BMPR2 mutations and survival in pulmonary arterial hypertension: An individual participant data meta-analysis

Pulmonary arterial hypertension (PAH) is a rare disorder characterised by progressive remodelling of the small pulmonary arteries, resulting in increased pulmonary vascular resistance and ultimately right ventricular failure and death.[1,2] The diagnosis of PAH requires a mean pulmonary artery pressure of 25 mmHg or more with a pulmonary artery wedge pressure of 15 mmHg or less at right heart catheterisation in the absence of chronic thromboembolic, left heart or respiratory disease. The classification of PAH includes both inheritable and idiopathic forms. Heterozygous germline mutations in the gene encoding the bone morphogenetic protein receptor type II (*BMPR2*) have been identified as the main genetic cause of familial PAH.[3,4] It is estimated that over 300 different *BMPR2* mutations have been identified, with a prevalence of greater than 75% in families with PAH.[5,6] BMPR-II is a receptor for the bone morphogenetic proteins (members of the transforming growth factor-β superfamily). Mutations in the *BMPR2* gene cause loss of function and reduced signalling downstream of the receptor. It has been hypothesised that abnormal pathway activity may permit excess endothelial cell growth and proliferation in response to a variety of injuries.[7]

In a recent article, Evans *et al.*[8] analysed the individual patient data of 1 550 patients with idiopathic, heritable and anorexigen-associated PAH from eight cohorts that had been systematically tested for *BMPR2* mutations. The primary outcome was the composite of death or lung transplantation; all-cause mortality was the secondary outcome.

The findings of this data meta-analysis showed that 448/1 550 (29%) patients had a *BMPR2* mutation. Mutation carriers were younger at diagnosis (mean age (standard deviation) 35.4 (14.8) v. 42.0 (17.8) years), had a higher mean pulmonary artery pressure (60.5 (13.8) v. 56.4 (15.3) mmHg) and pulmonary vascular resistance (16.6 (8.3) v. 12.9 (8.3) Wood units), and lower cardiac index (2.11 (0.69) v. 2.51 (0.92) L/min per m^2) (all $p<0.0001$).

Patients with *BMPR2* mutations were less likely to respond to acute vasodilator testing (3% (10/380) v. 16% (147/907); $p<0.0001$). Among the 1 164 individuals with available survival data, age-adjusted and sex-adjusted hazard ratios (HRs) comparing *BMPR2* mutation carriers with non-carriers were 1.42 (95% confidence interval 1.15 - 1.75; $p=0.0011$) for the composite of death or lung transplantation and 1.27 (1.00 - 1.60; $p=0.046$) for all-cause mortality.

The HRs were attenuated after adjustment for potential mediators including pulmonary vascular resistance, cardiac index and vasoreactivity. HRs for death or transplantation and all-cause mortality associated with *BMPR2* mutation were similar in men and women, but higher in patients with a younger age at diagnosis ($p=0.003$ for death or transplantation, $p=0.011$ for all-cause mortality).

These findings therefore show that patients with PAH and *BMPR2* mutations are more likely to present at a younger age and with more severe disease, and are at an increased risk of death or transplantation, compared with those without *BMPR2* mutations. The recently revised 2016 European guidelines for the diagnosis and treatment of PAH now recommend offering genetic counselling and screening for *BMPR2* mutations in patients diagnosed with idiopathic, heritable and anorexigen-associated PAH, mainly to enable the predictive genetic testing of relatives.[9]

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