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CETL 2023

Explorations Omiques de la Maladie de Fabry

12 juin 2023

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Conflit d'intérêt

Financements : Sanofi, Takeda, Biomarin, Amicus, Alexion, Ultragenyx, Orchard.

Biomarqueurs et maladies lysosomales

Hétérogénéité clinique

Biomarqueur diagnostique

Suivi et pronostic

Biomarqueur de suivi

Biomarqueur

Diagnostic de tous les patients

Prédictif

Recherche active pour identifier de nouveaux biomarqueurs et les voies métaboliques altérées

Explorations biologiques

LysoGb3 : Plasma/DBS

Diagnostic/Suivi

Troponine NT-proBNP

Diagnostic/Suivi

Albuminurie, eGFR, créatinine

Diagnostic/Suivi

Anticorps anti-drogue

Suivi

Gb3 Plasma/Urine

Non recommandé

LysoGb3 : Urine

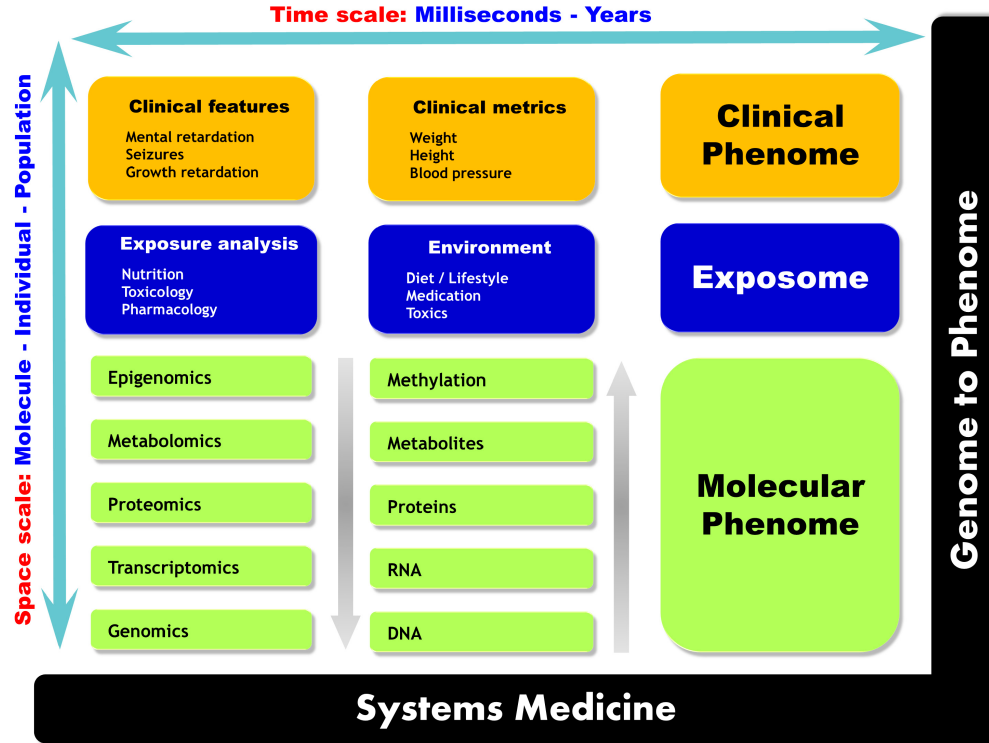
Non recommandé

Podocyturie

Non recommandé

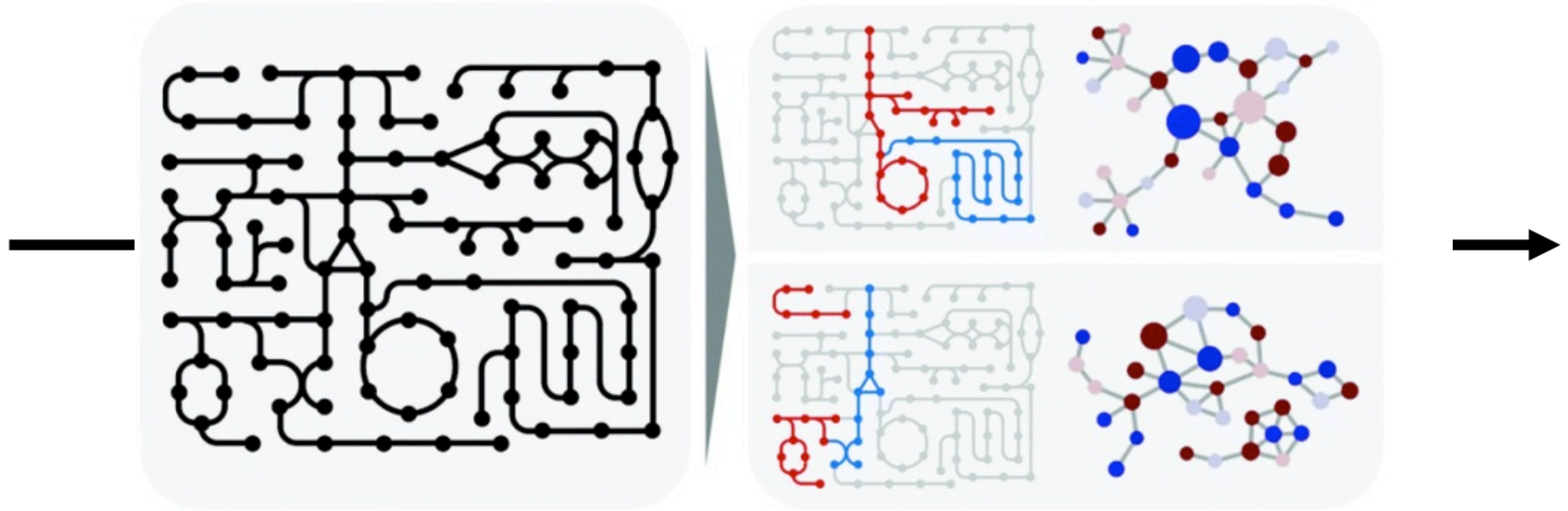
[Burlina A. Molecular Genetics and Metabolism 2023](#)

Sciences Omiques & Médecine des Systèmes



Tebani, A. *Int. J. Mol. Sci.* 2016

Organisation modulaire des réseaux biologiques : modules pathologiques



Signatures Moléculaires

Modèles prédictifs : phénotype/pronostic
Diagnostic et suivi - Stratification des patients



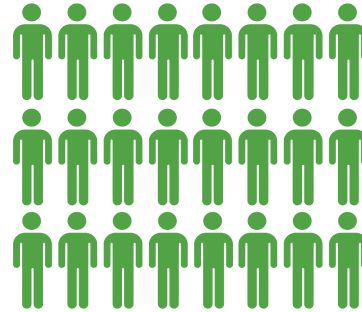
Identification de biomarqueurs



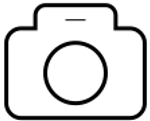
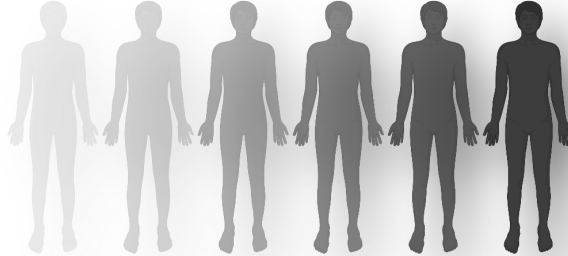
Mécanismes physiopathologiques
Nouvelles cibles thérapeutiques

Patients

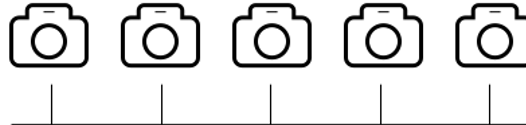
Contrôles



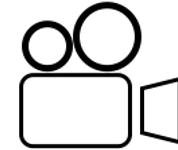
Individualité Bio-Clinique



Snapshot

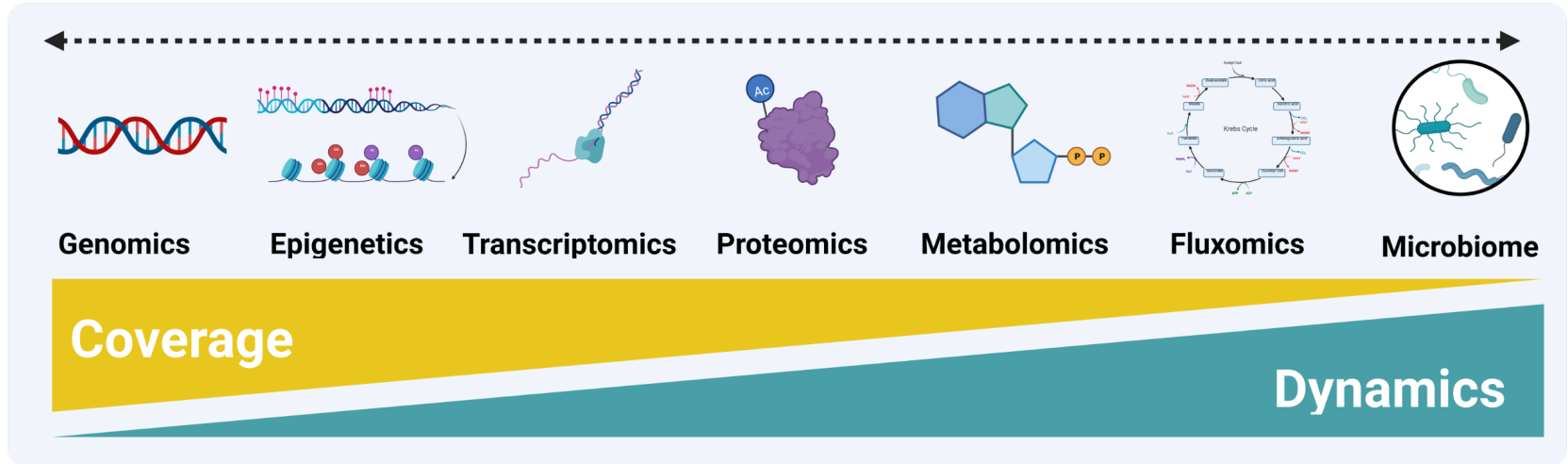


Longitudinal



Real-time

Investigations Omiques



Tebani, A. Bekri, S. *RMI*. 2022

Projet LDeep

Altérations Lysosomales

Transporteur or déficit enzymatique

Maladies Chroniques
Maladies Neurodégénératives

Maladies Rares
Lysosomal Diseases

Disease

Cohort

Mucopolysaccharidoses

G2M

Fabry disease

French Fabry

Fabry disease

Switzerland Fabry

Fabry disease

UK Fabry

Gaucher disease

French Gaucher

Cohorts

Phenotype Omics

Multimodal data

Integrative
Analysis

Deep Clinical and Molecular Phenotyping

Data-driven
modeling

Biomarker
discovery Patients
Stratification

Disease insights

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Analyses protéomique et métabolomique de plasma Fabry vs Contrôles

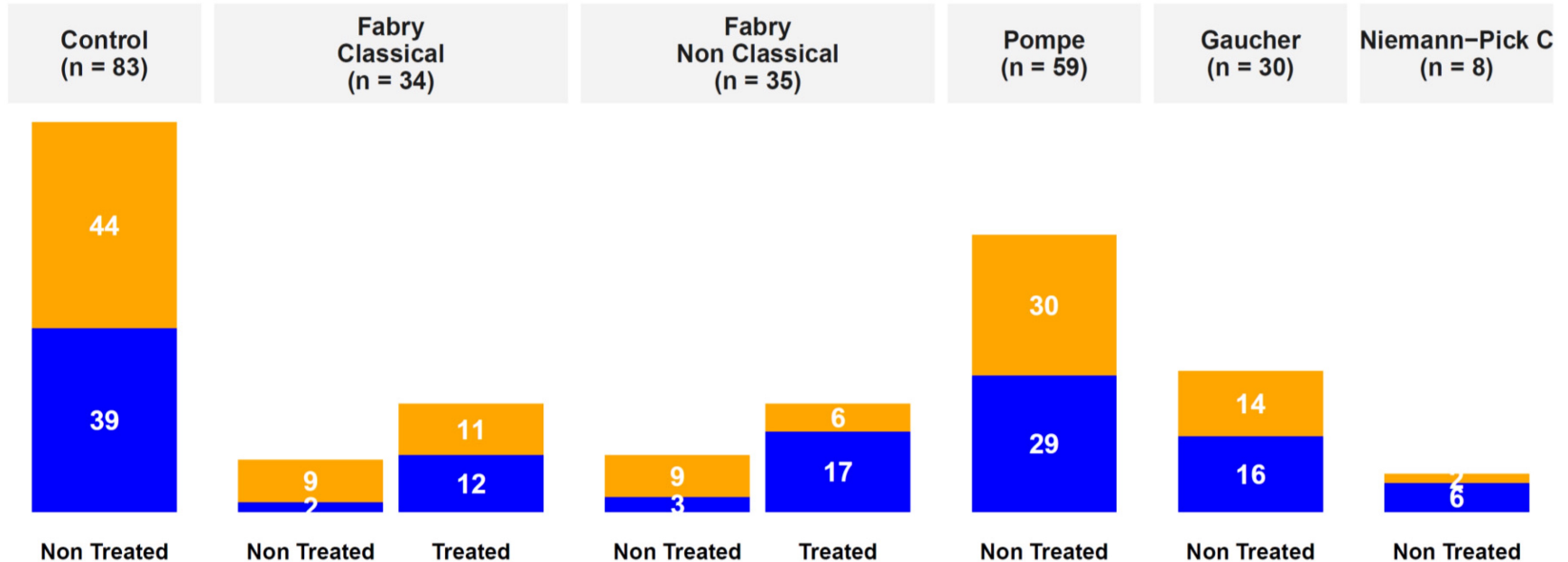
Analyse et intégration des données clinico-biologiques

Modélisation prédictive des données

Caractérisation de profils de biomarqueurs

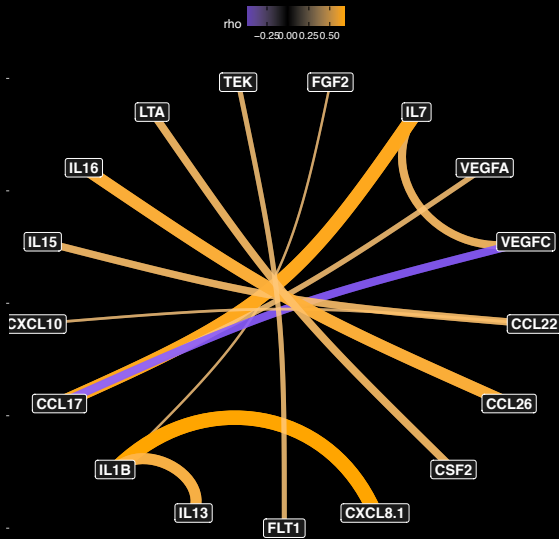
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Female Male



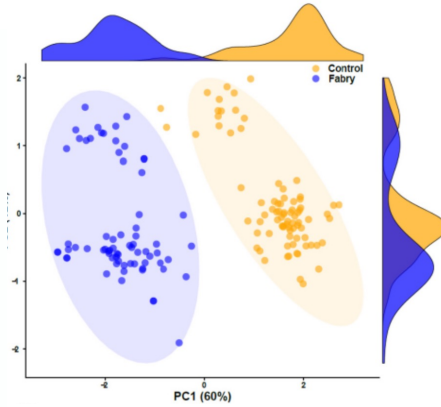
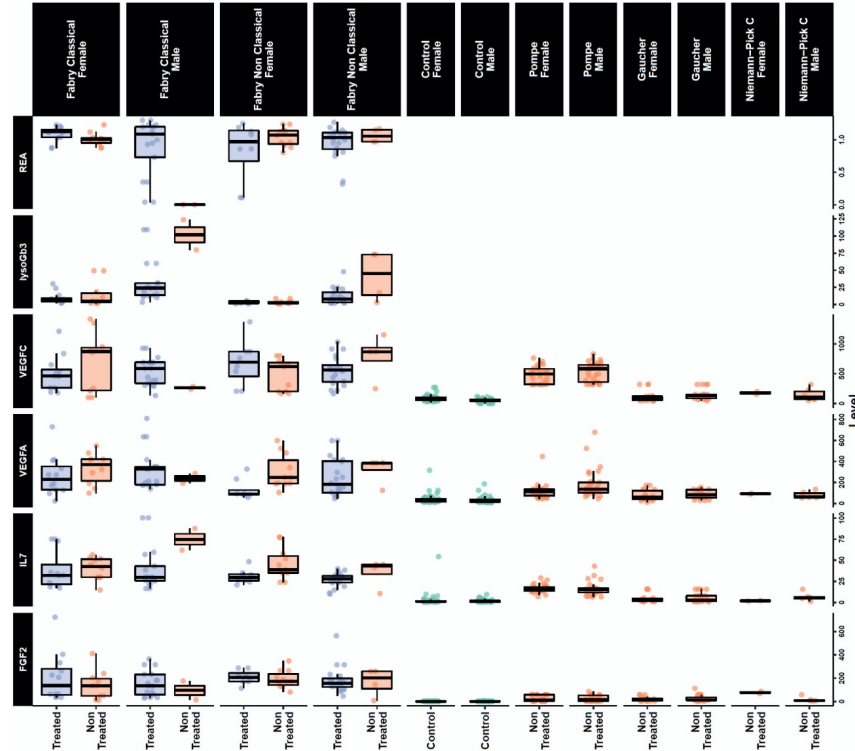
Tebani A et al. *J Clin Med* 2020;9:1325

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Tebani et al. Trans Res 2023

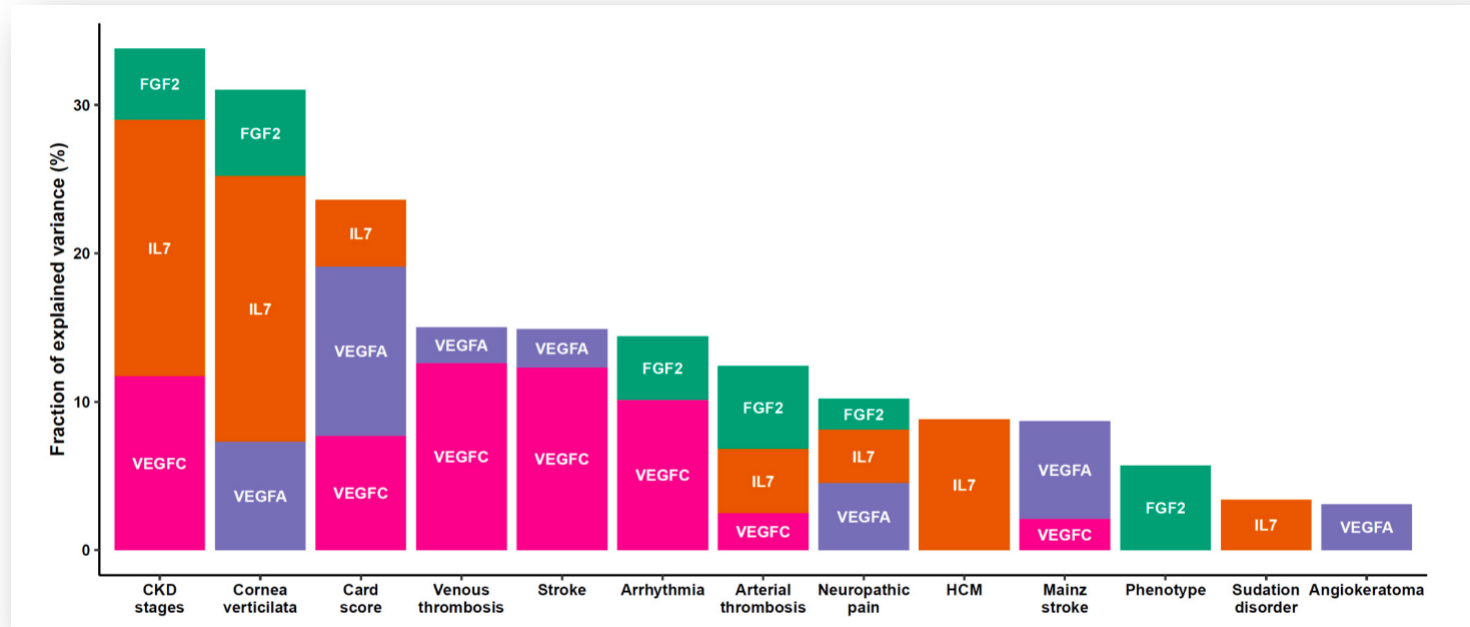
12/06/2023



IL7
 FGF2
 VEGFA
 VEGFC

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Validation sur une cohorte indépendante - Impact de l'augmentation du FGF2 et de l'IL7

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IL-7

Indispensable à la survie des cellules T¹

Intervient dans le processus autophagique²

Rôle dans la prédisposition aux processus auto-immuns³

FGF2

Régule la différenciation cellulaire, la croissance des tissus et l'angiogénèse^{5,6}

Altéré dans certains cancers et maladies cardiovasculaires⁵

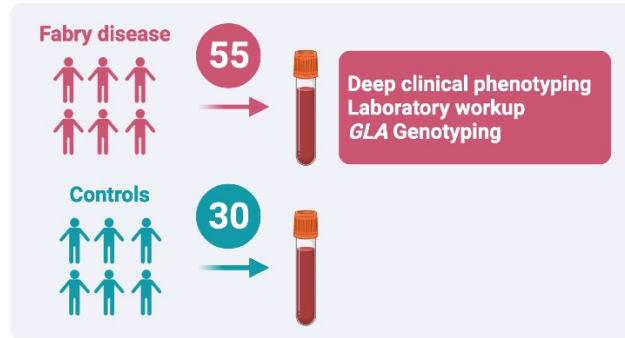
Inhibition de la voie de signalisation FGF2/FGFR → Réduction de la progression des tumeurs⁷

IL7, interleukin-7; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor

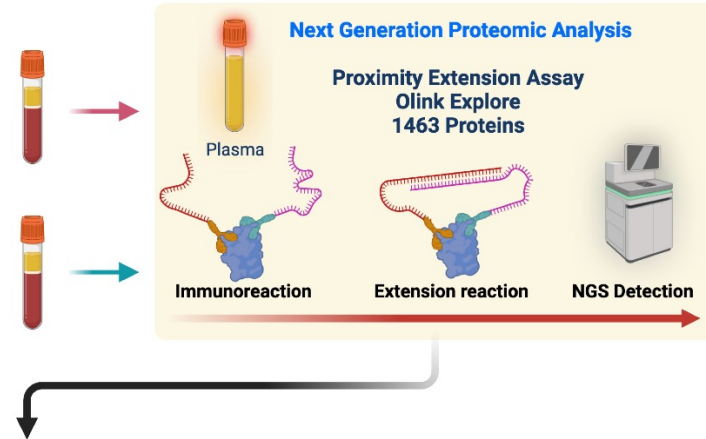
1. El Kassar N et al. *J Immunotoxicol* 2010;7:1-7;
2. McLeod IX et al. *J Immunol* 2011;187:5051-5061;
3. Lundstrom W. et al. *Semin Immunol* 2012;24:218-224;
4. Opinion personnelle
5. Beenken A et al. *Nat Rev Drug Discov* 2009;8:235-253;
6. Murakami M et al. *Curr Opin Hematol* 2008;15:215-220;
7. Cai Y et al. *Cancer Sci* 2016;107:1141-1150

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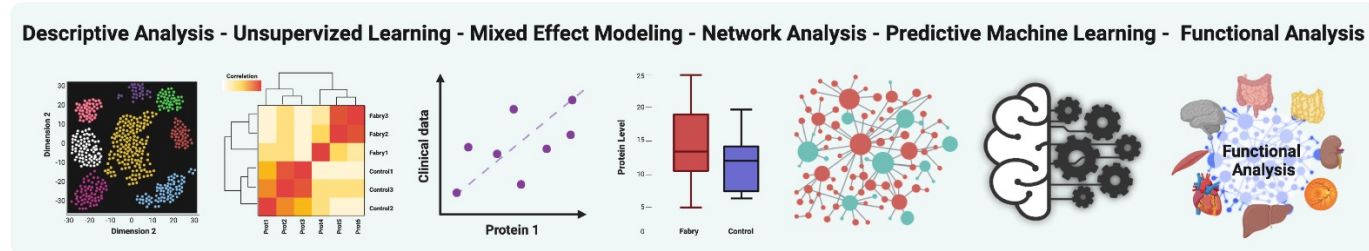
Cohort Description



Proteomic Data Generation

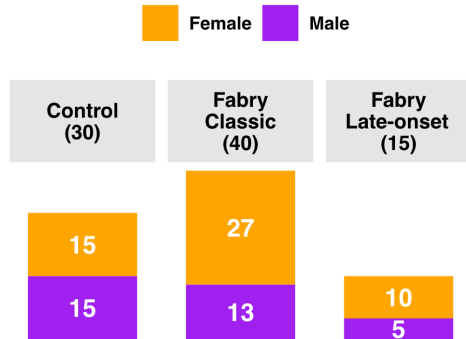


Integrative Data Analysis

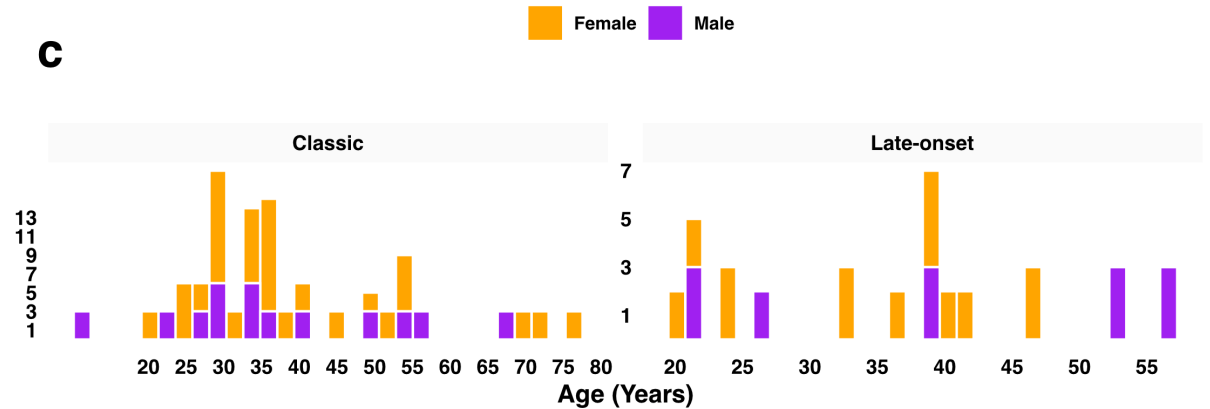


Tebani et al. Trans Res 2023

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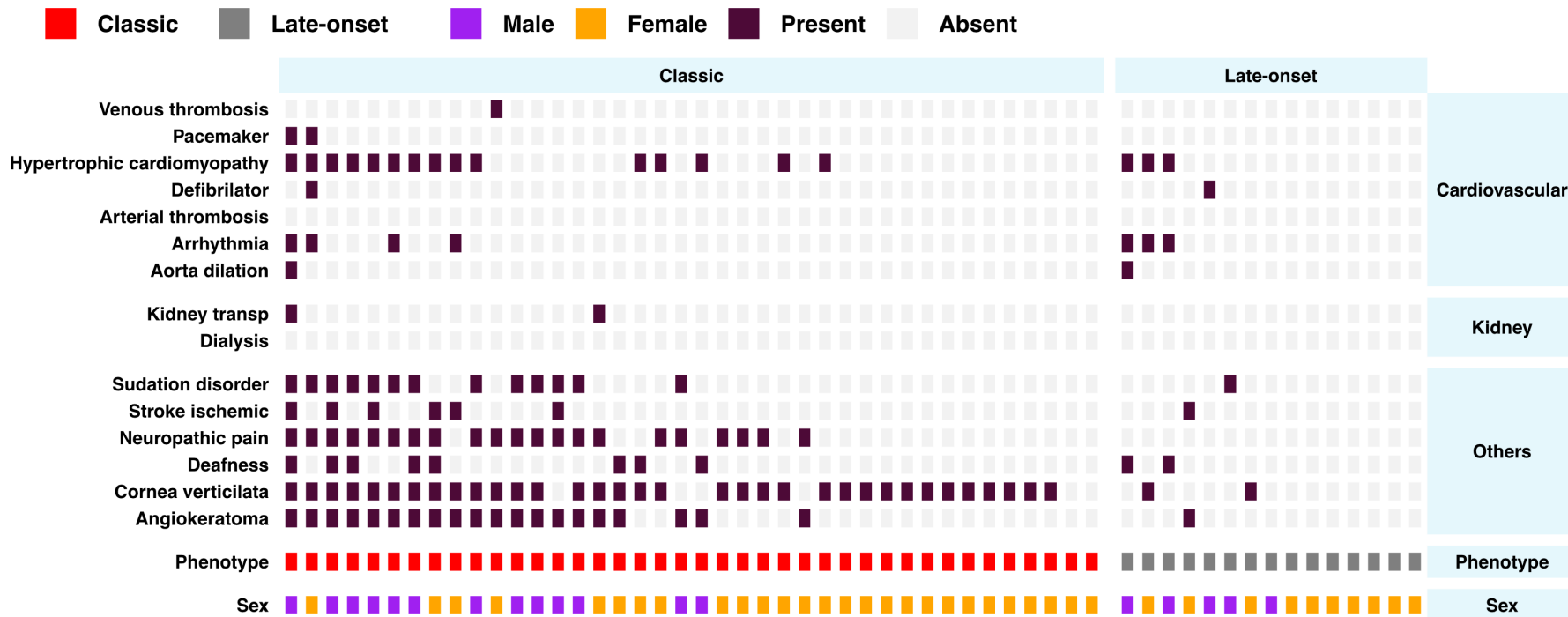


C



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Missense

Classical

Missense

Non Classical

Nonsense

Classical

Deletion

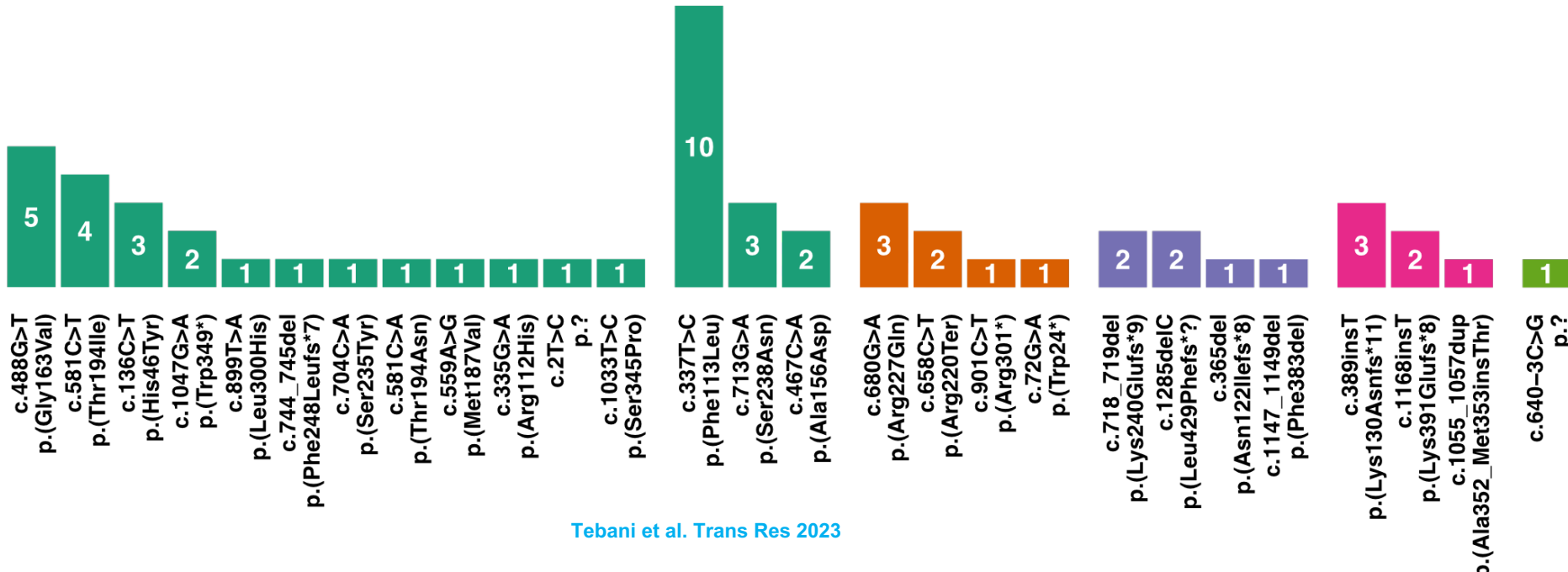
Classical

Insertion

Classical

Splicing

Classical



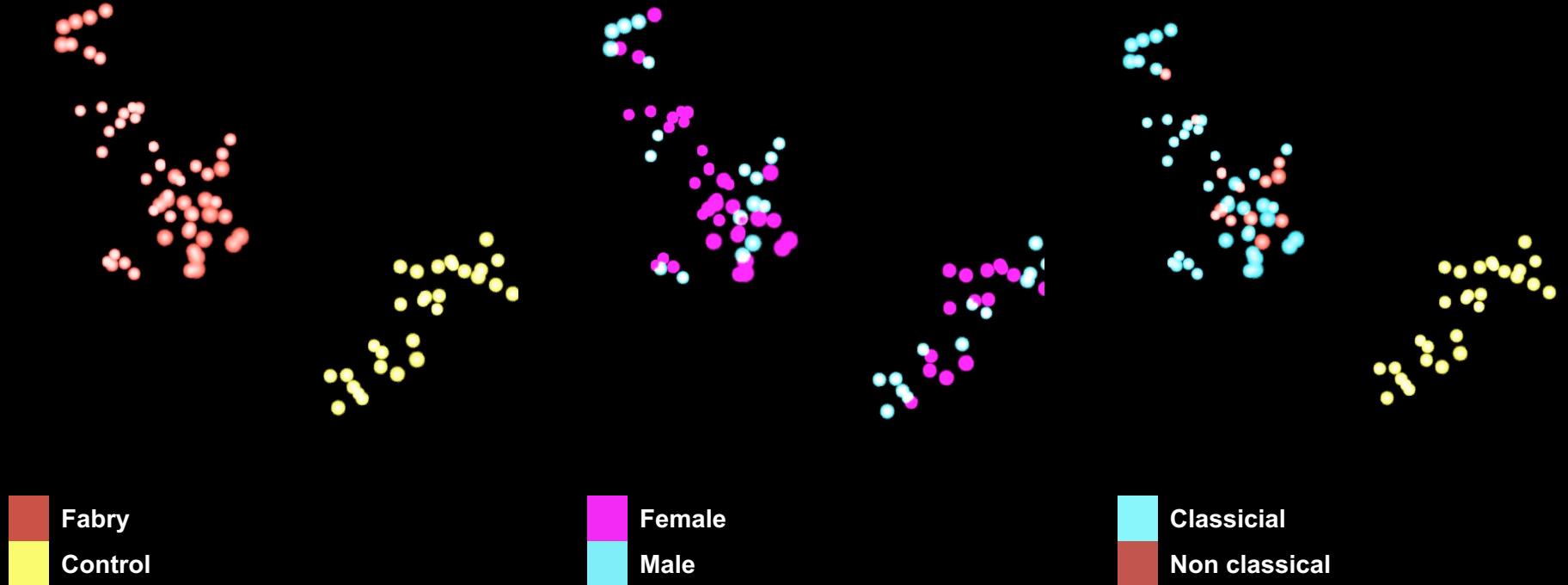
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Disease

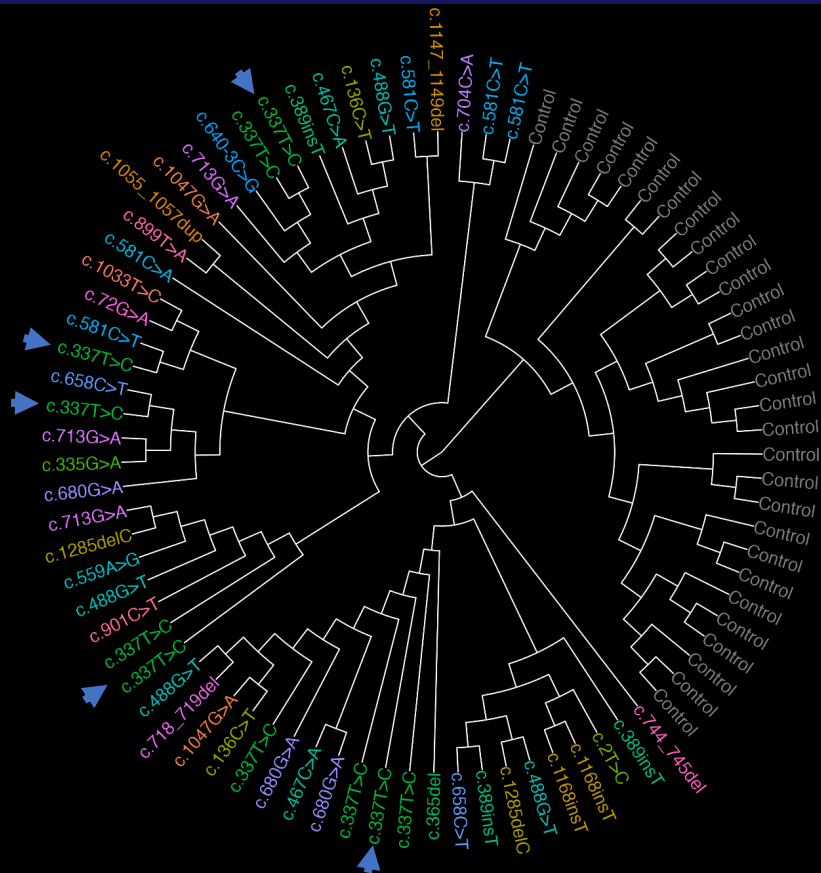
Sex

Phenotype



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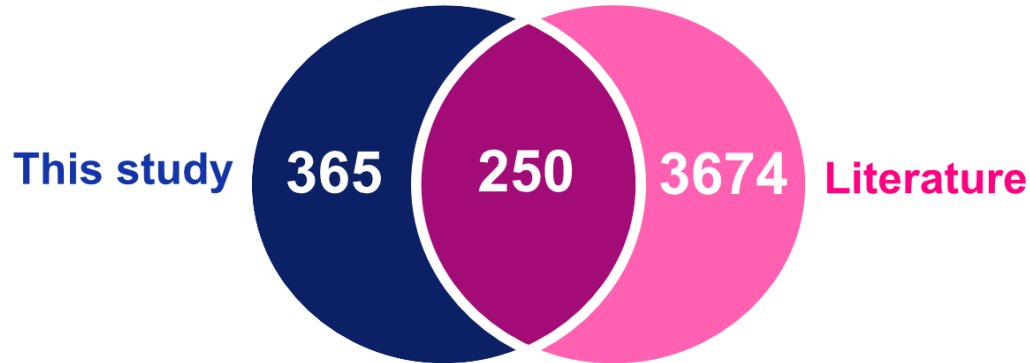
Analyse Differentielle

615/1463 protéines différentiellement exprimées

42%

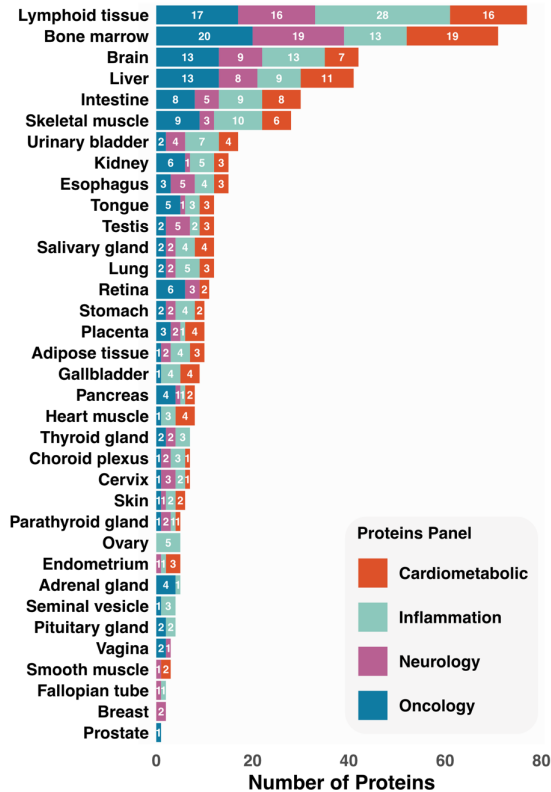
476 sur-exprimées

139 sous-exprimées



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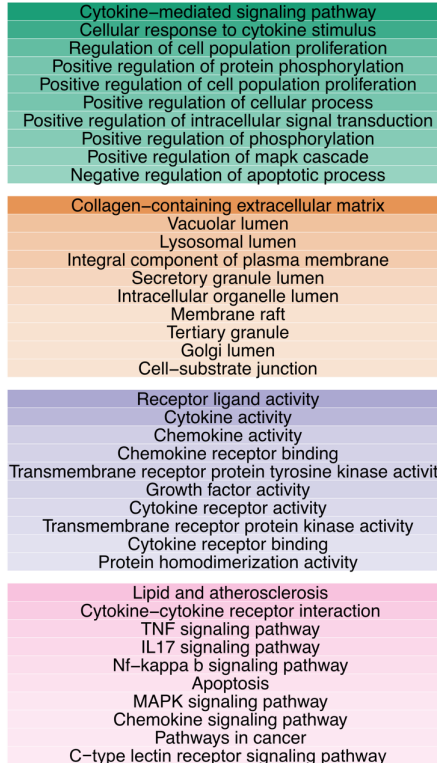


GO Biological Process

GO Cellular Component

GO Molecular Function

KEGG 2021



Inflammation immune response

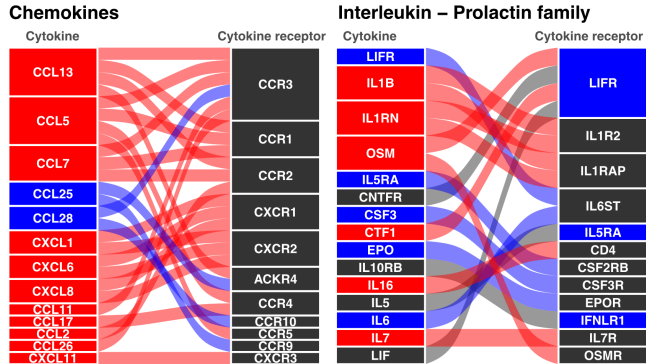
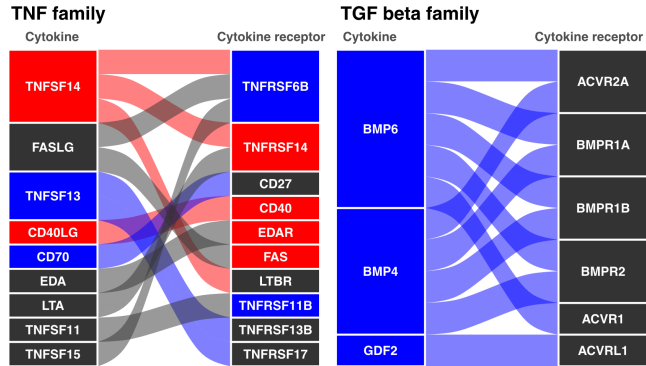
Extracellular Matrix

Lipid Metabolism

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Inflammation (161)



Extracellular Matrix (60)

Downregulated (Blue) | Upregulated (Red)

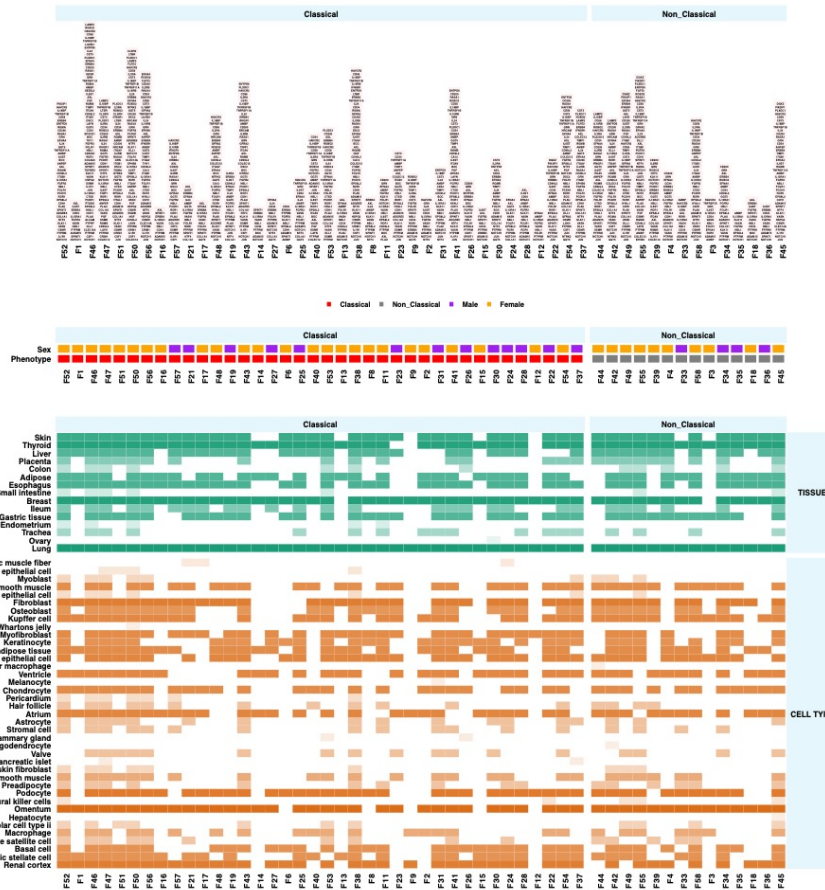
ECM Regulators Downregulated	ECM Regulators Upregulated	Secreted Factors Downregulated	Secreted Factors Upregulated	ECM Glycoproteins Downregulated	ECM-affiliated Proteins Upregulated	Proteoglycans Downregulated
MMP12	SERPINE1	IL6	PDGFA	TNC	LGALS9	NCAN
ADAMTS15	MMP7	SFRP1	PDGFB	SMOC2	CLC	BCAN
CTSV	MMP1	ANGPT2	S100A4	SMOC1	ANXA4	BGN
CTSH	MMP9		IL7	MFAP5	ANXA11	OGN
	MMP8		ANGPT1	DPT		
	ADAM8			VWA1		
	TGM2			SPON1		
	SERPINB9			PCOLCE		
	SERPINB8			MATN2		
	SERPINB6			EFEMP1		
	SERPINB1			EDIL3		
	CSTB					

Interactions lysosome/ECM → Fibrose plusieurs organes

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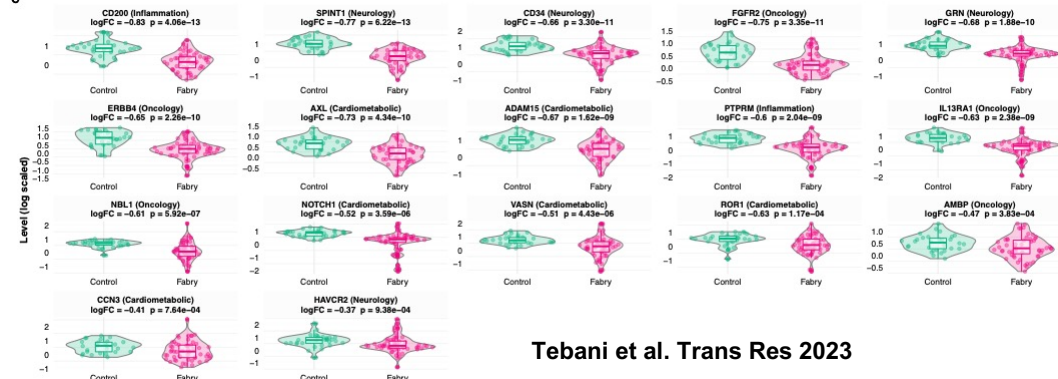
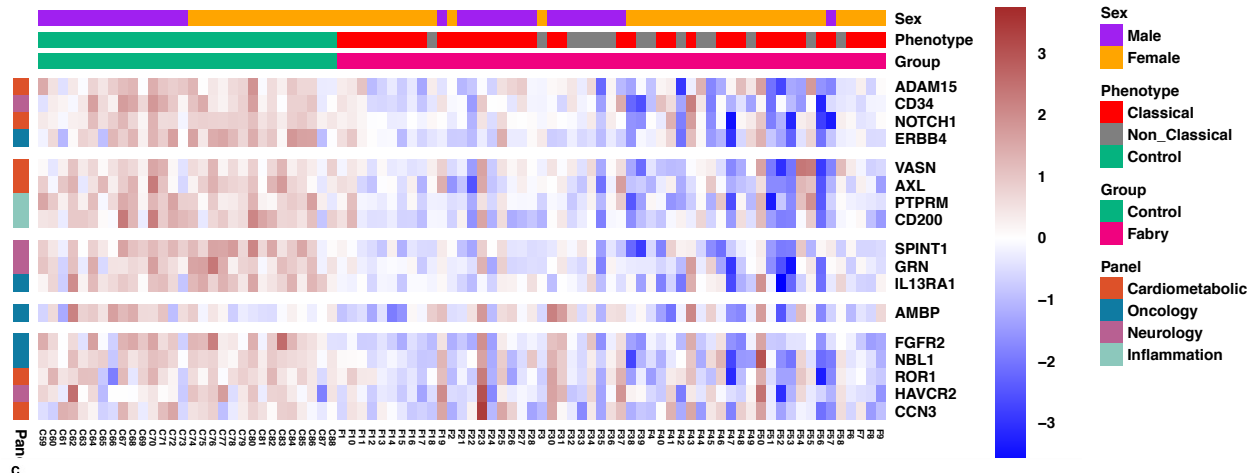
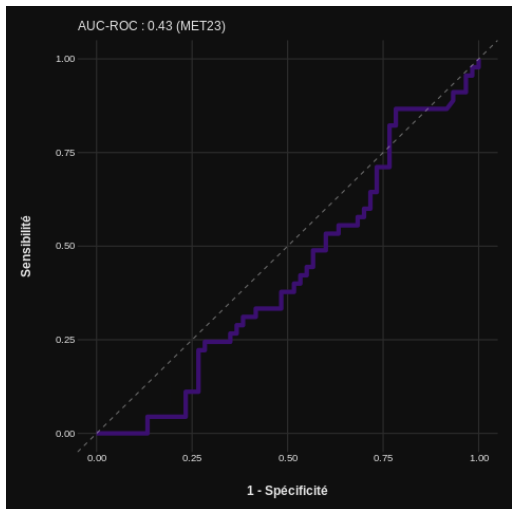
Étude de la spécificité tissulaire et cellulaire



	Classical	Non_Classical
Lung	38 (95%)	14 (93%)
Breast	37 (92%)	13 (87%)
Thyroid	35 (88%)	14 (93%)
Skin	32 (80%)	12 (80%)
Esophagus	30 (75%)	10 (67%)
Liver	27 (68%)	11 (73%)
Gastric tissue	27 (68%)	11 (73%)
Adipose	27 (68%)	11 (73%)
Omentum	33 (82%)	14 (93%)
Podocyte	31 (78%)	11 (73%)
Renal cortex	32 (80%)	9 (60%)
Fibroblast	30 (75%)	11 (73%)
Gastric epithelial cell	27 (68%)	11 (73%)
Atrium	27 (68%)	11 (73%)
Ventricle	26 (65%)	11 (73%)

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Signature Consensuelle

[J Clin Med](#). 2020 May; 9(5): 1325.

PMCID: PMC7290805

Published online 2020 May 2. doi: [10.3390/jcm9051325](https://doi.org/10.3390/jcm9051325)

PMID: [32370284](https://pubmed.ncbi.nlm.nih.gov/32370284/)

A Proteomics-Based Analysis Reveals Predictive Biological Patterns in Fabry Disease

[Abdellah Tebani](#),¹ [Wladimir Mauhin](#),² [Lenaig Abily-Donval](#),^{3,4} [Céline Lesueur](#),^{1,4} [Marc G. Berger](#),^{5,6} [Yann Nadjar](#),⁷
[Juliette Berger](#),^{5,6} [Oliver Benveniste](#),⁸ [Foudil Lamari](#),⁹ [Pascal Laforêt](#),¹⁰ [Esther Noel](#),¹¹ [Stéphane Marret](#),^{3,4}
[Olivier Lidove](#),² and [Soumeya Bekri](#)^{1,4,*}

Translational Research

The Journal of Laboratory and Clinical Medicine

RESEARCH ARTICLE | [ARTICLES IN PRESS](#)

Deep next-generation proteomics and network analysis reveal systemic and tissue-specific patterns in Fabry disease

[Abdellah Tebani](#) • [Frédéric Barbey](#) • [Olivier Dormond](#) • [Franklin Ducatez](#) • [Stéphane Marret](#) • [Albina Nowak](#) •
[Soumeya Bekri](#)   • [Show less](#)

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