INTRODUCTION

The growing use of next generation sequencing techniques has revolutionized the diagnostic odyssey for many families with intellectual disability, and continues to elucidate and implicate pathways and genes not previously associated with syndromic or nonsyndromic intellectual disability in humans.

A unique group of genes which have been associated with various phenotypes of intellectual disability is that of epigenetic regulators. Of these, several dozen chromatin regulators...
have been implicated, including lysine acetyltransferases, histone deacetylases, DNA methyltransferases, ATP-dependent helicases and others. Several well-recognized examples include CREBBP and EP300, both associated with Rubinstein-Taybi syndrome (Grozeva et al., 2014); KANSL1 associated with the 17q21.31 microdeletion (Koolen-de Vries) syndrome (Kaiser et al., 2014); and HDAC8 implicated in a Cornelia de Lange-like phenotype (Koolen et al., 2012), among others. However, less is known regarding the association of chromatin readers with human disease (Kuechler et al., 2015).

One such chromatin reader now linked to a recognizable intellectual disability phenotype, is Bromodomain and PHD finger-containing protein 1 (BRPF1; OMIM *602410). By its interaction with several histone acetyltransferases (KAT6A, KAT6B and HBO1), BRPF1 promotes histone acetylation (Laue et al., 2008; Li & Durbin, 2009). Most recently, two groups had simultaneously described and characterized a new autosomal dominant disorder manifesting with intellectual disability, ptosis, and/or blepharophimosis and additional features, in 22 individuals, caused by deleterious mutations in BRPF1 (Li, Gui, & Kwan, 2012; Mattioli et al., 2017).

We describe herein four additional affected individuals of a single family, exhibiting intellectual disability of variable severity and distinct facial features, found to harbor a novel mutation in BRPF1.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients were evaluated at the Sheba Medical Center, Tel-Hashomer, Israel. Written informed consent was obtained from the affected individuals or their legal guardians for both genetic analysis and publication of patients’ facial photographs. Approval for human subject research was obtained from the Institutional Review Board of the Sheba Medical Center.

![FIGURE 1](image-url) (a) Genogram of a multiply affected family with BRPF1-associated phenotype. Proband is denoted by the arrow. Full symbols designate affected individuals. Partially full symbols designate individual with Leber’s Hereditary Optic Neuropathy. Mut, allele harboring the p.Q186* mutation in BRPF1. WT, wild type allele. (b) Facial features of individuals harboring the heterozygous BRPF1 variant. Note the ptosis, blepharophimosis, downslanted palpebral fissures and mild retrognathia.
Whole exome sequencing (WES) was performed using an Agilent v5 SureSelect capture kit and Illumina 2,500 sequencing technology. For each sample, paired end reads (2 × 100 bp) were obtained, processed, and mapped to the genome. We used the BWA-MEM algorithm (version 0.7.12) (McKenna et al., 2010) for alignment of the sequence reads to the human reference genome (hg19). The HaplotypeCaller algorithm of GATK version 3.4 was applied for variant calling, as recommended in the best practice pipeline (Musselman, Lalonde, Côté, & Kutateladze, 2012). KGG-seq v.08 was used for annotation of identified variants (Narahara et al., 1990) and in house scripts were applied for filtering based on family pedigree and local dataset of variants detected in previous sequencing projects.

### RESULTS

#### Clinical characteristics

A nonconsanguineous family of mixed Jewish descent with three siblings affected with intellectual disability was referred to our Genetics Institute for evaluation, during an ongoing pregnancy of their healthy 27-year-old sister (Figure 1).

The proband (designated patient III:7) is a 30-year-old male, reported to have developmental delay and intellectual disability. As a child he required special schooling and currently finds employment in manual labor. He has never experienced seizures, nor visual or hearing deficits. Upon physical examination, he showed dysmorphic facial features, most notably bilateral ptosis, hypertelorism and downsloped palpebral fissures. Brain imaging was not performed, and previous genetic workup had included molecular studies for Fragile X (30 repeats) and a chromosomal microarray analysis considered to be normal.

Interestingly, two additional male siblings, 42 years old (patient III:1) and 25 years old (patient III:9) also share dysmorphic facial features including bilateral ptosis, downsloped palpebral fissures and retrongnathia, and both have intellectual disability, with the eldest sibling (III:1) most severely affected. At 42 years of age, he is unemployed and dependent on his parents for daily living. The clinical characteristics of the affected individuals in the family are summarized in Table 1.

The family history is also notable for one male sibling (III:6) who had been previously diagnosed with Leber Hereditary Optic Neuropathy due to a m.3460G > A mutation in MT-ND1, however is otherwise healthy and does not share his brothers' facial features nor intellectual impairment.

#### Molecular analysis

In order to reach a molecular diagnosis in the family, DNA was extracted from whole blood samples from the proband, his siblings and parents. WES was performed for the proband and his parents (trio WES), and had led to the identification of the previously unreported c.556C>T (p.Q186*) truncating mutation on exon 2 of the BRPF1 gene (NM_004634), in the proband and his mother.

Further analysis of the mutation status in family members available for testing, revealed that the mutation fully segregated with the disease in the family (Figure 1), with affected individuals found to be heterozygous, and unaffected found wild type to the mutation.
4 | DISCUSSION

The family described herein exhibited a variable phenotype, including intellectual disability of varying severity, accompanied by facial dysmorphic features and especially ptosis, blepharophimosis and dowsllanting palpebral fissures. Due to limited medical and developmental history, and nonspecific findings upon physical examination, reaching an accurate clinical diagnosis or pursuing gene-specific sequencing would have been extremely challenging. Through WES, however, a timely molecular diagnosis was reached, implicating a heterozygous variant in BRPF1 as the causative mutation in the family.

Consistent with the recent description of the BRPF1-associated phenotype, the affected individuals showed developmental delay and mild to moderate intellectual disability (Li et al., 2012; Mattioli et al., 2017). Interestingly, at 61 years of age, their mother—reportedly healthy upon initial medical history—was also found to harbor the heterozygous pathogenic variant in BRPF1. Indeed, the mother (patient II:2) shares her sons' bilateral ptosis, and her cognitive status was self-perceived as normal. This underscores both the variable neurodevelopmental phenotype of BRPF1 haploinsufficiency, as well as the importance of thorough history taking and accurate phenotyping of probands’ family members, as her initial misclassification as unaffected (or partially affected) might have caused a misdiagnosis or misinterpretation of the WES findings.

Of note, terminal 3p deletions, as well as deletions of the 3p25-p26 region, have been previously associated with a distinct microdeletion syndrome (OMIM #613792), manifesting with intellectual disability of variable severity, microcephaly, ptosis, and additional dysmorphic features (Park et al., 2014). Several genes are encompassed within these deletions, including BRPF1 and SETD5, with the majority of the phenotype previously considered to be attributed to the latter (Yan et al., 2017; You et al., 2015). Upon describing the BRPF1-associated disorder, Mattioli and colleagues compared the phenotypes of individuals harboring point mutations or small deletions of BRPF1 alone or SETD5 alone, to those with a 3p25 deletion encompassing both genes (Mattioli et al., 2017). Their data demonstrated that microcephaly and ptosis (either unilateral or bilateral) and/or blepharophimosis were significantly more common in those with BRPF1 disruptions, while strabismus and small stature were enriched in this group, however did not reach statistical significance. The features seen in the affected individuals in the family described herein, harboring a pathogenic BRPF1 variant, are consistent with these findings, further validating the previous conclusion that several specific phenotypic characteristics, including ptosis and blepharophimosis, are mainly attributable to BRPF1 haploinsufficiency.

To conclude, BRPF1 haploinsufficiency is an underdiagnosed cause of intellectual disability of variable severity, ptosis and/or blepharophimosis and additional nonspecific features, and should be considered in relevant clinical circumstances.

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CONFLICT OF INTEREST

All authors declare no conflict of interests.

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