Genetic of autosomal recessive intellectual disability and developmental delay

Intellectual disability and developmental delay (ID/DD) constitute a highly heterogeneous group of disorders both in etiology and clinical presentation. ID/DD affects 1-3% of European individuals and, due to their life-long consequences, have a major impact on families, healthcare systems and society. ID/DDs are the most common reasons for referrals to genetic services and their most severe forms are caused by single genetic defects. While autosomal dominant *de novo* mutations are the predominant cause of ID/DD in Western countries, autosomal recessive gene defects are the leading genetic cause of ID/DD in countries with frequent parental consanguinity. Approximately 5% of the world's population practices consanguinity, i.e. the marriage of close relatives, for religious, cultural, economic, traditional and/or other reasons. Consanguinity dramatically increases the homozygous regions in the genome of the offspring, and therefore brings to homozygosity deleterious alleles that cause autosomal recessive disorders. While the advent of high-throughput sequencing technologies and research efforts in countries that practice consanguinity allowed the identification of hundreds of novel "recessive" causative genes, we are far from reaching a plateau.

To start filling this gap, we propose to study multiplex consanguineous families from Pakistan, which has one of the highest inbred populations in the world. Causality of the variants identified in novel genes will be further verified by (i) data aggregation of multiple laboratories and clinical centers, (ii) 3D protein modeling and/or (iii) study in cellular or animal models like zebrafish, drosophila or mouse We are confident that the enrollment and sequencing of the affected individuals of these families would lead to the discovery of novel autosomal recessive ID/DD genes. Our study will provide insights into pathological mechanisms underlying ID/DDs and associated complex traits. It will improve the overall genetic diagnosis of ID worldwide.