



Mutation in *RTTN*, a regulator of ciliary function, causes a complex syndrome characterized by severe congenital microcephaly, lissencephaly and profound growth failure in two siblings.

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Background

Primary autosomal recessive microcephaly (MCPH) is a developmental disorder that is characterized by prenatal onset of abnormal brain growth, resulting in an occipitofrontal head circumference (OFC) at birth which is at least two to three standard deviations below the mean for sex-, age and ethnicity. MCPH occurs both in isolation and as part of a broad range of neurodevelopmental syndromes with or without other cortical malformations and with or without growth retardation, being part of a spectrum of disorders affecting brain development and growth. Cellular mechanism involved in determining MPCH, primordial dwarfism (PD) and ciliopathies are in part overlapping, although patients with PD do not seem to have those clinical signs that are typically related to ciliopathies (i.e. cortical malformation, retinopathy, polydactyly).

Case study

Herein we report a consanguineous Maroccan family with 2 siblings affected by primary microcephaly associated with cortical malformation, severe post natal growth failure and dermatitis due to a homozygous mutation of rotatin gene (*RTTN*), a gene involved in ciliogenesis. Birth weight and length were normal (25th and 10th percentile respectively) while head circumpherences were extremely small, 28 cm in the male, and 27 cm in the female, 5 SD below the age- and sex-matched means.

At 18 months the boy was 6.5 kg (<2th) and 68.7 cm (<4 SDS), W/L<2th; head circumference 34 cm; the girl at 6 months was 4.559 kg (<2th) and 57 cm (<4 SDS), W/L<2th; head circumference 31 cm); they had both dermatitis from newborn period and have very high level of IgE. Brain MRI documented severe microcephaly, mainly at the level of the anterior cranial fossa, reduced he number of convolutions, prevailing at the frontal lobes, heterotopia of the gray matter, corpus callosum hypoplasia, severe hypoplasia of the pons (Figure 1). We identified by next generation sequencing a new homozygous mutation in exon 23 of *RTTN* gene (A2953G; Arg985Gly). We analyzed cDNA from leukocytes of the patients and found an abnormal splicing with two different transcripts: one lacking the entire exon 23 and one lacking exons 22 and 23 and causing frameshift (Figure 2 and 3).

Figure 1: Clinical features and brain MRI of the probands.

a: the boy, b: the girl, c: on the left the girl and on the right the boy, arrows indicate grey heterotopia

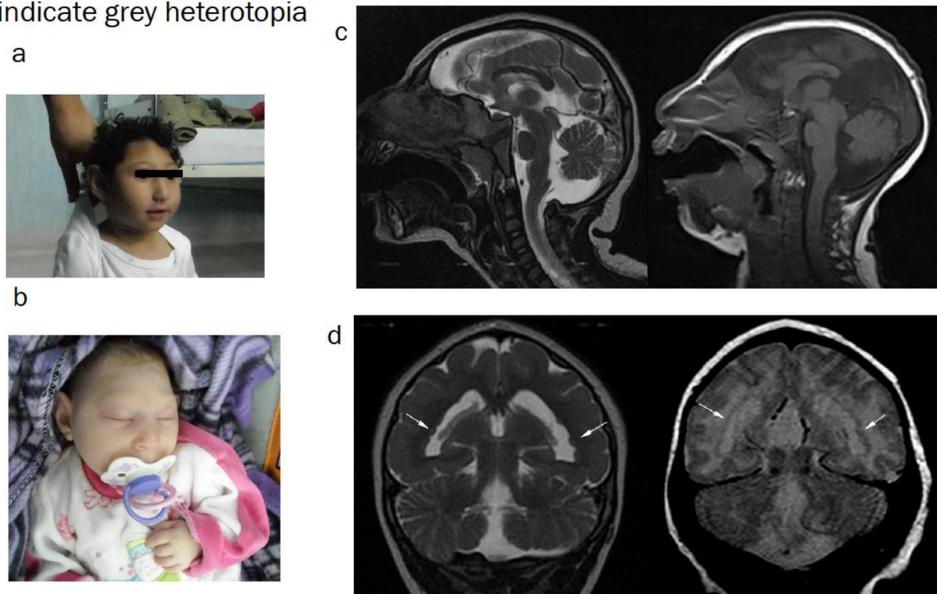


Figure 2: Pedigree genotype of the family members

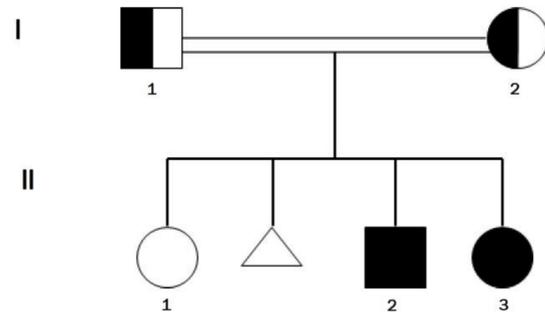
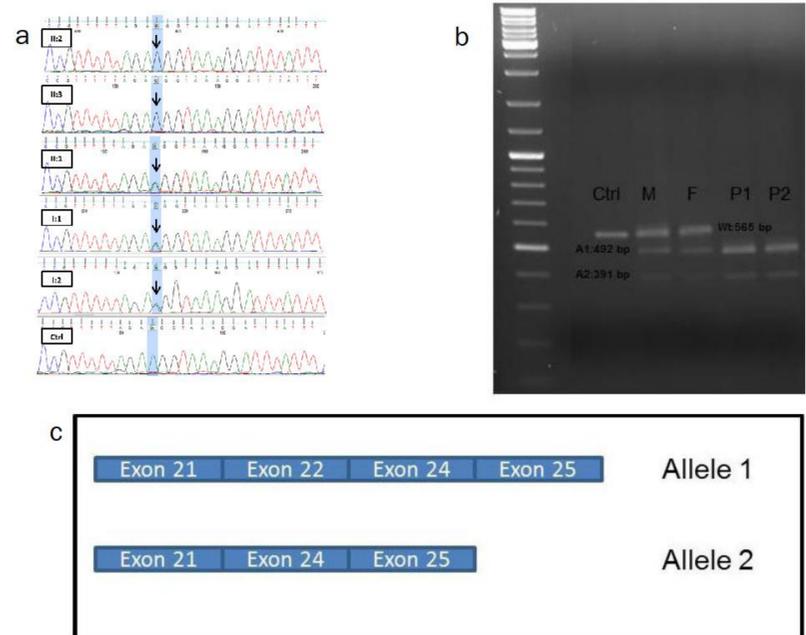


Figure 3: a: sequencing analysis of the entire family; b: Product amplified by PCR on the *RTTN* coding sequence c: Sequencing of each clone showed that there are 2 different cDNAs, encoded by either allele's cDNA: allele 1 shows the skipping of exon 23, while allele 2 shows skipping of exon 22 and 23.



Conclusions

In 2012 mutations in *RTTN*, a protein involved in cilia structure and function, have been described in individuals with bilateral diffuse polymicrogyria, but not growth failure.

For the first time we describe a new phenotype characterized by primordial microcephaly, severe growth failure, cortical malformation and severe dermatitis caused by a mutation in *RTTN*, a gene involved in ciliary function. The different and more severe phenotype of our patients respect those with isolated polymicrogyria described by Kia et al, might be due to the different nature of our mutation. We hypothesize that more severe is the mutation in terms of small amount of residual functional protein, more severe and complex is the phenotype, that affecting splicing, probably causes a more severe protein function derangement. Moreover we found that severe growth failure associated to severe primary microcephaly can be part of the clinical manifestations of ciliopathies and calls for further investigation of the role played by other ciliopathy related genes in the pathogenesis of microcephalic dwarfism.

References

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We have no conflicts of interest to declare.