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CASE REPORT

Retinitis Pigmentosa and Polydactyly in a Patient with a Heterozygous Mutation on the BBS1 Gene

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Purpose: To report retinitis pigmentosa and a history of polydactyly in a Bardet–Biedl syndrome mutation carrier.

Observations: A 25-year-old male presented to the clinic complaining of poor visual acuity since childhood, night-blindness, and progressive peripheral vision loss. The patient also had a history of polydactyly in both feet. Ophthalmic evaluation was remarkable for a best-corrected visual acuity of 20/400 in both eyes. Imaging revealed a "salt-and-pepper" appearance surrounding the macula, bone-spicule retinal pigment epithelium hyperplasia, paravenous retinal pigment epithelium hyperplasia, and arteriolar attenuation. In addition, bilateral macular autofluorescence with a surrounding granular hypoautofluorescence and an additional hyperautofluorescent zone was present. Full-field ERG results showed non-recordable scotopic ERG responses and diminished photopic ERG responses OU, consistent with progressive rod-cone dystrophy. Genetic testing was positive for a pathogenic heterozygous mutation in the BBS1 gene of the variant c.1169T>G (p.Met390Arg) and several variants of uncertain significance in other genes.

Conclusions and Importance: Ascertainment of the inheritance patterns in BBS is an evolving discussion. Our case, a BBS carrier with retinitis pigmentosa and a history of polydactyly, could support previous research suggesting non-Mendelian genetics in this ciliopathy. Furthermore, genetic testing and analyses of additional mutations and variants of uncertain significance could potentially explain the reason for BBS-like phenotype in presumed BBS carriers.

Keywords: Bardet–Biedl syndrome, heterozygous carrier, retinitis pigmentosa, polydactyly

Introduction

Patients with the Bardet–Biedl syndrome (BBS) have a constellation of clinical features associated to several inherited genetic mutations that cause a widespread ciliopathy and thus multisystem complications.[1] The most common manifestation and one of the primary features of BBS is a retinal rod-cone dystrophy described as an atypical retinitis pigmentosa, which starts developing at a young age.[2] By the third decade of life, patients have markedly impaired vision due to early macular deterioration.[3]

Even though patients with the BBS have a heterogeneous phenotype, several physical characteristics have been identified and need to be present to establish the diagnosis.[4] The BBS diagnosis is clinical, and patients have to display either four primary features or three primary and two secondary features.[4] Primary characteristics include retinal degeneration, truncal obesity, polydactyly, renal dysfunction, genital anomalies, and learning difficulties.[5] Secondary features include diabetes mellitus, congenital heart disease, hypertension, hepatic disease, among others.[5,6]

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The Bardet–Biedl syndrome is an autosomal recessive disease caused by mutations in at least twenty-four different genes.[7] BBS patients are classified according to the gene in which two allelic mutations are present.[1,8,9] In addition to homozygotes, compound heterozygotes, which have different mutant alleles within the same gene, also have the syndrome.[8] Triallelic inheritance has been suggested, given that some BBS homozygotes with an additional heterozygous mutation exhibit more severe phenotypes than their primary mutation would have predicted.[10–13] Confirmation of the syndrome can be made through genetic sequencing 80% of the time.[4,14,15] We report on a patient with retinitis pigmentosa and a history of polydactyly with a single pathogenic heterozygous mutation in the BBS1 gene.

Case Report

A 25-year-old male presented to the clinic complaining of poor visual acuity since childhood, night-blindness, and progressive peripheral vision loss in both eyes (OU). The patient also had a history of post-axial polydactyly in both feet (Figure 1). Ophthalmic evaluation was remarkable for a best-corrected visual acuity of 20/400 OU.

Infrared fundus photography (Optos, Inc.) showed a "salt-and-pepper" appearance surrounding the macula, bone-spicule retinal pigment epithelium (RPE) hyperplasia, paravenous RPE hyperplasia, and arteriolar attenuation OU (Figure 2A and B). Fundus autofluorescence showed macular autofluorescence with a surrounding granular hypoautofluorescence and an additional hyperautofluorescent zone OU (Figure 2C and D). Macular optical coherence tomography revealed decreased macular thickness of 212 microns and 199 microns in the right (OD) and left eye (OS), respectively. Visual field testing (30–2) revealed a mean deviation of −31.52 dB ($p<0.5\%$) and −33.04 dB ($p<0.5\%$) in OD and OS, respectively. Full-field ERG results showed non-recordable scotopic ERG responses and diminished photopic ERG responses OU, consistent with progressive rod-cone dystrophy.

Saliva sample was sent for genetic testing. Full-gene sequencing and deletion/duplication analysis using next-generation sequencing, covering select non-coding variants, coding exons and 10–20 base pairs of adjacent intronic sequence (Invitae Corporation, San Francisco, California), was positive for a single pathogenic heterozygous mutation in the BBS1 gene of the variant c.1169T>G (p.Met390Arg). He had five additional variants of unknown uncertain (VUS) at the ADGVR1, CACNA2D4, COL2A1, IMPG1, and MKKS genes (Table 1).

Discussion

The Bardet–Biedl syndrome is an autosomal recessive disease with great genetic heterogeneity.[7] Our patient, being heterozygous for a single pathogenic mutation in the BBS1 gene (c.1169T>G (p.Met390Arg)), was therefore classified as a carrier and, according to Mendelian inheritance, not expected to show the phenotype. Yet, heterozygous carriers have been reported to be somewhat affected.[16,17]

Previous studies have explored the possibility of BBS heterozygotes having an increased risk of certain BBS characteristics.[18,19] Beales et al[20] correlated an increased risk of renal cancer with BBS heterozygous carriers. However, these findings have not been constant

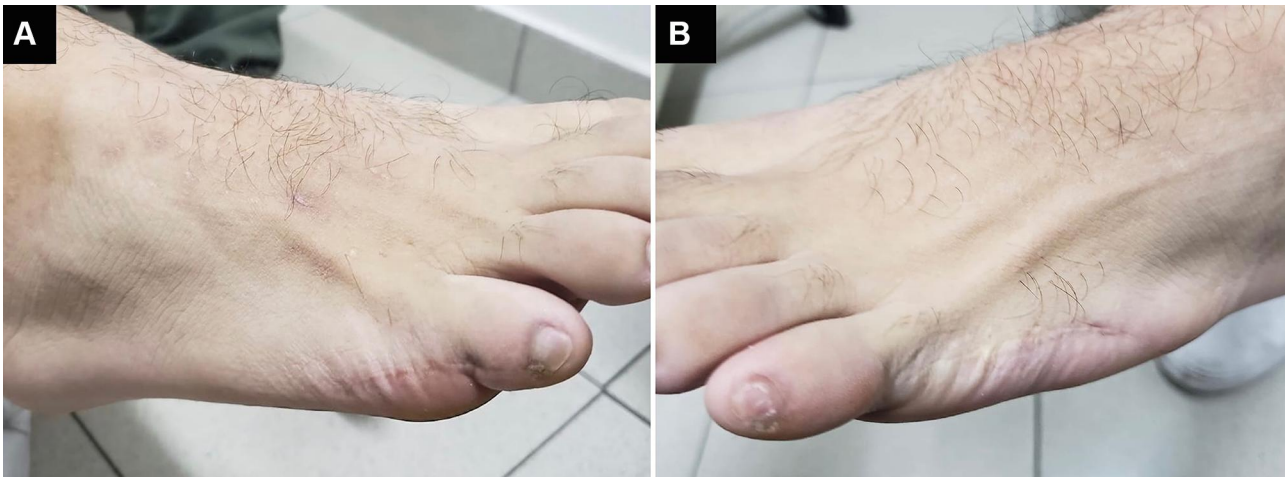

Figure 1 Evidence of post-axial polydactyly surgery. (**A**) Right foot, surgical scar where additional digit was removed. (**B**) Left foot, surgical scar where additional digit was removed.

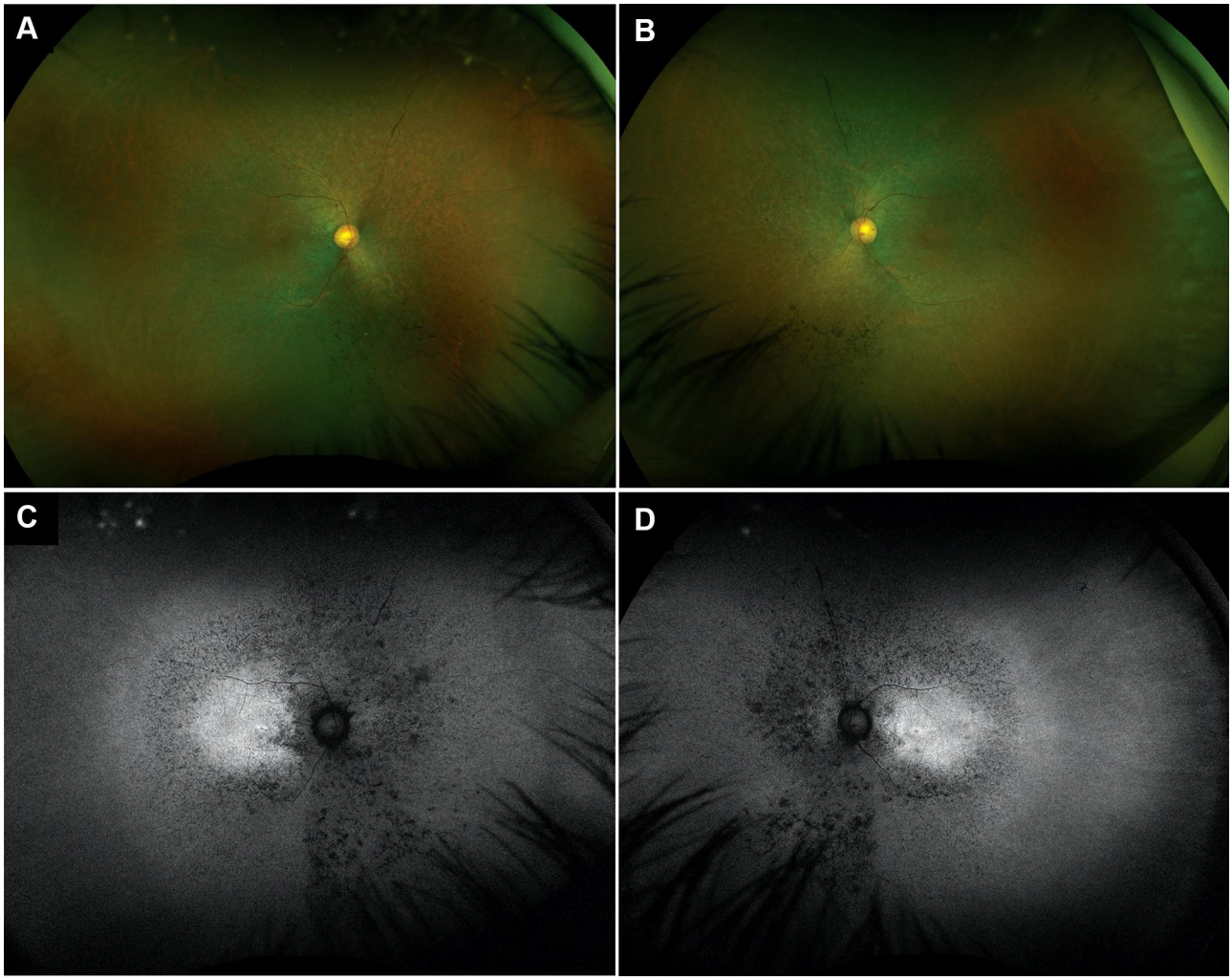

Figure 2 Color fundus photography and autofluorescence showing Retinitis Pigmentosa changes. (**A**) Right eye, there is a "salt-and-pepper" appearance surrounding the macula, which extends towards the nasal mid-periphery. There is bone-spicule RPE hyperplasia, predominantly present in the nasal mid-periphery, and paravenous RPE hyperplasia. Arteriolar attenuation is also evident in all quadrants. (**B**) Left eye, same findings as the right eye. (**C**) Right eye, increased macular autofluorescence surrounded by a ring of granular hypoautofluorescence extending towards the mid-periphery surrounded by an additional zone of hyperautofluorescence. (**D**) Left eye, same findings as the right eye.

throughout the literature. For example, after analyzing a large cohort of BBS carriers, Hjortshøj et al[21] found no association between carriers and renal cancer risk. Croft and Swift[19] suggested that some carriers could have mild characteristics of the condition, like high blood pressure, obesity, and renal complications. Still, a study of Newfoundland's BBS population by Webb et al,[18] with a cohort largely composed of patients with mutations in the BBS1 gene, stated that there is no association between being heterozygous for BBS and an increased frequency of obesity, high blood pressure, diabetes and renal impairment.

Electroretinography (ERG) has shown retinal structural and functional abnormalities in visually asymptomatic BBS carriers with a normal appearing fundus.[2,22] In contrast, our patient presented with advanced retinitis pigmentosa and severe visual decline.

Genetic testing of our patient showed a heterozygous mutation in the MKKS gene of the variant c.1161+3A>G (Intronic) which was listed in ClinVar as a variant of uncertain significance (VCV000860468.2, rs192968747).[23] This MKKS gene sequence change, occuring within intron 4, does not alter the amino acid sequence of the protein.[23] In silico analysis using Mutation Tester described the c.1161 +3A>G (Intronic) variant as a probably harmless polymorphism.[24] However, the mutation disturbs a nucleotide in the intron's consensus splice site, a known cause of aberrant splicing.[24–26] Pathogenic MKKS variants are responsible for approximately 6.3% of BBS cases, specifically BBS6.[22]

Table 1 In silico Analysis of Additional Mutations in Our Patient

Additional VUS Mutations	Variant	Molecular Consequence	Inheritance	Disease	Variant Interpretation of Prediction Programs (In Silico Analysis)			
					Mutation Taster	Provean	SIFT	PolyPhen-2
MKKS	c.1161+3A>G (intronic)	Intronic	AR	Bardet–Biedl	Polymorphism	-	-	-
ADGRV1	c.11579C>T (p.Pro3860Leu)	Missense	AR	Usher Syndrome	Disease Causing	Deleterious	Damaging	-
CACNA2D4	c.2406C>A (p.Tyr802*)	Nonsense	AR	Retinal cone dystrophy	Disease causing	-	-	-
COL2A1	c.526G>A (p.Gly176Ser)	Missense	AD	Achondrogenesis and others.	Disease causing	Neutral	Tolerated	Probably damaging
IMPG1	c.2294T>C (p.Phe765Ser)	Missense	AD	Macular dystrophy	Polymorphism	Deleterious	Damaging	Benign

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

One possibility for our patient's phenotypic and genetic findings is that the MKKS variant found is indeed pathogenic and that he is not a BBS carrier but an actual BBS patient. The occurrence of digenic heterozygous BBS cases, where one allele in two different affected genes is involved, has been previously supported by some researchers.[16,17,27] Another explanation could be that there exists a variation within the BBS1 gene that was undetected by the methodology used, making our patient a compound heterozygote.[28]

The fact that our patient does not meet the full clinical criteria for a BBS diagnosis at present does not mean that he never will, as some primary and secondary characteristics could develop later in life. There are reports of genetically confirmed BBS patients who do not necessarily meet the clinical diagnosis criteria at the time of evaluation.[15,29] Additionally, some BBS patients can present with independent retinal dystrophy without any other BBS feature.[4] Furthermore, some BBS patients with fewer clinical features could have a weakened form of the syndrome.[15]

On the other hand, our patient could truly be a BBS carrier, which would support previous theories regarding BBS inheritance and phenotype penetrance. Some studies suggest that inheritance in patients with the BBS follows a classical Mendelian pattern.[22,28] However, it has been proposed that, like with some other ophthalmic diseases (eg, Leber congenital amaurosis with CRB1 mutations), BBS inheritance is not as purely Mendelian as previously thought.[10,12,17,27,30] Findings of asymptomatic carriers of biallelic BBS mutations pointed out the possibility of incomplete penetrance in certain BBS genes.[10,31] Concurrently, the discovery of an additional BBS heterozygous mutation in many affected homozygous patients implied potential triallelic inheritance.[10–13] Seemingly, the findings in our patient, who had a single pathogenic BBS1 mutation but developed BBS-related features, support previous reports showing the existence of complex inheritance in BBS.[10–13,17]

Conclusion

Ascertainment of the inheritance patterns in BBS is an evolving discussion. Our case, a BBS carrier with retinitis pigmentosa and a history of polydactyly, could support previous research suggesting non-Mendelian genetics in this ciliopathy. Furthermore, genetic testing and analyses of additional mutations and variants of uncertain significance could potentially explain the reason for BBS-like phenotype in presumed BBS carriers.

Ethics Approval and Informed Consent

Institutional review board (IRB) approval for this study was not required. The patient provided informed written consent for the case and images to be published.

Disclosure

The authors report no conflicts of interest in this work.

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