Genetics and Molecular Biology, 41, 4, v-ix (2018)

Obituary

Francisco Mauro Salzano (1928-2018): A life dedicated to science

On September 27, 2018, science lost one of its most devoted followers, Francisco Mauro Salzano. His life extended for 90 most incredibly productive years, involving studies that covered almost all aspects of human genetics.

Historians of science have continuously searched for the factors that determine why certain persons achieve prominence in their area. Of prime importance, of course, is their biological constitution; only persons with a given degree of intelligence can reach success. But there are many additional factors that are also important, including work drive, persistence, as well as appropriate family and academic environments. This combination of factors contributed to Francisco Salzano's brilliant career. He had a happy and fruitful family life. He married Theresa Torres Salzano in 1952, and they had two sons Felipe and Renato Salzano both practicing physicians, and five grandchildren.

Francisco M. Salzano was born in Cachoeira do Sul, RS, in the South of Brazil on July 27, 1928, but he lived all his life in Porto Alegre, except for varied periods of time in São Paulo, where he obtained his doctoral degree having worked under the supervision of Crodowaldo Pavan, and also outside of Brazil. The most important stay abroad occurred between 1956 and 1957, at the University of Michigan, where he began his collaboration with the American geneticist James V. Neel (1915-2000).

After primary and secondary school education (the latter in a public school, Colégio Júlio de Castilhos), he was approved at the entrance exam for Biological Sciences at the Federal University of Rio Grande do Sul (UFRGS), where he graduated in 1952. Soon he developed an interest in research, and as a consequence, he was invited by Prof. Dr. Antonio R. Cordeiro to join his laboratory as an undergraduate student.

Table 1 presents in chronological order the main events of his life. As most geneticists who started careers in the first half of the 20th century, his introduction to genetics was through the fruit fly *Drosophila*. But in the mid 1950s he became increasingly interested in human genetics, with his first paper on this subject published in 1957 (Salzano, 1957). More than 400 full scientific papers, 26 books and 55 book chapters were subsequently produced, documenting his phantastic work capacity and phenomenal erudition. As a result of his achievements, Francisco Salzano received many distinctions along his career. Not less than 50 awards and honors are listed in his *Curriculum Vitae*, and a few of them are indicated in Table 1.

In his 68 years of dedication to Academia and science, Francisco Salzano showed an extraordinary ability to generate knowledge. He always acknowledged and celebrated his collaborations, which reveals his generosity in the recognition of students (he supervised 48 master's dissertations and 41 doctoral theses) and partners that he had during his long professional life. His supervision and collaborative capacity, as well as intellectual versatility can be observed in the diverse and varied subjects of his work, including anthropology, medical genetics, epidemiology, population genetics, history of science, history of genetics, molecular evolution, and bioethics, among others. He worked with diverse organisms, from plants, to the iconic *Drosophila* (study organism of his PhD thesis), as well as humans and other primates. He was one of the pioneers in the implantation of the discipline of Medical Genetics in southern Brazil, by investigating twins and the differential action of teratogenic drugs. He also studied the genetic causes of hemoglobinopathies, including the description of new variants, such as Hemoglobin (Hb) Porto Alegre (Tondo *et al.*, 1963). Heterozygotes of Hb Porto Alegre are generally asymptomatic, but concomitance with other variants leads to a clinical picture of severe hemolytic anemia, requiring spleen removal (Kimura *et al.*, 2008). However, the most frequent focus of Prof. Salzano was the study of South American Native peoples, especially Brazilian tribes. Supported by the Brazilian Native Indian Foundation (FUNAI), he and his collaborators began expeditions and contacts with these autochthonous groups early in the 1950s. The first results were published at that time in important scientific journals, and by the first time this illustrated the genetic diversity and some rare genetic conditions in Native Americans (Salzano, 1957; Tondo and Salzano, 1960; Salzano, 1961). Other studies, concerning blood groups and other protein polymorphisms, revealed a general diversity pattern (Salzano, 1968) that has since been corroborated through investigations at the DNA level: South Amerindian hunter-gatherers have lower intra-population genetic variation and higher levels of population structure when compared to autochthonous populations living in other continents (Wang *et al.*, 2007). These findings

Table 1 - Main events related to the life of Francisco Mauro Salzano.

Year	Event
1928	Was born on July 27 in Cachoeira do Sul, RS, Brazil.
1950	Bachelor of Science in Natural History at the Universidade Federal do Rio Grande do Sul
1952	Graduation (*Licenciatura*) in Natural History at the Universidade Federal do Rio Grande do Sul
1952	Marriage with Thereza Torres (Salzano)
1955	Doctoral degree in Biological Sciences (Genetics) at the Universidade de São Paulo, Dissertation : The criptic species problem – Studies in the Bocainensis (Drosophila) subgroup; under the supervision of Crodowaldo Pavan.
1956/1957	Fellowship from the Rockefeller Foundation to spend a year in the Human Genetics Department at The University of Michigan , Ann Arbor, MI, USA under the supervision of James V. Neel
1960	Assistant Professor at the Universidade Federal do Rio Grande do Sul
1960	Senior Lecturer (*Livre-Docente*) thesis defense at the Instituto de Filosofia of the Universidade Federal do Rio Grande do Sul. Dissertation title: Genetic and Demographic studies on Indians from Rio Grande do Sul.
1962	First Field work with the Xavante of Central Brazil
1966-1968	President of the Brazilian Society of Genetics (Sociedade Brasileira de Genética)
1973	Nominated Member of the Brazilian Academy of Sciences (Academia Brasileira de Ciências)
1981	Professor of Genetics at the Department of Genetics at Universidade Federal do Rio Grande do Sul
1989	Nominated Honorary Member of the Royal Anthropological Institute of Great Britain and Ireland
1994	Almirante Álvaro Alberto Award for Science and Technology, Biological Sciences, Federal Government of Brazil
1995	Member of the National Order of Scientific Merit, in the Grand Cross Class, Brazil
1997	Annual Award of the Ibero-American Society of Human Genetics
1998	Formal retirement at the age of 70 and continuation as Emeritus Professor until his death
1999	Nominated Foreign Associate Member of the National Academy of Sciences of the United States of America
1999	Franz Boas High Achievement Award, Human Biology Association
2001	Nominated Corresponding Member of the Chilean Academy of Sciences
2001	Nominated Foreign Member of the Third World Academy of Sciences
2007	Moinhos Santista Prize in the area of Genetics, Fundação Bunge
2007	Scopus Award, Elsevier Publishing House
2010	Doctor Honoris Causa, Paul Sabatier (Toulouse III) University, France
2011	Doctor Honoris Causa, University of Costa Rica, San José, Costa Rica
2014	Simões Lopes Neto Medal, Government of the State of Rio Grande do Sul and FAPERGS
2018	Recognition of services rendered to CNPq
2018	Died on September 27

indicated low levels of gene flow between hunter-gatherer villages and low effective population sizes, favoring the role of genetic drift.

Regarding the settlement of the Americas, Bonatto and Salzano (1997) pioneered the use of mitochondrial DNA (mtDNA) sequences to unravel the role of Beringia (a land mass of about 1 million km^2 that emerged during the last glacial maximum in the late Pleistocene) as a key geographic area for the formation of the particular Native American genetic pool, a finding that has been corroborated by subsequent studies (Bisso-Machado *et al.*, 2016; Skoglund *et al.*, 2015).

Before the DNA era, Neel and Salzano (1967) provided the description of the fission-fusion concept, which proposes that fissions in South American hunter-gatherer groups occur along kinship lines and are generally associated with social tension. The fissioning group may form another village, rejoining the first after some time, or even join another village. This concept has been revisited (Salzano, 2009) and, based on mtDNA sequences, was used to explain the dispersal of Tupi and Je speakers (Ramallo *et al.*, 2013).

In the context of the "neutralist–selectionist" debate Prof. Salzano – asa convinced selectionist – postulated that it was a matter of time for new analytic methods to show signs of natural selection in the genome of Amerindians. He was right. For example, Hünemeier *et al.* (2012) described that the *ABCA1**230Cys allele has an American origin and that it could have had a selective advantage during the periods of food scarcity experienced by Mesoamericans during

the implementation of maize-based agriculture and the consequential lifestyle shift towards sedentarism. Recent studies on the *TP53* pathway showed that some allelic combinations were potentially involved in the human adaptation to the Andean high altitudes (Jacovas *et al.*, 2015, 2018). A set of studies on metabolism-related genes has also provided instigating results: Native Americans living in a diverse range of environments share signatures of positive selection in the fatty acid desaturases (FADS) (Amorim *et al.*, 2017), indicating a single and strong instance of local adaptation to cold climate and a protein-rich diet that took place in Beringia, prior to their entrance into the Americas. Noteworthy, Reales *et al.* (2017) observed significantly higher frequencies for a thrifty allele (rs429358C, *APOE*) in hunter-gatherers, when compared with Andean agriculturalists and camelid-herding communities. Altogether, these results illustrate for the first time the gene-culture co-evolution phenomenon involving Native groups and the key role of natural selection in the successful adaptive trajectory of these populations throughout the Americas.

The historical, cultural, demographic, and evolutionary trajectories of Native Americans were hard hit after the arrival of the Europeans settlers. Based on several studies, Salzano and Bortolini (2002) estimated that approximately 43 million Native Americans in different stages of cultural and demographic development were living in Latin America at the beginning of the European conquest. This number rapidly declined as a consequence of several factors, including epidemics. For example, tuberculosis (TB) was an important cause of population decline among Brazilian indigenous peoples, and it is still a cause of morbidity and mortality among them, indicating that these groups are particularly vulnerable to this disease. This dramatic scenario also inspired Prof. Salzano and his collaborators to develop research projects throughout the 1960s. They described the prevalence of TB among the Kayapó (Ayres and Salzano, 1968), and showed that the most recent exposure of Xavante individuals to a variety of infections, along with variants in cytokine genes, may be the cause of their increased immunological susceptibility to TB (Zembrzuski *et al.*, 2010). In a more recent study, they suggested that certain HLA class II genotypes (*DRB1*04*, *DQA1*03* and *DQB1*03:02*) were associated with TB response in Aché Indians from Paraguay (Lindenau *et al.*, 2014). Other data specific to demographic, epidemiological, genetic, evolutionary, and historical aspects of the Kayapó, Xavante, Aché, as well as other native peoples, can be found in the books by Salzano and Callegari-Jacques (1988), Salzano and Hurtado (2004), and Coimbra *et al.* (2002).

The impact of the Amerindian heritage on the formation of Brazilian and Latin American populations was also extensively studied by Prof. Salzano and his collaborators since the 1980s, using classical polymorphisms (Franco *et al.*, 1982; Castro-de-Guerra *et al.*, 1996; Sans *et al.*, 1997). At this time, it was already possible to see how heterogeneous and highly admixed Brazil and other South American countries actually are. However, the details about this complex process were revealed only after the advent of studies at the DNA level, using both uniparental (mtDNA and Y chromosome) and biparental (autosomal) markers (Tarazona-Santos *et al.*, 2001) Admixture involved primarily European men and Native American women, characterizing the process as demographically asymmetric. Since the early 16th century, the process became more complicated by the introduction of African slaves to the Americas. As a result, for example, most of the Y-chromosomes in contemporary Brazilian populations are of European origin, but a significant portion of the mtDNA lineages have Amerindian or African origin, a scenario that is also observed in other Latin American countries (Salzano and Sans, 2014).

At a more global population scale, a study published in 2007 using DNA data from 50 nuclear loci sequenced in African, Asian and Native American samples, dated the origin of our species at ~141 thousand years ago (Fagundes *et al.*, 2007). This same study also found that the African replacement model explains not only the shallow ancestry of mtDNA or Y-chromosomes, but also the occurrence of deep lineages at some autosomal loci (Fagundes *et al.*, 2007). In a recent work, Prof. Salzano and colleagues suggested that a genetic repertoire common to immune and behavioral systems could have been maintained by balancing selection starting before the split between archaic and modern humans (Viscardi *et al.*, 2018).

Prof. Salzano used to embrace new scientific projects with great openness and optimism. In the last years he was an enthusiastic collaborator of the studies that described new oxytocin functional variants with extraordinary evolutionary meaning in New World monkeys (Vargas-Pinilla *et al.*, 2015; Parreiras-e-Silva *et al.*, 2017). Another study that connects molecular evolution and functional divergence of alcohol dehydrogenases (ADHs) in animals, fungi, and plants was recently published (Thompson *et al.*, 2018).

Finally, we could not leave out the works and timely reflections of Prof. Salzano on Bioethics. He had a deep sense of humanity and was concerned with anti-science attacks. Back in the 1960s, he was one of the few experts who wrote on behalf of the World Health Organization (WHO) the principles to be followed in genetic and evolutionary research (WHO 1964, 1968). These documents provided guidelines that included: respect for the privacy of volunteers,

as well as their comfort and well-being, access to medical, dental, and other biomedical services, clear explanations of possible research developments, and respect for the cultural integrity of groups. Posteriorly he published other papers, and, together with A. Magdalena Hurtado, he edited a book regarding this subject (Salzano and Hurtado, 2004). In a recent review, he made a strong criticism of what he called "geneticophobia" (Salzano, 2015). On September 10-14th, 2018, he would have been personally honored during the International Congress of Genetics in Foz do Iguaçu, Brazil, but he was not able to participate due to health problems. Instead, he sent a message to the organizers of the event that illustrated his profile as a man committed to science and his conviction in some universal values that make us human. The final paragraph of that message was as follows: "We are living in times of deep contrasts. On one way, we have the phantastic progress in science and technology, which is advancing our knowledge about ourselves and the outside world; but simultaneously, threats of several kinds have arisen from anti-science movements, especially those promoted by mythical and mystical beliefs. These movements should be firmly opposed. If there is a social institution that has significantly contributed to human happiness, this institution is science, and this fact should be clearly informed to lay persons. But science alone is not sufficient for a brighter future. It is necessary a deep engagement towards a world in which the social differences between nations and persons would be more equitable than today, leading to the goal of the maximum of happiness to the largest number of persons".

Francisco Salzano had a cordial relationship with colleagues, laboratory, and administrative personnel. His example of intellectual honesty, sense of responsibility, perseverance, and his incredible intellectual ability stood always out to us and many other colleagues in the profession as a paradigm to be followed. Salzano will certainly be sorely missed.

References

Amorim CE, Nunes K, Meyer D, Comas D, Bortolini MC, Salzano FM and Hünemeier T (2017) Genetic signature of natural selection in first Americans. Proc Natl Acad Sci USA 114:2195-2199.

Ayres M and Salzano FM (1968) Tuberculosis survey in Caiapos Indians from Xingu. J Bras Doencas Torac 4:24-26.

Bisso-Machado R, Ramallo V, Paixão-Côrtes VR, Acuña-Alonzo V, Demarchi DA, Sandoval JR, Granara AA, Salzano FM, Hünemeier T and Bortolini MC (2016) *NAT2* gene diversity and its evolutionary trajectory in the Americas. Pharmacogenomics J 16:559-565.

Bonatto SL and Salzano FM (1997) A single and early migration for the peopling of the Americas supported by mitochondrial DNA sequence data, Proc Natl Acad Sci USA 94:1866-1871.

Castro de Guerra D, Arvelo H, Rodríguez Larralde A and Salzano FM (1996) Genetic study in Panaquire, a Venezuelan population. Hum Hered 46:323-328.

Coimbra Jr CEA, Flowers NM, Salzano FM and Santos RV (2002) The Xavante in Transition. Health, Ecology, and Bioanthropology in Central Brazil. University Michigan Press, Ann Arbor, 376 p.

Fagundes NJ, Ray N, Beaumont M, Neuenschwander S, Salzano FM, Bonatto SL and Excoffier L (2007) Statistical evaluation of alternative models of human evolution. Proc Natl Acad Sci USA 104:17614-17619.

Franco MH, Weimer TA and Salzano FM (1982) Blood polymorphisms and racial admixture in two Brazilian populations. Am J Phys Anthropol 58:127-132.

Hünemeier T, Amorim CE, Azevedo S, Contini V, Acuña-Alonzo V, Rothhammer F, Dugoujon JM, Mazières S, Barrantes R, Villarreal-Molina MT *et al.* (2012) Evolutionary responses to a constructed niche: Ancient Mesoamericans as a model of gene-culture coevolution. PLoS One 7:e38862.

Jacovas VC, Rovaris DL, Peréz O, de Azevedo S, Macedo GS, Sandoval JR, Salazar-Granara A, Villena M, Dugoujon JM, Bisso-Machado R *et al.* (2015) Genetic variations in the TP53 pathway in Native Americans strongly suggest adaptation to the high altitudes of the Andes. PLoS One 10:e0137823.

Jacovas VC, Couto-Silva CM, Nunes K, Lemes RB, de Oliveira MZ, Salzano FM, Bortolini MC and Hünemeier T (2018) Selection scan reveals three new loci related to high altitude adaptation in Native Andeans. Sci Rep 8:12733.

Kimura EM, Oliveira DM, Jorge SEDC, Abreu CF, Albuquerque DM, Costa FF and Sonati MF (2008) Identification of characterization of novel and rare variants of human hemoglobin. Rev Bras Hematol Hemoter 30:316-319.

Lindenau JD, Guimarães LS, Hurtado AM, Hill KR, Tsuneto LT, Salzano FM, Petzl-Erler ML and Hutz MH (2014) Association between HLA-DR4 haplotypes and tuberculin skin test response in the Aché population. Tissue Antigens 84:479-483.

Neel JV and Salzano FM (1967) Further studies on the Xavante Indians. X. Some hypotheses-generalizations resulting from these studies. Am J Hum Genet 19:554–574.

Parreiras-e-Silva LT, Vargas-Pinilla P, Duarte DA, Longo D, Espinoza Pardo GV, Dulor Finkler A, Paixão-Côrtes VR, Paré P, Rovaris DL, Oliveira EB *et al.* (2017) Functional New World monkey oxytocin forms elicit an altered signaling profile and promotes parental care in rats. Proc Natl Acad Sci USA 14:9044–9049.

Ramallo V, Bisso-Machado R, Bravi C, Coble MD, Salzano FM, Hünemeier T and Bortolini MC (2013) Demographic expansions in South America: Enlightening a complex scenario with genetic and linguistic data. Am J Phys Anthropol 150:453-463.

Reales G, Rovaris DL, Jacovas VC, Hünemeier T, Sandoval JR, Salazar-Granara A, Demarchi DA, Tarazona-Santos E, Felkl AB, Serafini MA *et al.* (2017) A tale of agriculturalists and hunter-gatherers: Exploring the thrifty genotype hypothesis in native South Americans. Am J Phys Anthropol 163:591-601.

Salzano FM (1957) The blood groups of South American Indians. Am J Phys Anthropol 15:555-579.

Salzano FM (1961) Rare genetic conditions among the Caingang Indians. Ann Hum Genet 25:123-130.

Salzano FM (1968) Intra- and inter-tribal genetic variability in South American Indians. Am J Phys Anthropol 28:183-189.

Salzano FM (2009) The fission-fusion concept. Curr Anthropol 50:959–959.

Salzano FM (2015) Bioethics, population studies, and genetico-phobia. J Community Genet 6:197-200.

Salzano FM and Bortolini MC (2002) The Evolution and Genetics of Latin American Populations. Cambridge University Press, Cambridge, 511 p.

Salzano FM and Calegari-Jacques S (1988) South American Indians: A case study in Evolution. Oxford University Press, Oxford. 259 p.

Salzano FM and Hurtado AM (2004) Lost Paradises and the Ethics of Research and Publications. Oxford University Press, New York, 238 p.

Salzano FM and Sans M (2014) Interethnic admixture and the evolution of Latin American populations. Genet Mol Biol. 37(Suppl 1):151-170.

Sans M, Salzano FM and Chakraborty R (1997) Historical genetics in Uruguay: Estimates of biological origins and their problems. Hum Biol 69:161-170.

Skoglund P, Mallick S, Bortolini MC, Chennagiri N, Hünemeier T, Petzl-Erler ML, Salzano FM, Patterson N and Reich D (2015) Genetic evidence for two founding populations of the Americas. Nature 525:104-108.

Tarazona-Santos E, Carvalho-Silva DR, Pettener D, Luiselli D, De Stefano GF, Labarga CM, Richards O, Tyler-Smith C, Pena SD and Santos FR (2001) Genetic differentiation in South Amerindians is related to environmental and cultural diversity: evidence from the Y chromosome. Am J Hum Genet 68:1485–1496.

Thompson CE, Freitas LB and Salzano FM (2018) Molecular evolution and functional divergence of alcohol dehydrogenases in animals, fungi and plants. Genet Mol Biol 41(Suppl 1):341-354.

Tondo CV and Salzano FM (1960) Hemoglobin types of the Caingang Indians of Brazil. Science 132:1893-1894.

Tondo CV, Salzano FM and Rucknagel Dl (1963) Hemoglobin Porto Alegre, a possible polymer of normal hemoglobin in a Caucasian Brazilian family. Am J Hum Genet 15:265-279.

Vargas-Pinilla P, Paixão-Côrtes VR, Paré P, Tovo-Rodrigues L, Vieira CMAG, Xavier A, Comas D, Pissinatti A, Sinigaglia M, Rigo MM *et al.* (2015) Evolutionary pattern in the OXT-OXTR system in primates: Coevolution and positive selection footprints. Proc Natl Acad Sci USA 112:88–93.

Viscardi LH, Paixão-Côrtes VR, Comas D, Salzano FM, Rovaris D, Bau CD, Amorim CEG and Bortolini MC (2018) Searching for ancient balanced polymorphisms shared between Neanderthals and Modern Humans. Genet Mol Biol 41:67-81.

Wang S, Lewis CM, Jakobsson M, Ramachandran S, Ray N, Bendoya G, Rojas W, Parra MV, Molina JA, Gallo C *et al.* (2007) Genetic variation and population structure in Native Americans. PLoS Genet 3:e185.

WHO (1964) Research in population genetics of primitive groups. World Health Organization, Geneva.

WHO (1968) Research on human population genetics. World Health Organization, Geneva.

Zembrzuski VM1, Basta PC, Callegari-Jacques SM, Santos RV, Coimbra CE, Salzano FM and Hutz MH (2010) Cytokine genes are associated with tuberculin skin test response in a native Brazilian population. Tuberculosis 90:44-49.

Mara H. Hutz and Maria Cátira Bortolini
Departamento de Genética,
Universidade Federal do Rio Grande do Sul,
Porto Alegre, RS, Brazil.