Screening asymptomatic *BMPR2* mutation carriers: a new frontier for pulmonary hypertension physicians?

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Pulmonary hypertension physicians must embrace this new and exciting aspect of clinical care of PAH patients for the benefit of our present and future patients https://bit.ly/3pf7GhG

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It has been over 20 years since the discovery of heterozygous germline mutations in the gene encoding the bone morphogenetic protein type 2 receptor (*BMPR2*) in families with pulmonary arterial hypertension (PAH) [1, 2]. Much has been learned since then regarding how mutations in *BMPR2* cause PAH, although many questions remain unanswered. Mechanistically, loss of *BMPR2* signalling in vascular cells, and particularly endothelial cells, greatly increases the likelihood of initiating the characteristic vascular pathology seen in the lungs of patients with PAH [3]. Although asymptomatic carriers of *BMPR2* mutations are at markedly increased risk of developing PAH (at least 10 000-fold greater risk than non-carriers), one of the features of *BMPR2* mutations is that they exhibit reduced penetrance [4]. In other words, carriers of *BMPR2* mutations do not inevitably develop PAH. This is of great interest scientifically because it implies the need for additional "triggering" factors in the context of *BMPR2* mutations that are required in order for disease to develop. The potential triggering factors identified to date come from *in vitro* studies of patient-derived cells and in genetically modified mice [5, 6]. Inflammation-induced injury seems to stimulate a greater degree of pulmonary vascular remodelling in *BMPR2* deficient mice than in wild-type littermates, and *BMPR2* deficient mice possess an exaggerated inflammatory response to injury [7]. This amplification of certain inflammatory pathways may initiate and propagate the vascular changes. In addition, the presence of a *BMPR2* mutation in pulmonary vascular endothelial cells increases susceptibility to apoptosis and increases vascular permeability in response to injury [8–10]. These extrinsic factors act to further suppress *BMPR2* signalling, or exacerbate a dysfunctional endothelium already primed by the presence of mutation.