Kevin O'Malley is a second generation Irish American, with dual citizenship of the United States and Ireland until he returned his Irish citizenship in order to become ambassador. He has Irish ancestry on both sides of his family, and his paternal grandparents came from Westport, County Mayo.

O'Malley is a Catholic, and attended St. Vincent's Seminary at second level in Cape Girardeau, Missouri, and the novitiate at St. Mary's Seminary in Perryville, Missouri, where he studied for the priesthood. O'Malley received an A.B. in 1970 from Saint Louis University and a J.D. in 1973 from Saint Louis University School of Law.

O'Malley has been an active member of the Democratic Party in Missouri, and White House Chief of Staff Denis McDonough described O'Malley as a "close personal friend" of US President Barack Obama. He was previously an officer in the United States Army Reserve. He has two sons – Brendan and Ryan – with his wife, Dena, and two grandsons.