Lowitja O'Donoghue was born into the Yankunji tribe at Indulkana, South Australia, the youngest of five children. Her parents were persuaded to surrender her to the United Aborigines’ Mission and she was educated at their Home in Quorn and Unley Girls’ Technical High School. Prevented initially from studying nursing because of her race, Lowitja O'Donoghue was finally accepted into the Royal Adelaide Hospital in 1954. Thirty years later, in 1984, she was voted Australian of the Year.

She joined the Australian Department of Aboriginal Affairs in 1967, and was Regional Director for South Australia from 1975 to 1979. She chaired Aboriginal Hostels Limited and the Aboriginal Development Commission. She was foundation Chair of the Aboriginal and Torres Strait Islander Commission from 1990 to 1996. During this time she oversaw the restructuring of the bureaucracies dealing with Indigenous affairs.

Lowitja O'Donoghue became a member of the Australian Republic Advisory Committee in 1993 and of the Aboriginal Negotiating Team for Native Title Legislation. She chaired the National Indigenous Olympic Committee. In 1998, she presented the fifth F. Oswald Barnett oration, which was later published as Can We Call Australia Home?: an Indigenous Perspective of Housing.

In 2000, at a ceremony to mark the tenth anniversary of the Yunggorendi First Nations Centre for Higher Education and Research of Flinders University, Lowitja O'Donoghue was made a Professorial Fellow. She had been an Honorary Visiting Fellow since 1998. She is also the inaugural Chair of the Board of Management of the Cooperative Research Centre in Aboriginal and Tropical Health. She holds honorary doctorates from no fewer than five Australian universities.

Lowitja O'Donoghue has nominated Martin Luther King Jnr, Nelson Mandela and Archbishop Desmond Tutu as her heroes. Her own consistent and longstanding involvement in Indigenous rights issues, combining absolute determination and avoidance of the politics of confrontation has made her a hero to Australians of all races and political persuasions.