Rare case of Bardet-Biedl syndrome type 8 caused by a 3.5kb deletion and a splice acceptor variant detected by whole genome sequencing

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INTRODUCTION

Bardet-Biedl Syndrome (BSS) is an ultra-rare autosomal recessive ciliopathy affecting around 1:160,000 live births. BBS8 (OMIM#615985) is caused by homozygous *TTC8* (chr14q31.3) pathogenic variants, accounting for 2% of all BBS cases. Major phenotypic features include retinal cone-rod dystrophy, central obesity, postaxial polydactyly, cognitive impairment, genitourinary abnormalities, and kidney disease. Here we describe the clinical presentation of the rare BBS type 8 in a Brazilian patient, caused by *TTC8* compound heterozygosity.

CASE REPORT

Female patient, 23 years old (yo), was referred to the Genetics Outpatient Clinic of Hospital Universitário Júlio Müller (HUJM, Cuiabá-MT, Brazil) for evaluation. She was born with tetrapolydactyly to healthy, non-consanguineous parents. During infancy, she did not achieve motor milestones within the expected timeframe, sitting without support at 1 yo and walking without support at 2 yo. At 8 yo, she underwent corrective surgery for polydactyly. At 14 yo, the patient began to experience a decline in reading and writing abilities, which ultimately resulted in school withdrawal. Ophthalmological assessment revealed low visual acuity in both eyes due to retinal dystrophy and mild optic atrophy, meeting blindness criteria. Hypotonia of the lower limbs was also noted, prompting a neurological evaluation; however, no definitive diagnosis was established at the time. At 18 yo, the patient underwent initial evaluation at our facility. Upon physical examination, it was observed hyperchromic lesions on the dorsal surface of both hands and anteromedial surface of both knees, bilateral clinodactyly, brachydactyly affecting both hands and feet, upper limb hirsutism, and wide-based gait.

A molecular panel for neuromuscular dystrophies failed to identify causative variants. Whole genome sequencing (WGS), however, identified two likely pathogenic variants:NM_144596.4(TTC8):c.7992A>G:p.?,rs771218088, a splice acceptor variant; and NM_144596.4(TTC8):Seq[GRCh38]del(14)(q31.3)NC_000014.9:g.(88822472_88826002)del/1x, a 3.5kb deletion in TTC8 exon 1.

DISCUSSION

BBS diagnosis is mainly based on clinical criteria, requiring the presence of at least four major features or three major plus two minor features. However, due to variable expressivity and the progressive emergence of symptoms from infancy through early adulthood, a definitive diagnosis may be difficult or delayed. In the present case, diagnosis was even more challenging given negative results from initial molecular testing. WGS was instrumental in detecting the causative mutations carried by this patient, thus allowing identification of one of the rarest BBS types.

Pictures 1 and 2: bitemporal narrowing, long and marked nasolabial filter, and low-set ears are shown.

Pictures 3 and 4: bilateral clinodactyly and brachydactyly affecting both hands and feet, and mallet fingers affecting both feet are shown.

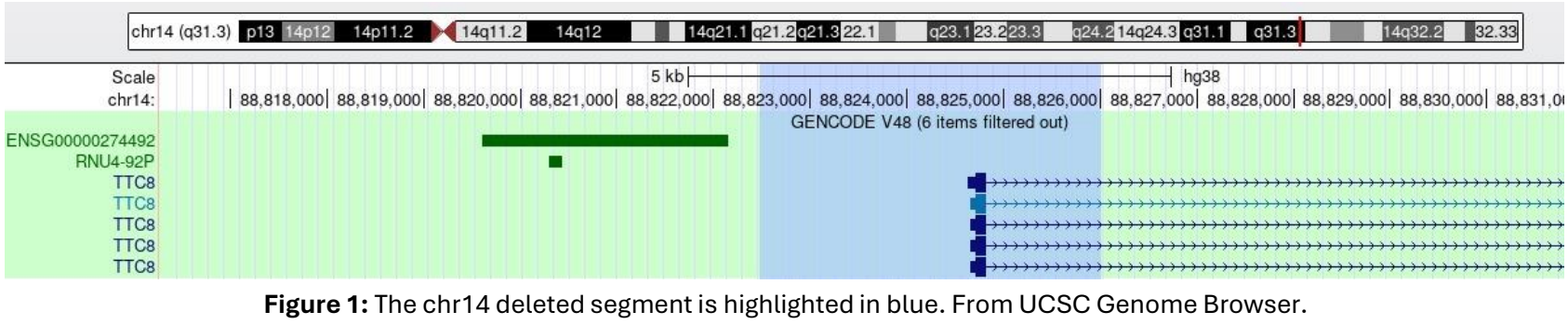

Figure 1: The chr14 deleted segment is highlighted in blue. From UCSC Genome Browser.