Case Report: Novel homozygous MAN1B1 mutation in two Italian patients with Rafiq syndrome.

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Objectives: Rafiq syndrome (RAFQS) is a rare congenital disorder of glycosylation (CDG) characterized by variably impaired intellectual and motor development, truncal obesity, hypotonia, characteristic facial dysmorphisms, sometimes behavioral problems. RAFQS molecular cause is biallelic pathogenic variants in the MAN1B1 gene (mannosidase alpha class 1B member 1) on chromosome 9q34.3. We report the case of two Italian sisters, born to non-consanguineous and healthy parents, aged 48 and 47 years, with generalized muscle hypotonia, mental retardation, facial dysmorphisms.

Materials and methods: the family is originally from a small town in the northern Italy. The elder sister medical history was positive for infantile strabismus and motor-developmental delay with first steps at 18 months and retarded language milestones. The younger sister medical history revealed infantile febrile seizures and myopic traction maculopathy, anxiety disorder and motor developmental delay During adulthood, they were re-evaluated for a slight worsening of general conditions; in first instance, they underwent a neurological assessment: the examination revealed attitude tremor, general hypotonia, logopenic aphasia and dysarthria. Moreover, they were subjected to new neuropsychological tests (Wechsler Adult Intelligence Scale IV – WAIS-IV), which showed results below the normal range in all the areas studied, allowing to confirm moderate-mild intellectual disability. General examination of both sisters revealed bilateral upper limbs dysmetria, ligament hyperlaxity, bilateral exophthalmos, ogival palate and skin laxity. Among the facial dysmorphisms, we described dolichocephaly, peculiar eyebrows (broad and highly arched with lateral thinning), downslanted palpebral fissures, long face with malar flattening, wide nasal bridge, thin upper lip vermilion with everted lower lip. Moreover, they both showed low-set ears and a short neck. The patients were referred for the clinical Exome (SureSelect Custom Constitutional Panel17 Mb – Agilent Technologies).

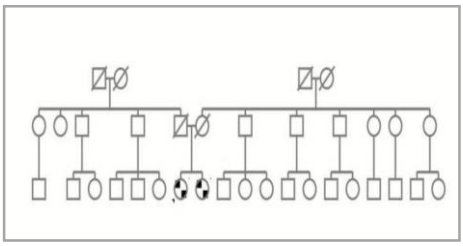

Figure 1. Our patients' pedigree diagram.

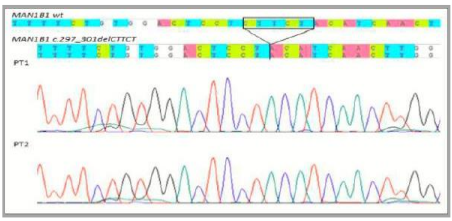

Figure 2. MAN1B1 (NM_016219.5) exon 2 electropherogram. Sanger sequencing confirmed the homozygous deletion of CTTCT nucleotides in both patients.

Results: the analysis showed a novel variant in MAN1B1 (NM_016219.5) gene in homozygosity, c.297_301delCTTCT; p. (Phe100Hisfs*5) at the exon 2, confirmed by Sanger sequencing. According to ACMG guidelines, the variant has been classified as likely pathogenic (PVS1, PM2).

Discussion: to date, almost 40 patients with MAN1B1-CDG mutations, belonging to a few families mostly from middle east countries and in their childhood, have been reported worldwide. To our knowledge, this syndrome has not been diagnosed in Italy before.

Conclusion: in conclusion, we report the first two Italian siblings with Rafiq syndrome and, according to our knowledge, the eldest patients described so far, thus expanding current literature on these disorders.