

Genetics and Genomics of Pulmonary Arterial Hypertension



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The Genomic Complexity Underlying Pulmonary Arterial Hypertension: From Mendel to Networks

Pulmonary arterial hypertension (PAH) is a life-threatening condition characterized by remodeling of pulmonary muscular arterioles and pulmonary vascular obstruction and vasoconstriction, leading to increased pulmonary vascular resistance (PVR), a mean pulmonary artery pressure of at least 25 mmHg at rest, and right heart failure. PAH in the absence of an obvious cause is classified as heritable (HPAH) in the 4% of cases with a positive family history and is an additional 10-40% of cases previously classified as idiopathic PAH who are found to have an underlying genetic mutation despite a negative family history. Mutations have been found most commonly in bone morphogenetic protein receptor 2 (BMPR2), a member of the transforming growth factor β (TGF β) superfamily of receptors; less commonly in genes encoding other members of the TGF β signaling pathway, such as ALK-1, ENG, SMAD4, SMAD8, and CAV1; and rarely in KCNK3, which encodes a member of the two-pore domain potassium channels expressed in pulmonary artery smooth muscle cells (1). However, there is considerable phenotype heterogeneity, including incomplete penetrance, so that only a fraction of individuals with the same mutation develop PAH. This phenotype heterogeneity is likely related to environmental factors and to

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Gregor Mendel (1822-1884)

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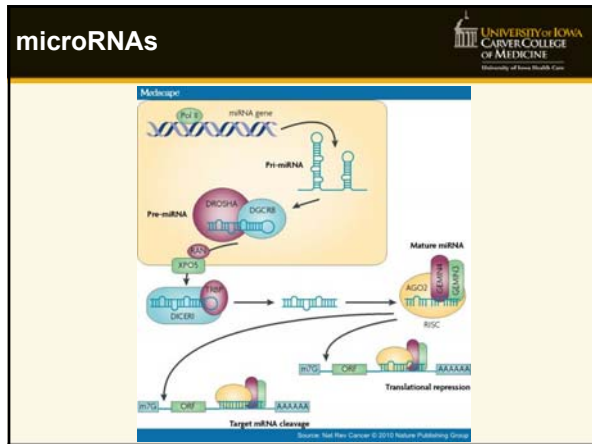
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Santa Clara, California

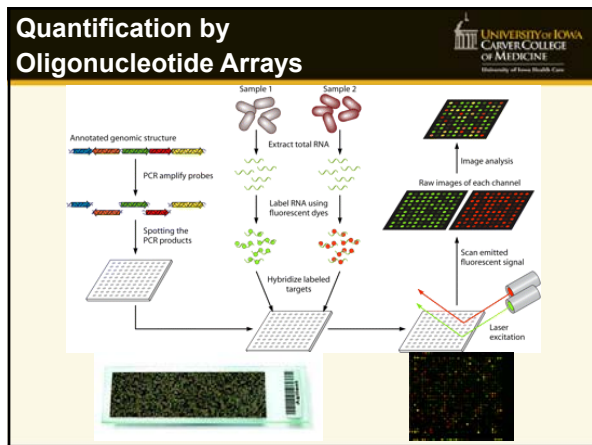
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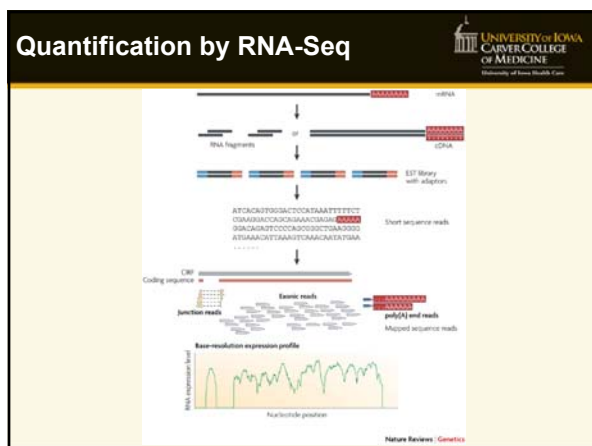
Transcription and Translation

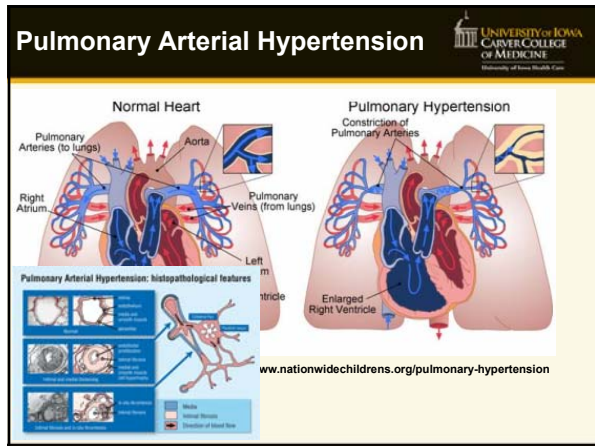
DNA = Book of Life
Gene = Chapter
A, C, G, T = Alphabet
3-Letter Codons = Words

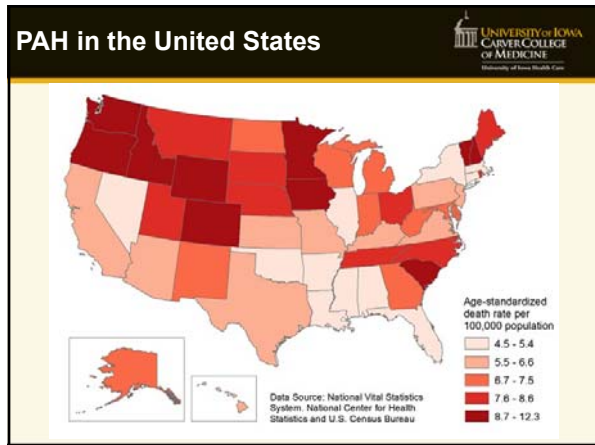
Codons Code for Amino Acids
Amino Acids Make Up Proteins

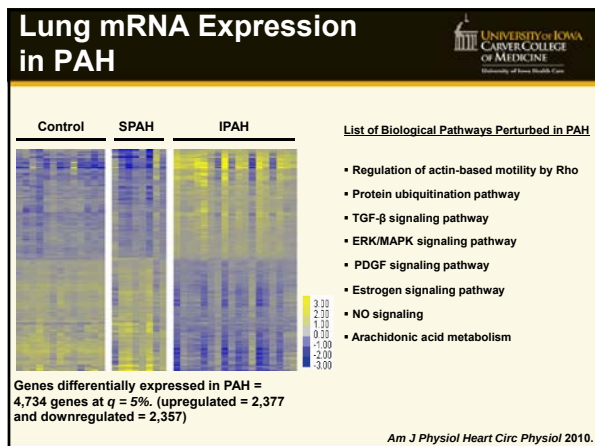


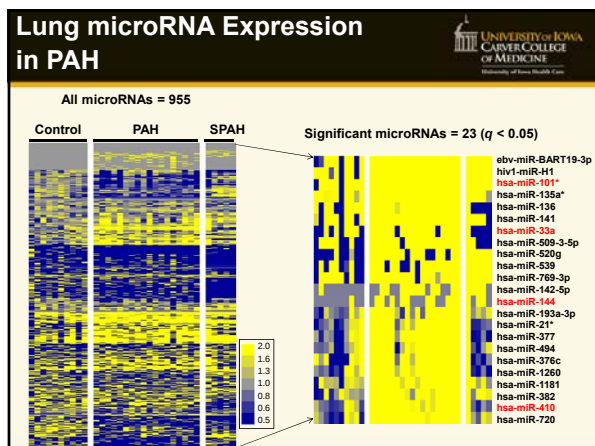


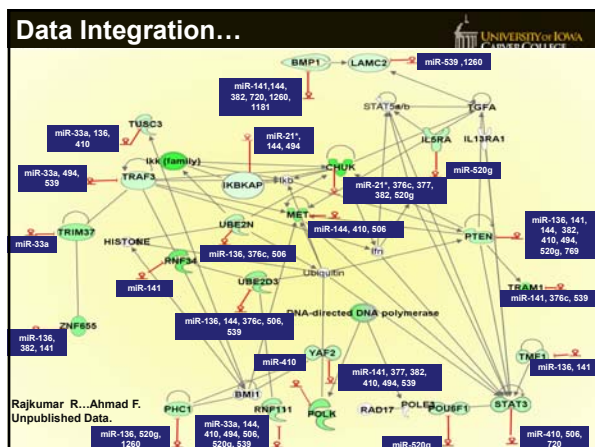


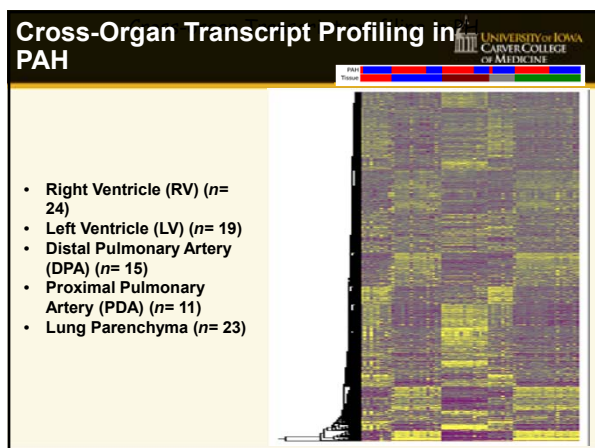


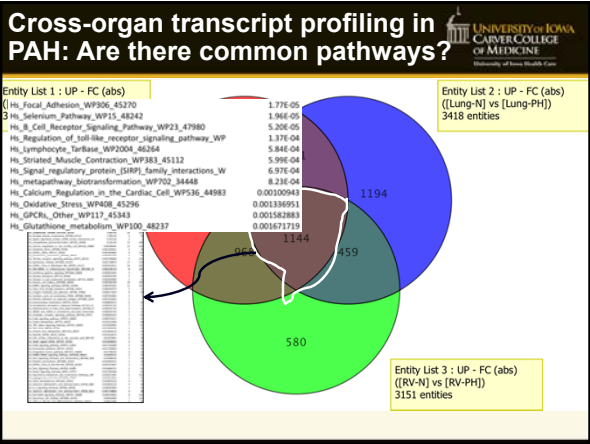


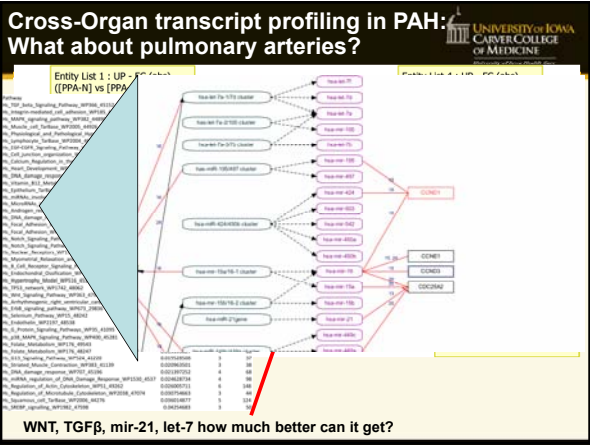






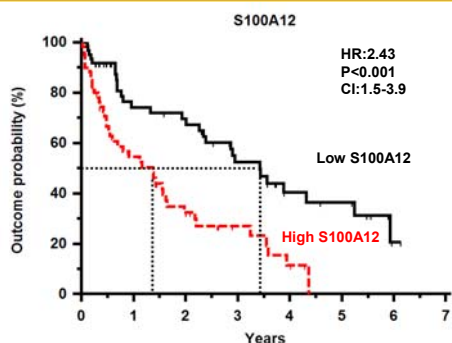




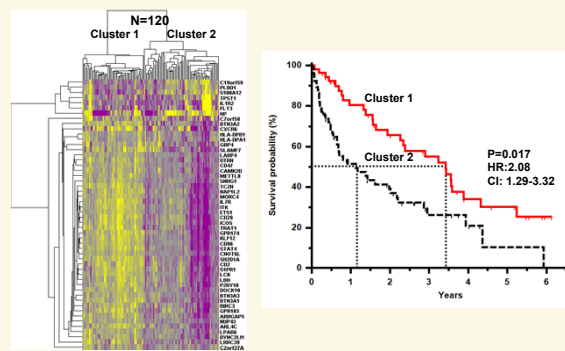




Blood S100A12 is predictive of patient survival.



52 genes at baseline identify patients who improve with drug therapy.



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