Motivated by applications in genomics, we consider in this paper global and multiple testing for the comparisons of two high-dimensional linear regression models. A procedure for testing the equality of the two regression vectors globally is proposed and shown to be particularly powerful against sparse alternatives. We then introduce a multiple testing procedure for identifying unequal coordinates while controlling the false discovery rate and false discovery proportion. Theoretical justifications are provided to guarantee the validity of the proposed tests and optimality results are established under sparsity assumptions on the regression coefficients. The proposed testing procedures are easy to implement. Numerical properties of the procedures are investigated through simulation and real data analysis. The results show that the proposed tests maintain the desired error rates under the null and have good power under the alternative at moderate sample sizes. The procedures are applied to the Framingham Offspring study to investigate the interactions between smoking and cardiovascular related genetic mutations important for an inflammation marker.