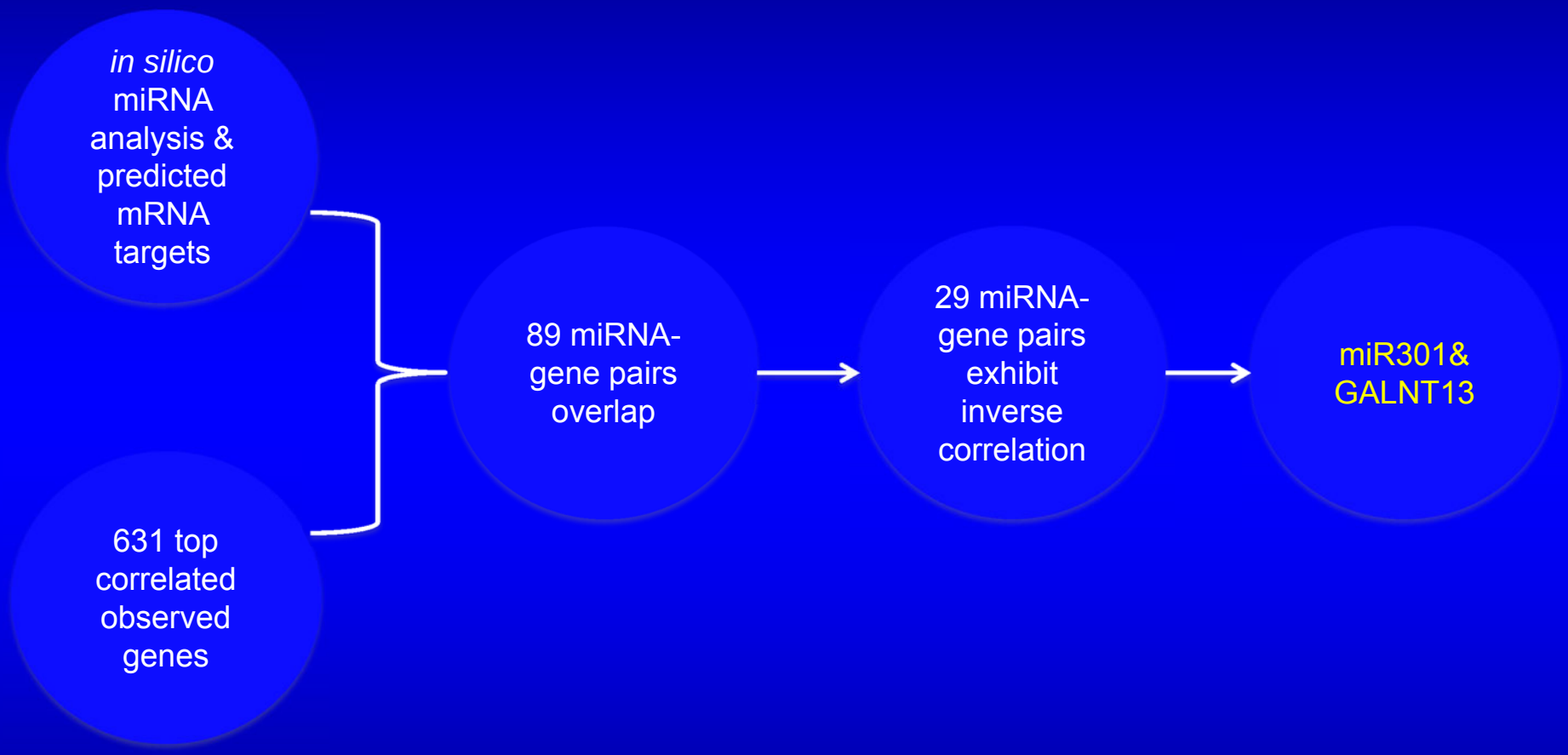
Elevated RVSP Signature miRNAs

- Correlation analysis between miRNA expression levels and RVSP (ρ_R^2 > 0.15) yielded 12 unique miRNAs.



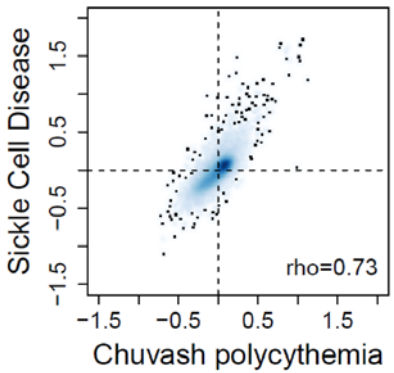
Desai, AA, Am J Respir Crit Care Med. 2012;186(4):359-68

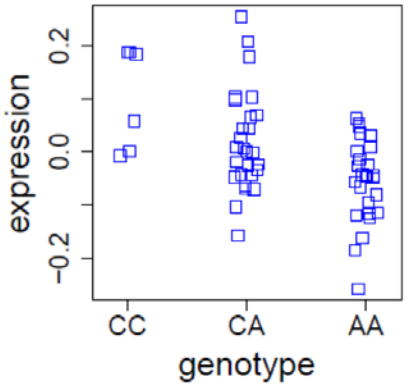
Gene-miRNA Integrative Analyses

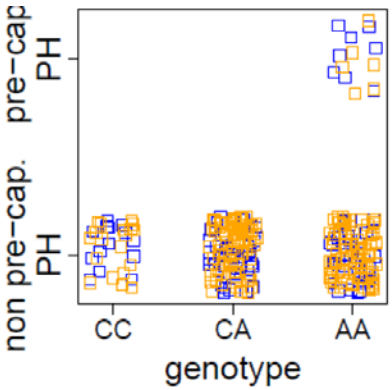


- The presence of GALNT13, a signature gene, further strengthens the association of the gene signature to elevated RVSP and highlights it as a potential candidate gene in SCD

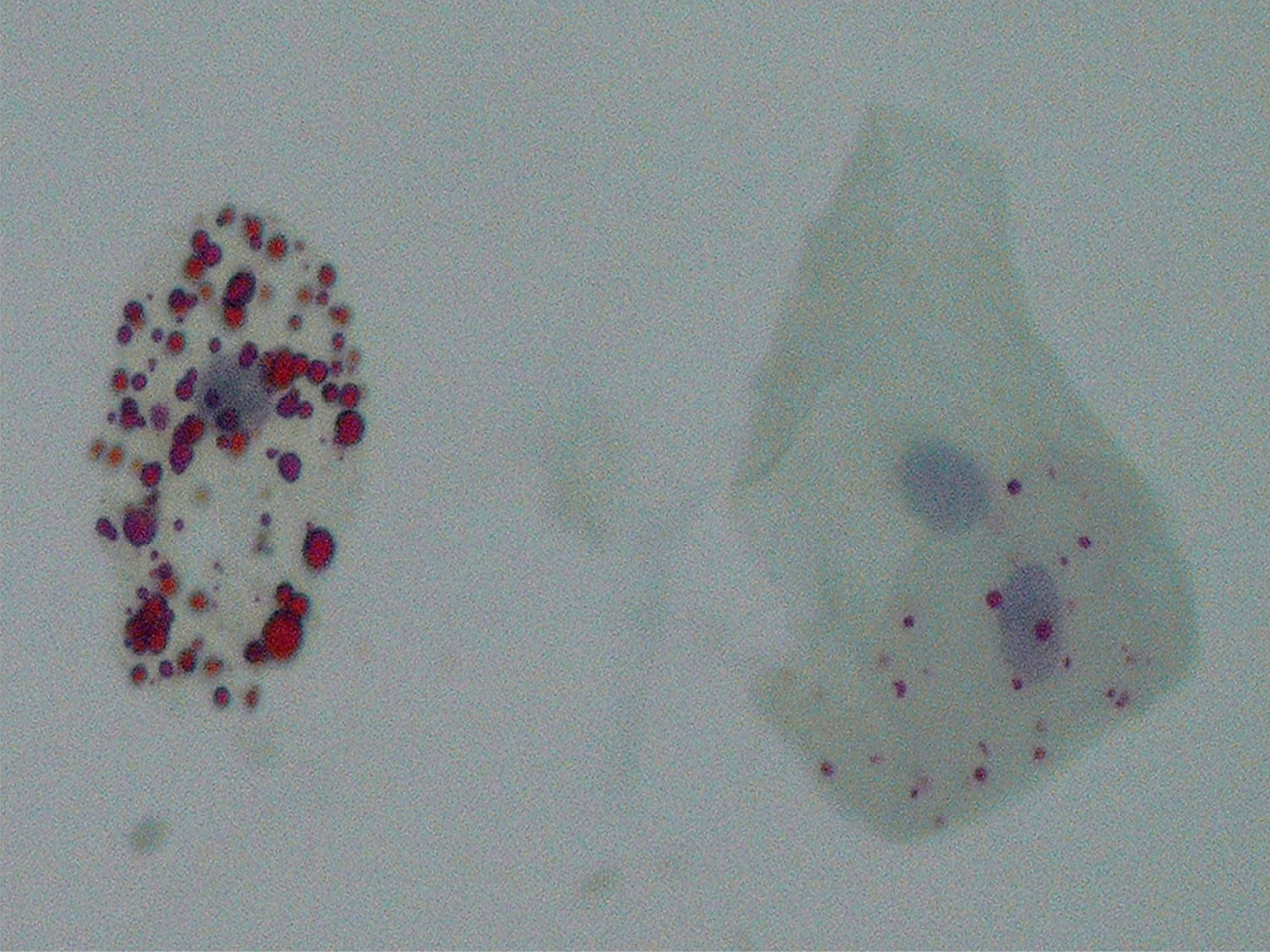
MAPK8 and Pulmonary Hypertension





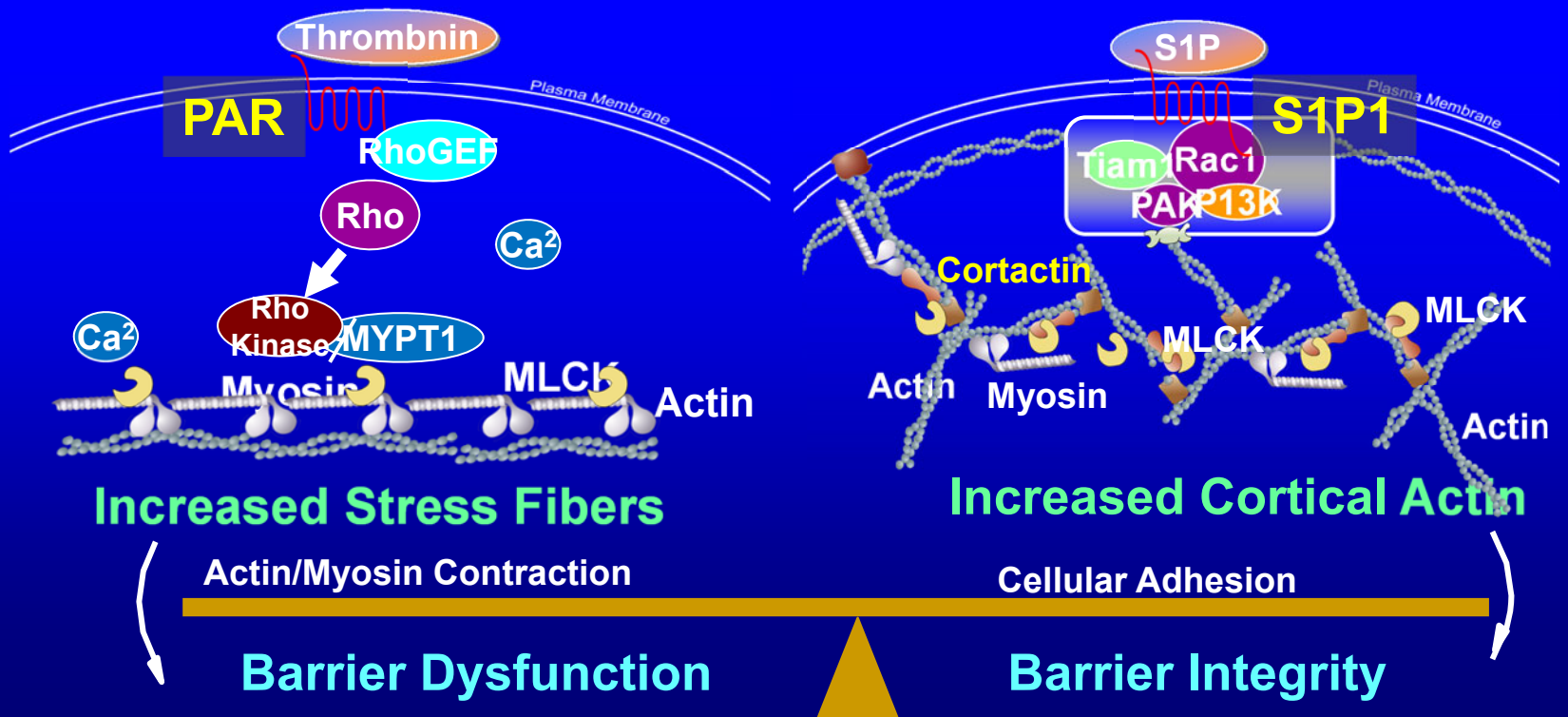


Cohort	Samples analyzed	Genotype: Non pre-capillary pulmonary hypertension			Genotype: pre-capillary pulmonary hypertension			Armitage trend test		logistic regression	
		CC	CA	AA	CC	CA	AA	r	P	OR	P
UIC	All patients	28	108	94	0	0	8	0.19	0.0039	4.4	0.00037
	[a]TRV <2.5 m/sec or patients with right heart cath	14	40	34	0	0	8	0.30	0.0033	5.4	0.00011
Walk-PHaSST	All patients	64	233	216	0	0	6	0.11	0.011	7.2	0.0025
	[a]TRV <2.5 m/sec or patients with right heart cath	19	82	87	0	0	6	0.17	0.019	18	0.0052

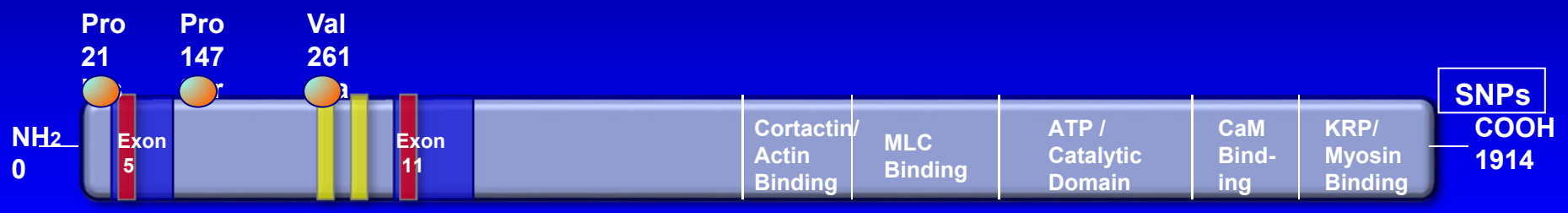


Vascular Barrier-Regulatory Pathways

- Disruption of PAEC barrier occurs during ALI and results in the movement of fluid and macromolecules into the interstitium
- EC cytoskeleton regulates cell shape and transduces signals which balance competing EC contractile forces, which generate centripetal tension, and adhesive cell-cell and cell-matrix tethering forces
- Racially-specific genetic variants in two endothelial cytoskeletal genes, myosin light chain kinase and cortactin contribute to ALI risk and subsequent severity of outcome



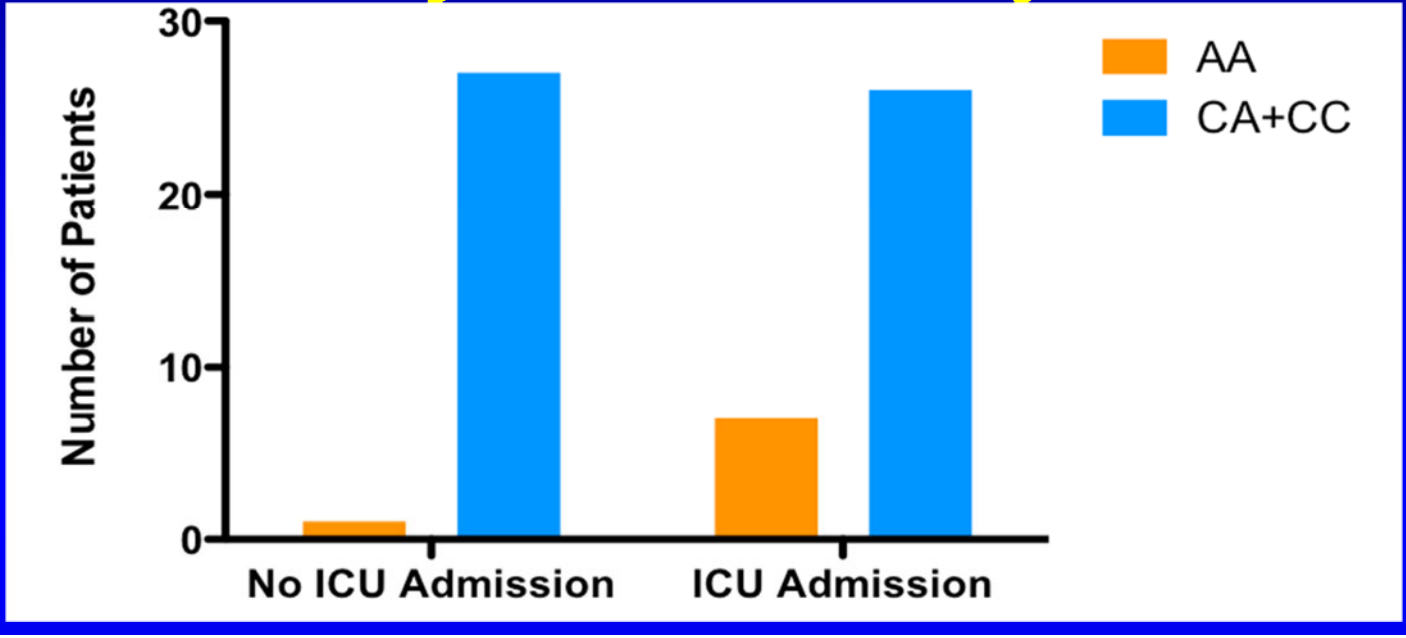
Association of Myosin Light Chain Kinase SNPs with Acute Chest Syndrome Susceptibility



- Cohort of 177 adult SCD patients

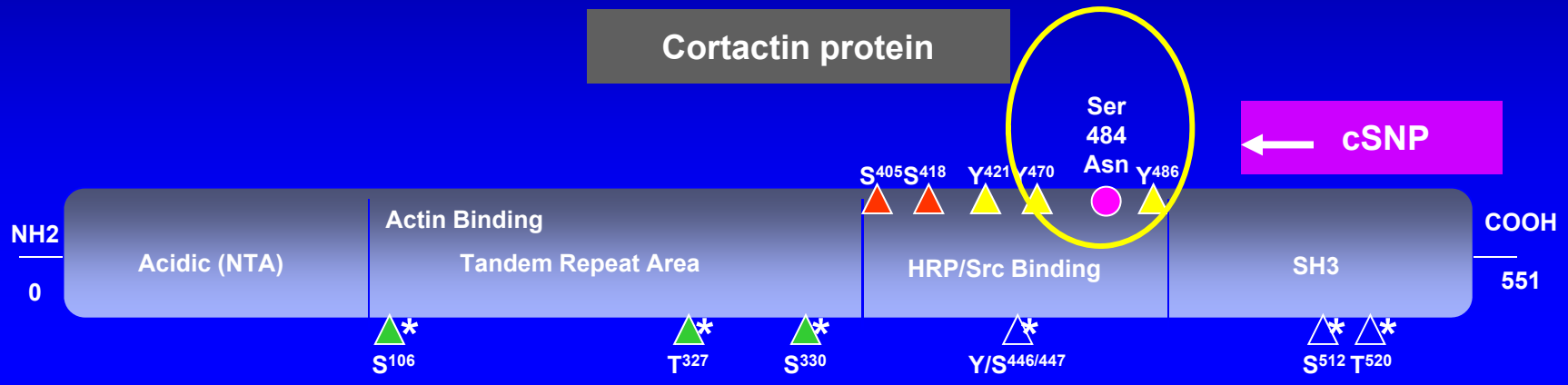
Ser147Pro	TT	TC	CC	P
No ACS	15	11	6	
≥ 1 episode ACS	56	65	18	0.95
Val261Ala	TT	TC	CC	
No ACS	10	13	9	
≥ 1 episode ACS	44	75	20	0.29
Pro21His	CC	CA	AA	
No ACS	11	16	1	
≥ 1 episode ACS	51	60	22	0.04

Association of Myosin Light Chain Kinase SNPs with Acute Chest Syndrome Severity



Pro21His	CC	CA	AA	OR (95% CI)	P
No ACS	11	16	1		
≥ 3 episodes ACS	33	31	16	6.75 (0.85-53.48)	0.02
Pro21His	CC	CA	AA		
< 3 episodes ACS	29	45	7		
≥ 3 episodes ACS	33	31	16	2.64 (1.02-6.83)	0.04
Pro21His	CC	CA	AA		
No ICU for admission ACS	11	16	1		
≥ 1 ICU for admission ACS	13	13	7	7.27 (0.84-63.25)	0.03

ALI Candidate Gene Approach: SNP Discovery in the Human Cortactin Gene



- Novel SNP (rs56162978): G>A (Ser>484>Asn)
- SNP is rare in EA (<1%); common in AA (15-20%)
- Associated with sepsis-induced ALI in preliminary patient studies

Sickle Cell-Associated Cortactin SNP = Ser484Asn

Coding SNP in EMS1 (G to A)

Serine to Asparagine

S484N

486

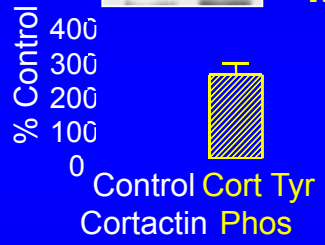
Human CRTN AEDSTYDEYE

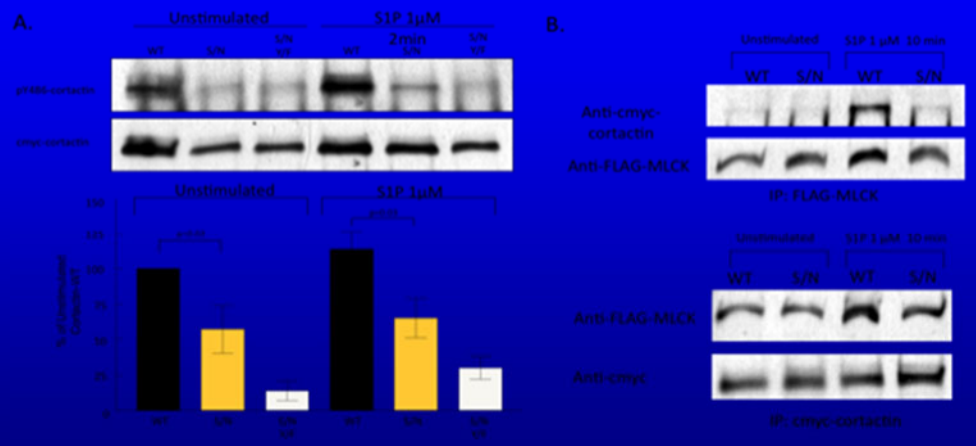
Human CRTN(S/N) AEDNTYDEYE

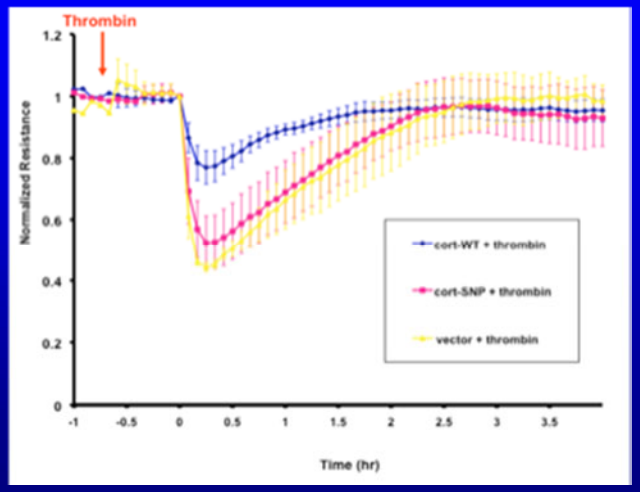
484

Cortactin-MLCK Binding

MLCK

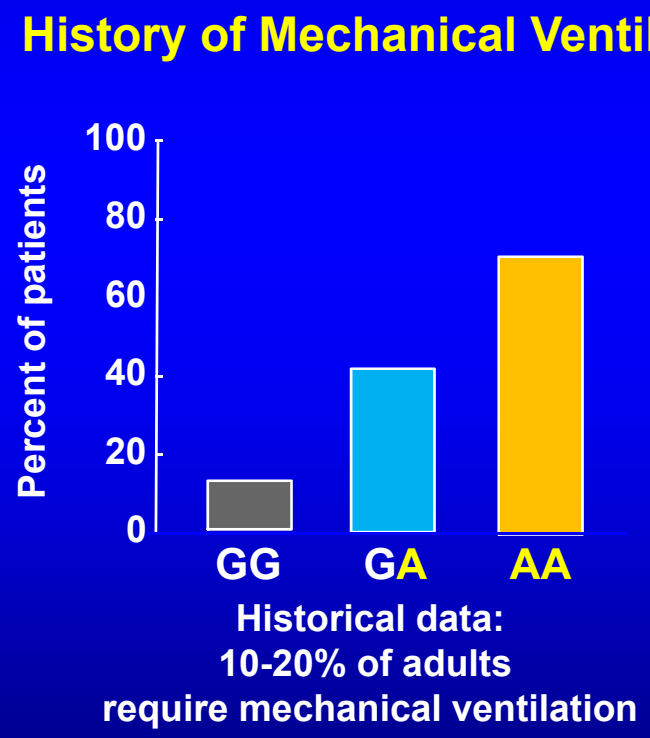




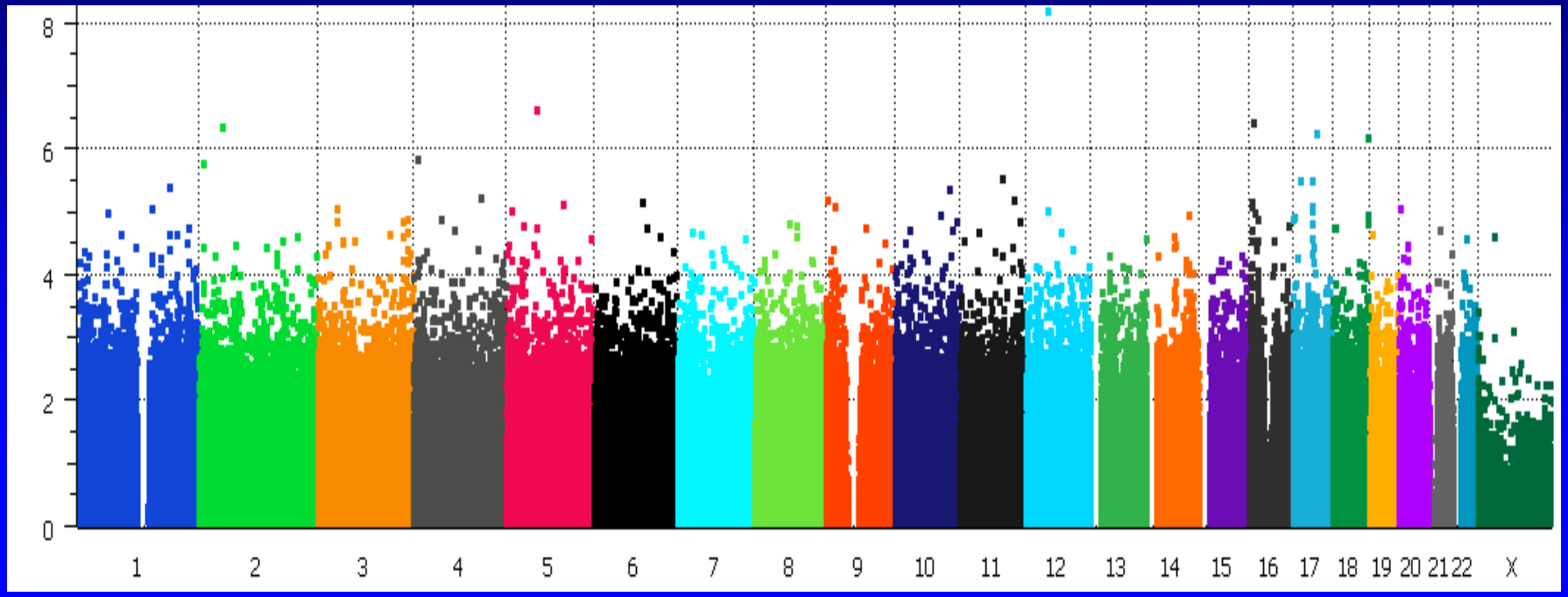


Association of Cortactin S484N with Acute Chest Syndrome Severity in Sickle Cell Patients

- Cohort of 177 adult SCD patients
- S484N *CTTN* SNP was associated significantly with increased risk for ACS (P=0.02)



Genomewide Association Study in ACS



- SCD patients with (n=206) and without (n=41) ACS
- Pan African Array
- ~ 2.2 million markers
- 90 percent coverage of YRI alleles with minor allele frequency (MAF) greater-than or equal to 2.0 percent

European Ancestry Increases ACS Risk

University of Illinois Cohort

	B	S.E.	Wald	df	Sig.	OR	95% C.I.for OR	
							Lower	Upper
Age	-.032	.018	3.158	1	.076	.968	.934	1.003
Hb SS/Sbeta0	1.640	.479	11.735	1	.001	5.157	2.017	13.180
WAA Binary	**-.881**	**.447**	**3.879**	**1**	**.049**	**.414**	**.172**	**.996**
Gender	.262	.441	.352	1	.553	1.299	.547	3.085
Constant	1.794	.717	6.260	1	.012	6.012		

Walk PHASST Screening Cohort

	B	S.E.	Wald	df	Sig.	OR	95% C.I.for OR	
							Lower	Upper
Age	.009	.007	1.649	1	.199	1.009	.995	1.023
Gender	.081	.181	.197	1	.657	1.084	.760	1.547
Hb SS/Sbeta0	.570	.220	6.697	1	.010	1.768	1.148	2.722
WAA	**-5.508**	**2.446**	**5.073**	**1**	**.024**	**.004**	**.000**	**.489**
Constant	-.031	.279	.012	1	.913	.970		

Summary: Genetics/Genomics

- A PBMC-derived gene signature is a novel biomarker of PH in SCD
- Beyond biomarker discovery, GALNT13 and MAPK8 are potential candidate gene associated with PH in SCD
- Cytoskeletal proteins that affect pulmonary vascular barrier function are novel candidate genes in ACS
- The use of population-optimized GWAS platforms may unravel new candidate genes in pulmonary complications of SCD
- Population structure and admixture influence the risk of ACS
- European ancestry is associated with ACS risk in two independent cohorts

Acknowledgements

- Victor Goreduk
- Steve Dudex
- Rick Kittles
- Joe G N Garcia
- Mark Gladwin (University of Pittsburgh)
- Xu Zhang
- Wei Zhang
- Taimur Abbasi
- Michael Wade

- K23HL098454
- R01HL111656-01

NIH National Heart, Lung, and Blood Institute

Update on Pulmonary Complications of Sickle Cell Disease

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Institute for Personalized Respiratory Medicine
Section of Pulmonary and Critical Care, Allergy and Sleep
University of Illinois at Chicago College of Medicine

UIC

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Cortactin SNP Ser484Asn in Sickle Cell Disease

- Two case groups:
  - 94 Sickle Cell patients from Univ. of Chicago cohort
  - 125 Sickle Cell patients from PUSH study (Howard Univ.)
- 132 Univ. of Chicago AA controls

Freq. A allele in control	Freq. A allele in cases	Dominant model OR	Dominant p-value
0.16	0.22	1.80 (1.12-2.92)	*0.02*

Cortactin SNP Ser484Asn in Sickle Cell Disease

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Acknowledgements

- Jiwang Chen
- Justin Sysol
- Jaime Torres
- Abhrahim Fahs

- Krystyna Shioura
- Sakshi Sahni
- Hisao Yamamura
- Liliana Moreno
- Carrie Evenoski
- Sara Camp
- Eddie Chiang
- Taimur Abbasi
- Michael Wade

- Joe G.N. Garcia
- Jason Yuan

- Raed Dweik (Cleveland Clinic)

- K23HL098454
- R01HL111656-01
- UIC Areas of Excellence Research Award

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NIH National Heart, Lung, and Blood Institute

Methods

- Genomic analyses
  - Two cohorts: Discovery (n=27) and Validation (n=20, RHC-defined PH)
  - Stepwise analytical approach
  - Correlation analysis to select the top genes and miRNAs based on strength of association between levels of expression and RVSP
  - SVM analysis to filter the top correlated genes & define RVSP signature

- Genetic Analyses (SNP discovery)
  - One SCD cohort (n=112)
  - Used simple case-control candidate gene approach searching for SNPs within the RVSP signature genes
  - Minor Allele Frequency >0.05, genotyping rate >90%, and HWE >1E-6

Desai, AA, Am J Respir Crit Care Med. 2012;186(4):359-68

Characteristics of SCD patients- Discovery Cohort

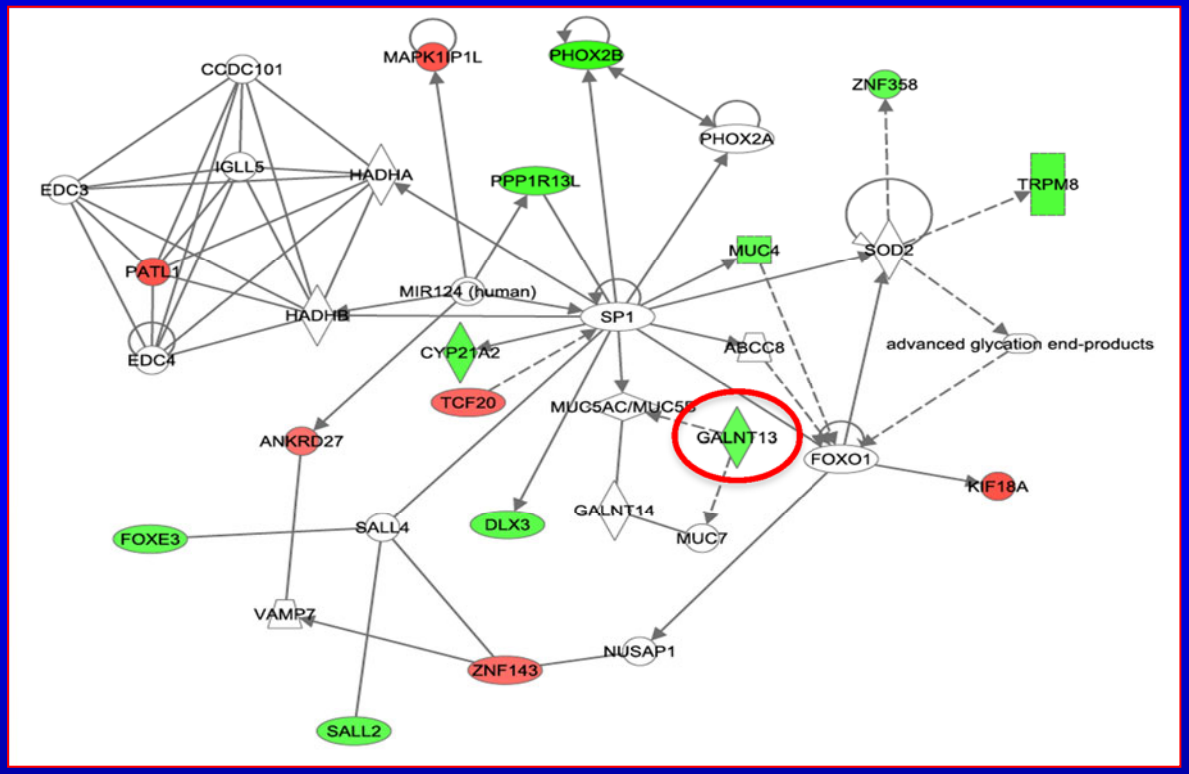
- No significant differences in clinical characteristics across the two groups separated by elevated and normal RVSP in SCD.

	Elevated RVSP (n=18)	Normal RVSP (n=9)	P value
Age (yrs)	34.7 ± 8.1	29.5 ± 6.2	0.10
Female / Male (n=)	13 / 5	3 / 6	0.06
Genotype- Hemoglobin SS	18	9	NA
Body mass index (kg/m^2)	21.9 ± 2.6	22.6 ± 4.5	0.64
Systolic Blood Pressure (mm Hg)	119 ± 19	115 ± 14	0.60
Diastolic Blood Pressure (mm Hg)	69 ± 13	59 ± 13	0.06
Hydroxyurea Therapy (n=)	16 (88%)	8 (88%)	1.00
History of acute chest syndrome (n=)	18	7	0.10
WBC Count (10^{-3}/mm^3)	10.0 ± 3.1	11.1 ± 5.1	0.49
Hemoglobin (g/dl)	8.1 ± 1.1	7.4 ± 1.1	0.17
Platelet Count (10^{-3}/mm^3)	383 ± 94	346 ± 113	0.39
Creatinine (mg/dl)	0.85 ± 0.61	0.73 ± 0.28	0.59
Ferritin (mg/liter)	2204 ± 2910	1664 ± 1546	0.61
RVSP (mm Hg)	33.5 ± 7.9	20.9 ± 4.8	<0.01

Desai, AA, Am J Respir Crit Care Med. 2012;186(4):359-68

Gene Signature for Elevated RVSP: Network Analysis

- 613 gene list was submitted to Ingenuity pathway analysis to identify gene association networks enriched with differentially expressed genes in SCD-related elevated RVSP with focus on selected signature genes

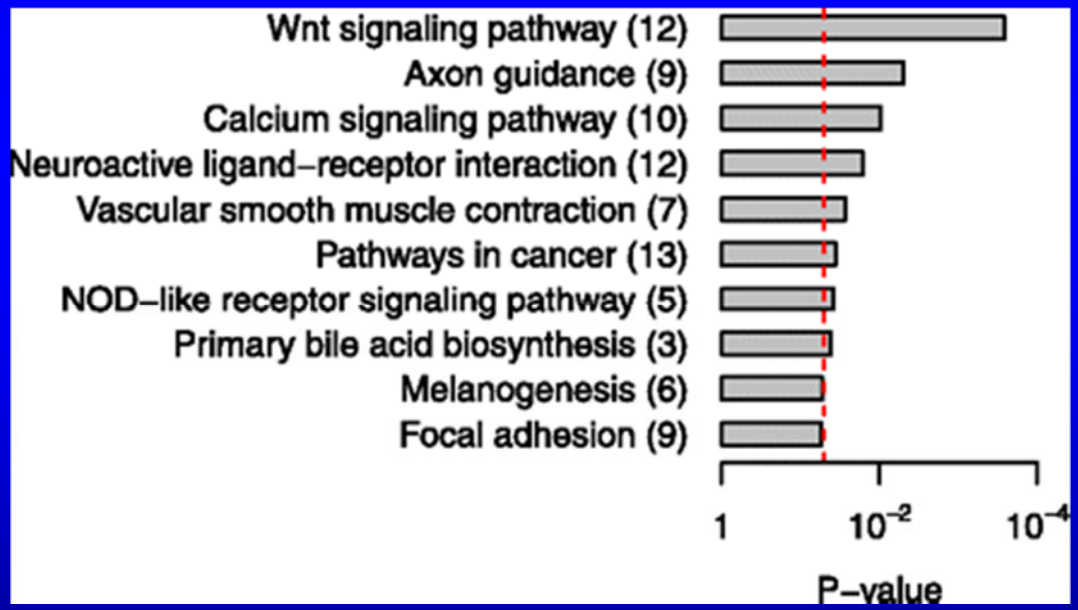


- Network involving *GALNT13* among a variety of top genes correlated with an elevated RVSP which are involved in cancer, cellular growth and proliferation and genetic disorders

Desai, AA, Am J Respir Crit Care Med. 2012;186(4):359-68

Gene Signature for Elevated RVSP

- Correlation analysis between gene expression levels and RVSP yielded 631 transcripts
- Biological pathway analysis revealed Wnt signaling, axon guidance, calcium signaling, neuroactive ligand–receptor interaction, vascular smooth muscle contraction, cancer, NOD-like receptor signaling, and primary bile acid biosynthesis pathways as the most significantly represented in patients with elevated RVSP



- The majority of these pathways have been linked to PH, strengthening the association of the microarray data to PH in SCD

Desai, AA, Am J Respir Crit Care Med. 2012;186(4):359-68

Pubmatrix evaluation of signature genes

- PBMC-derived gene signature was evaluated with PubMatrix, an automated biomedical literature search engine which enumerates citations of genes linked to PH-related biological processes in Pubmed.

Gene Names	Gene Symbols	PH	Inflammation	Cell Proliferation	Angiogenesis	Coagulation	Hypoxia
Myosin light chain 10, regulatory	MYL10	1	3	5	2	1	5
Adenosine A2b receptor	ADORA2B	27	88	50	17	1	50
Complement component 1, q subcomponent binding protein	C1QBP	0	35	25	0	10	0
Arginine decarboxylase	ADC	58	369	66	16	98	231
Proline/arginine-rich end leucine-rich repeat protein	PRELP	0	1	3	0	0	0
SAM pointed domain containing ets transcription factor	SPDEF	0	3	11	2	0	0
UDP-N-acetyl-alpha-D-galactos-amine:polypeptide N-acetylgalactosa	**GALNT13**	**0**	**0**	**0**	**0**	**0**	**0**
Solute carrier family 27, member 5	SLC27A5	0	0	0	0	0	0
N-acetyltransferase 8-like	NAT8L	0	0	0	0	0	0
Chrom 9 open reading frame 16	C9orf16	0	0	0	0	0	0

- Pubmatrix evaluation reveals that a PBMC-derived molecular signature is composed of genes that have been established in PH processes and also potentially novel genes that have not been identified in these processes

Desai, AA, Am J Respir Crit Care Med. 2012;186(4):359-68

Characteristics of SCD patients- Validation Cohort

	Validation Cohort (n=20)		
	PH (n=10)	No PH (n=10)	P value
Age (yrs)	49.3 ± 7.4	30.2 ± 8.0	<0.01
Female / Male	4 / 6	7 / 3	0.43
Genotype- Hemoglobin SS	10	10	NA
Body mass index (kg/m^2)	27.2 ± 13.7	20.5 ± 2.9	0.08
Systolic Blood Pressure (mm Hg)	132 ± 19	114 ± 12	0.01
Diastolic Blood Pressure (mm Hg)	77 ± 14	65 ± 11	0.03
Hydroxyurea Therapy (n=)	5 (50%)	8 (80%)	0.69
History of acute chest syndrome (n=)	8 (80%)	8 (80%)	1.00
WBC Count ($10^{-3}/mm^3$)	6.2 ± 2.4	8.3 ± 2.5	0.03
Hemoglobin (g/dl)	8.4 ± 1.2	9.1 ± 1.6	0.2
Platelet Count ($10^{-3}/mm^3$)	315 ± 134	326 ± 104	0.79
Creatinine (mg/dl)	2.5 ± 2.7	0.6 ± 0.1	<0.01
Ferritin (mg/liter)	1959 ± 1518	718 ± 597	0.03
RVSP (mm Hg)	43.2 ± 13.3	26.3± 2.5	<0.01
Mean Pulmonary artery pressure (mm Hg)	37.8 ± 8.7		
Cardiac output (L/min)/ Cardiac index ($L/min/m^2$)	9.9 ± 1.7 / 5.5 ± 1.7		
Pulmonary vascular resistance (WU)	2.1 ± 1.4		

GALNT13: Novel PH Candidate Gene?

- GALNT13 encodes a glycosyltransferase enzyme responsible for the synthesis of O-glycan
- Aberrant glycosylation patterns are a hallmark of the tumor phenotype influencing proliferation, invasion, angiogenesis, and metastasis
- We speculate that GALNT13 and glyocosylation patterns may be novel candidates in PH in SCD given the potential role of these processes in pulmonary vascular remodeling