Human hearing loss is a common neurosensory disorder about which many basic research and clinically relevant questions are unresolved. This review on hereditary deafness focuses on three examples considered at first glance to be uncomplicated, however, upon inspection, are enigmatic and ripe for future research efforts. The three examples of clinical and genetic complexities are drawn from studies of (1) Pendred syndrome/DFNB4 (PDS, OMIM 274600), (2) Perrault syndrome (deafness and infertility) due to mutations of CLPP (PRTLS3, OMIM 614129), and (3) the unexplained extensive clinical variability associated with TBC1D24 mutations. At present, it is unknown how different mutations of TBC1D24 cause nonsyndromic deafness (DFNB86, OMIM 614617), epilepsy (OMIM 605021), epilepsy with deafness, or DOORS syndrome (OMIM 220500) that is characterized by deafness, onychodystrophy (alteration of toenail or fingernail morphology), osteodystrophy (defective development of bone), intellectual disability and seizure