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VEITHSYMPOSIUM  
Connecting The Vascular Community

## Genetics and Venous Disease

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## Disclosures

- N/A

## Personalised medicine

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European Alliance for Personalised Medicine

The Precision Medicine Initiative Cohort Program - Building a Research Foundation for 21<sup>st</sup> Century Medicine

## Personalised medicine

Imperial College London

Personalised Medicine

### Systematic review

#### Pathogenesis of primary varicose veins

C. S. Lian and A. H. Davies  
Imperial Vascular Unit, St. George's Hospital, Cranmer Terrace, London SW17 0QT, UK  
Correspondence to Professor A. H. Davies (a.h.davies@imperial.ac.uk)

Stress to the vein wall (e.g. hypoxia, mechanical stretch, shear stress)  
Endothelial injury and subsequent inflammation

**Venous hypertension**

**Vein wall changes**

**Proteolytic factors**

**Vein wall weakening and repair**

**Pathophysiology of Chronic Venous Disease and Venous Ulcers**

Joseph D. Raffetto, MD<sup>1,2,3,4</sup>

Genetic predisposition, low shear stress, CMV injury, endothelial dysfunction, activation

Endothelial dysfunction, altered endothelial permeability

Leukocyte adhesion, migration, and transmigration

EC activation, adhesion, ICAM-1, VCAM-1, ELAM-1, MCP-1, MCP-2 expression

Remodelling and disruption of leukocyte/endothelium

Activated T lymphocytes

Proinflammatory matrix metalloproteinases (MMPs)

Proteolytic activity, collagen/elastin degradation

IL-1, TNF- $\alpha$ , chemokines (IL-6, MCP-1) locally expressed



## Systems biology

### GENOME

### PHENOME

## Why genetics?


- Heritability
- Major risk factor

**ORIGINAL ARTICLE**  
 Linkage to the FOXC2 region of chromosome 16 for varicose veins in otherwise healthy, unselected sibling pairs  
 N. Y. M. Ng, T. Andrews, T. D. Spector, S. Jeffery representing the Lymphoedema Consortium  
J. Med. Genet. 2005;42:225-229. doi: 10.1136/jmg.2004.026071

## Approaches

- Gene expression
  - Differences between healthy and diseased tissue
  - Models – stretch, pressure
  - Unable to determine causation





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  - Differences between healthy and diseased tissue
  - Models – stretch, pressure
  - Unable to determine causation
- Candidate gene approach
  - Existing knowledge of congenital abnormalities
  - Hypothesis driven



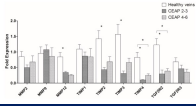

## Approaches

- Gene expression
  - Differences between healthy and diseased tissue
  - Models – stretch, pressure
  - Unable to determine causation
- Candidate gene approach
  - Existing knowledge of congenital abnormalities
  - Hypothesis driven
- Genome Wide Association Studies – GWAS
  - Large datasets
  - Data quality

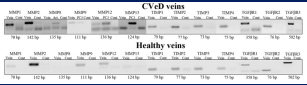
## Gene expression

- Extracellular matrix degradation
  - MMPs
  - TIMPs
  - ADAMTS



International Journal of Molecular Medicine

**2005**  
 Variability of MMP/TIMP and TGF-β1 Receptors throughout the Clinical Progression of Chronic Venous Disease  
Polina Semelkova<sup>1,2</sup>, D. Anahita-Nasab<sup>1</sup>, Silvia Galante<sup>1</sup>, Claudia Miao<sup>1</sup>, Carlos M. Cordero-Arenas<sup>3,4</sup> and Roberto Navea<sup>1</sup>



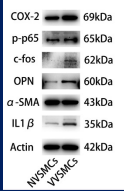
## Gene expression

- Extracellular matrix degradation
  - MMPs
  - TIMPs
  - ADAMTS
- Angiogenesis
  - c-fos

FROM BENCH TO BEDSIDE

Elevated c-fos expression is correlated with phenotypic switching of human vascular smooth muscle cells derived from lower limb venous varicosities

Zhenqin Guo, BS<sup>1</sup>, Chenchen Luo, BS<sup>1</sup>, Ting Zhu, PhD<sup>1</sup>, Li Li, MD<sup>1</sup>, and Wen Zhang, MD<sup>1</sup> Shanghai Children's Health Center



## Gene expression

- Extracellular matrix degradation
  - MMPs
  - TIMPs
  - ADAMTS
- Angiogenesis
  - cfos
  - CLOCK

**Biomechanical stretch-induced CLOCK upregulation in venous smooth muscle cells promotes phenotypic and functional transformation**

Zhenyu Guo<sup>1,2</sup>, Wux Zhang<sup>1,2</sup>, Xu Li<sup>1,2</sup>, Tao Wang<sup>1</sup>, Xiaohu Yang<sup>1</sup>, Longhua Fan<sup>1,2,3</sup>

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<sup>2</sup>Department of Vascular Biology, Institute of Biomedical Science, East China University of Science and Technology, Shanghai 200201, China  
<sup>3</sup>Department of Vascular Biology, Shanghai Institute of Vascular Medicine, East China University of Science and Technology, Shanghai 200201, China

## Gene expression

- Extracellular matrix degradation
  - MMPs
  - TIMPs
  - ADAMTS
- Angiogenesis
  - cfos
  - CLOCK
- Inflammation
  - NLRCS

**NLRCS modulates phenotypic transition and inflammation of human venous smooth muscle cells by activating Wnt/β-catenin pathway via TLR4 in varicose veins**

Tao Wang, Zhenyu Guo, Wux Zhang, Xiaohu Yang, Longhua Fan, Wux Zhang

Department of Vascular Biology, Institute of Biomedical Science, East China University of Science and Technology, Shanghai 200201, China

## Candidate genes

- FoxC2
- Notch3
- PIK3CA
- COL3A1

## Genome Wide Association Studies

**Genome-wide association study of varicose veins identifies a protective missense variant in GJD3 enriched in the Finnish population**

Yan Han, Zhenyu Guo, Wux Zhang, Xiaohu Yang, Longhua Fan, Wux Zhang

Department of Vascular Biology, Institute of Biomedical Science, East China University of Science and Technology, Shanghai 200201, China

**Exome sequencing identifies novel genetic variants associated with varicose veins**

Yan Han, Zhenyu Guo, Wux Zhang, Xiaohu Yang, Longhua Fan, Wux Zhang

Department of Vascular Biology, Institute of Biomedical Science, East China University of Science and Technology, Shanghai 200201, China

Biological process	Z-scores	P-values	FDR	Number of biological genes	Genes
Arterial blood oxygen-carrying capacity	3.81	0.0002	0.023	2	DNX, VEGFA
Gene ontology enrichment	3.79	0.0002	0.023	4	EPOR, HIF1A, HIF1L, HIF1R, HIF1S, HIF1T, HIF1U, HIF1V, HIF1W, HIF1X, HIF1Y, HIF1Z, HIF1AA, HIF1AB, HIF1AC, HIF1AD, HIF1AE, HIF1AF, HIF1AG, HIF1AH, HIF1AI, HIF1AJ, HIF1AK, HIF1AL, HIF1AM, HIF1AN, HIF1AO, HIF1AP, HIF1AQ, HIF1AR, HIF1AS, HIF1AT, HIF1AU, HIF1AV, HIF1AW, HIF1AX, HIF1AY, HIF1AZ, HIF1BA, HIF1BB, HIF1BC, HIF1BD, HIF1BE, HIF1BF, HIF1BG, HIF1BH, HIF1BI, HIF1BJ, HIF1BK, HIF1BL, HIF1BM, HIF1BN, HIF1BO, HIF1BP, HIF1BQ, HIF1BR, HIF1BS, HIF1BT, HIF1BU, HIF1BV, HIF1BW, HIF1BX, HIF1BY, HIF1BZ, HIF1CA, HIF1CB, HIF1CC, HIF1CD, HIF1CE, HIF1CF, HIF1CG, HIF1CH, HIF1CI, HIF1CJ, HIF1CK, HIF1CL, HIF1CM, HIF1CN, HIF1CO, HIF1CP, HIF1CQ, HIF1CR, HIF1CS, HIF1CT, HIF1CU, HIF1CV, HIF1CW, HIF1CX, HIF1CY, HIF1CZ, HIF1DA, HIF1DB, HIF1DC, HIF1DD, HIF1DE, HIF1DF, HIF1DG, HIF1DH, HIF1DI, HIF1DJ, HIF1DK, HIF1DL, HIF1DM, HIF1DN, HIF1DO, HIF1DP, HIF1DQ, HIF1DR, HIF1DS, HIF1DT, HIF1DU, HIF1DV, HIF1DW, HIF1DX, HIF1DY, HIF1DZ, HIF1EA, HIF1EB, HIF1EC, HIF1ED, HIF1EE, 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HIF1SS, HIF1ST, HIF1SU, HIF1SV, HIF1SW, HIF1SX, HIF1SY, HIF1SZ, HIF1TA, HIF1TB, HIF1TC, HIF1TD, HIF1TE, HIF1TF, HIF1TG, HIF1TH, HIF1TI, HIF1TJ, HIF1TK, HIF1TL, HIF1TM, HIF1TN, HIF1TO, HIF1TP, HIF1TQ, HIF1TR, HIF1TS, HIF1TT, HIF1TU, HIF1TV, HIF1TW, HIF1TX, HIF1TY, HIF1TZ, HIF1UA, HIF1UB, HIF1UC, HIF1UD, HIF1UE, HIF1UF, HIF1UG, HIF1UH, HIF1UI, HIF1UJ, HIF1UK, HIF1UL, HIF1UM, HIF1UN, HIF1UO, HIF1UP, HIF1UQ, HIF1UR, HIF1US, HIF1UT, HIF1UU, HIF1UV, HIF1UW, HIF1UX, HIF1UY, HIF1UZ, HIF1VA, HIF1VB, HIF1VC, HIF1VD, HIF1VE, HIF1VF, HIF1VG, HIF1VH, HIF1VI, HIF1VJ, HIF1VK, HIF1VL, HIF1VM, HIF1VN, HIF1VO, HIF1VP, HIF1VQ, HIF1VR, HIF1VS, HIF1VT, HIF1VU, HIF1VV, HIF1VW, HIF1VX, HIF1VY, HIF1VZ, HIF1WA, HIF1WB, HIF1WC, HIF1WD, HIF1WE, HIF1WF, HIF1WG, HIF1WH, HIF1WI, HIF1WJ, HIF1WK, HIF1WL, HIF1WM, HIF1WN, HIF1WO, HIF1WP, HIF1WQ, HIF1WR, HIF1WS, HIF1WT, HIF1WU, HIF1WV, HIF1WW, HIF1WX, HIF1WY, HIF1WZ, HIF1XA, HIF1XB, HIF1XC, HIF1XD, HIF1XE, HIF1XF, HIF1XG, HIF1XH, HIF1XI, HIF1XJ, HIF1XK, HIF1XL, HIF1XM, HIF1XN, HIF1XO, HIF1XP, HIF1XQ, HIF1XR, HIF1XS, HIF1XT, HIF1XU, HIF1XV, HIF1XW, HIF1XX, HIF1XY, HIF1XZ, HIF1YA, HIF1YB, HIF1YC, HIF1YD, HIF1YE, HIF1YF, HIF1YG, HIF1YH, HIF1YI, HIF1YJ, HIF1YK, HIF1YL, HIF1YM, HIF1YN, HIF1YO, HIF1YP, HIF1YQ, HIF1YR, HIF1YS, HIF1YT, HIF1YU, HIF1YV, HIF1YW, HIF1YX, HIF1YY, HIF1YZ, HIF1ZA, HIF1ZB, HIF1ZC, HIF1ZD, HIF1ZE, HIF1ZF, HIF1ZG, HIF1ZH, HIF1ZI, HIF1ZJ, HIF1ZK, HIF1ZL, HIF1ZM, HIF1ZN, HIF1ZO, HIF1ZP, HIF1ZQ, HIF1ZR, HIF1ZS, HIF1ZT, HIF1ZU, HIF1ZV, HIF1ZW, HIF1ZX, HIF1ZY, HIF1ZZ

## PRIMER

### Mendelian randomization

Elisavir Sandanger<sup>1,2,3</sup>, M. Alvaro Ojeda<sup>4</sup>, Michael F. Feeney<sup>1,2,3</sup>, Bjornar Wang<sup>1,2,3</sup>, Joon-Min Park<sup>1,2,3</sup>, Monica R. Krawiec<sup>1,2,3</sup>, Ben Palmer<sup>1,2,3</sup>, C. Argyropoulos<sup>1,2,3</sup>, Chris Whincup<sup>1,2,3</sup>, Qingquan Zhou<sup>1,2,3</sup> and George Davey Smith<sup>1,2,3</sup>

**Mendelian randomization**

**Randomized controlled trial**

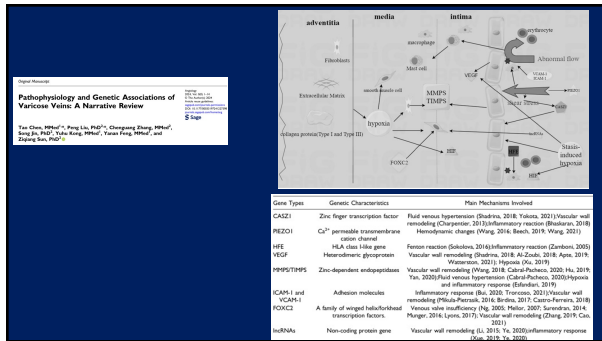
**An RCT to test whether lowering CRP lowers SBP**

**An MR study to test whether lowering CRP lowers SBP**

## Interpretation

- Genetic associations vary among ancestries
- Non additive genetic variation
- Epigenetics
- Gene environment correlations

**15 years of GWAS discovery: Realizing the promise**  
 Todd Alderson<sup>1</sup>, Lee Tong<sup>1</sup>, Katie J.H. Venous<sup>1</sup>, and Peter M. Visscher<sup>1</sup>



## Conclusion

- Increasing data from large scale population genetic studies
- Still limited understanding of clinical translation
- Heterogeneous studies
- Multidisciplinary approach
- Standardisation

PREVENTION

PROGRESSION

RECURRENCE

## Thank you