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CV

1991-92	Student at Microbiology Institute of the University of Bari, Italy; Supervisor: Prof. E.Jirillo.
1993-99	Fellow at Medical Genetics Service of IRCCS-"CSS" Hospital, San Giovanni Rotondo (FG), Italy; Supervisor: Dr. L.Zelante
Sep95-Jul96	Project fellow at Telethon Institute of Genetics and Medicine (TIGEM), Milan, Italy; Supervisor: Dr. B.Franco
1998	Research Associate at Department of Pediatrics of the Children's Hospital of Philadelphia, Philadelphia, PA, USA; Supervisor: Prof. P.Fortina
Nov99-Oct00	Researcher at BIRD (Baschirotto Institute for Rare Diseases), Costozza di Longare (VI), Italy
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The Genetics of Hearing Loss

Hereditary hearing loss comprises a broad spectrum of forms ranging from simple deafness to genetically determined syndromes. The incidence of prelingual hearing loss is 1/1000 births. The most common forms of genetic deafness are the non-syndromic neurosensory autosomal recessive deafness (NSRD) accounting for >75%, autosomal dominant inheritance accounts for a further 10 to 20% of cases, while X-linked inheritance accounts for 2-3%. We largely contributed to the identification of one common gene, named connexin 26 (CX26 or GJB2) and to the description of one very common mutation (35delG). Then, we defined the high worldwide carrier frequency of 35delG mutation in 3,270 random controls from 17 European countries, detecting a carrier frequency of 1 in 35 in southern Europe and 1 in 79 in Central and Northern Europe. In addition, 35delG was detected in 5 out of 376 Jewish subjects of different origin, but was absent in other non-European populations.. as regards to 35delG hystorical tracing. our studies suggest either a single origin for 35delG somewhere in Europe or in the middle East, and the possible presence of a carrier advantage together with a founder effect. The identification of families linked to DFNB1/DFNA3 but negative for GJB2 mutations within CX26, suggested the possible presence of other deafness genes within these loci. Mouse connexin-30 has been cloned and mapped to mouse chromosome 14 in a region syntenic to human chromosome 13q12. It is expressed in the cochlea and partly colocalize together with CX26. All these findings made the human homolog of mCX30 a good candidate gene for deafness. Thus, we have cloned the human connexin-30 gene and detected a missense mutation in a family affected by NSAD. The mutation affects a residue highly conserved across species. CX30 message, found at high levels in the trachea, thymus and thyroid gland, occurs also in the mouse embryos inner ear. Functional electrophysiological studies measuring the conductances of either wild-type and mutant in Xenopus oocytes clearly demonstrate a) the role of this mutation in affecting the protein function, b) its trans-dominant effect on the wild type providing a molecular explanation for the dominant effect.

Finally, a proportion of cases, yet to be defined is due to mutations in mitochondrial DNA, which play a significant role in both syndromic and non-syndromic sensorineural hearing impairment. All mutations apart one are in general specific and rare, while a large proportion of Spanish families with late-onset sensorineural deafness carries a mithochondrial DNA mutation named A1555G. This mutation has an age-dependent penetrance for deafness that is enhanced by the treatment with aminoglycosides. Until few years ago genetic deafness was a "mare magnum" in which the absence of knowledge was the main feature. Successively, several loci have been described and the presence of genetic heterogeneity, previously only hypothesized, was clearly demonstrated. Molecular biology techniques applied to the genetics of hearing loss shed a new light on old questions regarding hearing and deafness and already led to a better understanding of the biology of normal and abnormal hearing. These discoveries have major implications in terms of early molecular diagnosis, genetic counseling and possible prevention. For example, despite the large genetic heterogeneity in hearing loss, the identification of GJB2 as a major gene accounting for at least half of the cases of hearing loss and the identification of a very common mutation within it, make possible to provide at risk families and sporadic cases with a simple DNA test to ascertain whether one is carrier or not of 35delG mutated allele. This finding makes either risk calculations or genetic counseling more accurate, and hopefully will allow faster treatment of affected children. In addition, the identification of the above mentioned genes will facilitate development of animal models, which should be useful for studying pathophysiology as well as for development of new strategies for therapeutic intervention, such as gene therapy.