Background: Mitral valve prolapse (MVP) is a common disorder associated with mitral regurgitation (MR), endocarditis, heart failure and sudden death. Non-diagnostic morphologies (‘prodromal forms’ and ‘minimal superior displacement’ [MSD]) have been described in the familial context, and may represent early expression of MVP in those genetically predisposed. Both the prodromal phenotype and MSD share features of excessive leaflet motion with fully affecteds, as demonstrated by superior motion towards the left atrium, bulging of the posterior leaflet relative to the anterior (albeit not diagnostic by quantitative assessment) and coaptation asymmetry. In addition, in the prodromal form, leaflet excess can also manifest itself by anterior motion and a shift of the coaptation point towards the septum and the aortic root (greater or more anterior coaptation height).

Objectives: 1) To explore the spectrum of MVP abnormalities in the community and compare their clinical and echocardiographic features. 2) To use coaptation height as a quantitative trait for a genome wide association study (GWAS) of the MVP phenotype.

Methods: Participants: Individuals who participated in the fifth examination cycle of the FHS Offspring cohort (1991-1995), constituted the sampling frame for our investigation. At the fifth examination cycle, all attendees underwent routine transthoracic echocardiography. The echocardiograms of all subjects who had previously been identified as possibly having mitral valve (MV) leaflet displacement suggesting MVP in any two-dimensional view or on M-mode echocardiography at any prior examination of the Offspring cohort were
reviewed to ensure that no cases of MVP were missed among 3491 attendees at the fifth examination cycle. This broad approach identified 518 individuals with possible MVP. First, the echocardiograms obtained at the fifth examination of these subjects were assessed to identify those in whom qualitative superior displacement of the MV leaflets during systole warranted a quantitative evaluation to determine whether MVP was actually present. The 151 individuals identified in this way were paired with controls (1:1) matched for age and sex who were also drawn from the fifth examination cycle but who were initially coded as having no evidence of prolapse. Of this original sample of 302 individuals, echocardiographic images of 6 individuals were deemed of inadequate quality for detailed analysis. Therefore, the final sample for this investigation consisted of 296 individuals (151 controls). Also, for the purpose of this investigation, the total number of Offspring individuals in the fifth generation was 3485 (3491-6).

Echocardiographic methods: Using current two-dimensional echocardiographic criteria, the diagnosis of MVP was made by measurement of maximal MV leaflet superior systolic displacement (Ant/Post Disp) relative to the line connecting the annular hinge points (annulus). The projections of the anterior and posterior MV leaflets onto the mitral annulus (Ant/Post proj) also were assessed at end-systole. The meeting point of the MV leaflets relative to the annulus was quantified by the leaflet coaptation height (Coapt - calculated as Post proj/annulus). Normally, the MV leaflets meet posteriorly within the 25-30% of the left ventricular cavity because the posterior leaflet is shorter than the anterior. In patients with MVP, coaptation is typically displaced anteriorly, consistent with elongation of the posterior MV leaflet, which can produce excessive leaflet motion not only into the left atrium but also toward the aortic root. Finally, MR severity was quantified by color Doppler as the maximum systolic proximal MR jet height (Jetht). A Jetht of 2 mm effectively separates trace physiologic backflow from mild MR, while 5 mm or more indicate moderate severity. All of the above echocardiographic features were measured in the parasternal or apical long-axis views at end-systole using an average of three beats. MV leaflet thickness (Ant/Post leafthick) was measured at end-diastole in the same
views as the leading to trailing edge of the thickest area of the mid-portion of the leaflet, excluding focal areas of thickness and chordae.

Based on prior clinical and prognostic studies, MVP was diagnosed if leaflet displacement exceeded 2 mm. Subjects were classified as having classic MVP (displacement >2 mm, thickness ≥5 mm) or non-classic MVP (displacement >2 mm, thickness <5 mm). Participants with borderline degrees of displacement of the MV leaflets (≤2 mm) but posterior coaptation were designated as having MSD. Individuals without diagnostic leaflet displacement beyond the annulus, but with an anterior shift (> 40%) of the coaptation point, were diagnosed as having prodromal features.