Blueprint Genetics

Blueprint Genetics Whole Exome Family test

PATIENT

NAME	DOB	AGE	GENDER	ORDER ID
Anonymous	yyy-dd-mm	1	Female	123

PRIMARY SAMPLE TYPE	SAMPLE COLLECTION DATE	CUSTOMER SAMPLE ID
DNA	yyy-dd-mm	

SUMMARY OF RESULTS

TEST RESULTS

ACTB c.587G>A, p.(Arg196His) is pathogenic.

GENETIC VARIANTS

VARIANT TABLE: Genetic alterations

GENE	POS	ID	CODON	CONSEQUENCE	TRANSCRIPT	DNA	PROTEIN	GENOTYPE	1000G	CLASSIFICATION
ACTB	7:5568127	rs281875334	cGc/cAc	missense	NM_001101.3	c.587G>A	p.(Arg196His)	HET	-:	Pathogenic

SEQUENCING PERFORMANCE METRICS - WHOLE EXOME

TEST	GENES	EXONS	BASES	BASES >= 15X	MEAN COVERAGE	PERCENT >= 15X
Whole Exome	27107	410593	36968078	36635365	135.8	99.1

TEST INFORMATION

Blueprint Genetics Whole Exome Family Test (version 1, Sep 16, 2016) consists of sequence analysis of all protein coding genes (RefSeq) for the proband and parents. The test is targeting all protein coding exons and exon-intron boundaries. This diagnostic tool should be used to detect mutations such as single nucleotide substitutions and small insertions and deletions (INDELs). The test should not be used for detection of large copy number variations (CNVs), for analysis of sequence repeats or for diagnosis of disorders caused by mutations in the mitochondrial DNA.

STATEMENT

CLINICAL HISTORY

Patient is a 1-year-old girl with a multisystem disorder. She has distinctive facial features, palpebral fissures and arthrogryposis. Brain MRI revealed dilated lateral ventricles. Molecular karyotyping has been normal.

CLINICAL REPORT

Sequence analysis using the Blueprint Genetics (BpG) Whole Exome Family identified a heterozygous missense variant rs281875334, c.587G>A, p.(Arg196His) in the ACTB gene. The variant is not present in the parents, indicating that it is a newly arising (de novo) mutation. In silico predictions of the variants pathogenicity are contradictory: Mutation Taster interprets it as

disease causing, SIFT deleterious with low confidence and PolyPhen benign. There are no reported carriers of the variant in the Exome Aggregation Consortium (ExAC) data set, comprised in total of over 60,000 unrelated individuals (http://exac.broadinstitute.org).

Several changes affecting codon Arg196 in *ACTB* have been reported, the *ACTB* c.587G>A, p.(Arg196His) being the most common mutation found in patients with Baraitser-Winter syndrome, also known as Baraitser-Winter cerebrofrontofacial (BWCFF) syndrome. Rivière et al. identified the p.Arg196His mutation in seven patients. One additional patient carried also a mutation affecting codon Arg196 (c.586C>T, p.Arg196Cys), so in total 44% of the patients included in their study had codon Arg196 mutations (8/18). Mutations underlying *BWCFF* were shown to be de novo in 11 of the cases. (PubMed: 22366783). Di Donato et al. found the molecular cause for patient originally described by Der Kaloustian et al. (PubMed: 11311002). Patients disease was caused by the c.586C>T, p.(Arg196Cys) change in the *ACTB* gene (PubMed: 23756437), which was also identified in a female infant by Eker et al. (PubMed: 24211661).

Additionally, Genetic Services Laboratory, University of Chicago has seen the p.Arg196His variant in clinical testing (ClinVar: SCV000246315.1) and Department of Genetics, Robert DEBRE University Hospital has identified the p.Arg196Cys variant in clinical testing (ClinVarSCV000148643.1, reported in PubMed: 25052316). Department of Genetics, Robert DEBRE University Hospital has also identified a c.586C>A, p.(Arg196Ser) variant in clinical testing (ClinVar: SCV000148644.1, reported in PubMed: 25052316 mistakenly as p.Arg196His).

Mutations in the *ACTB* and *ACTG1* genes underlie Baraitser-Winter syndrome, a rare condition that affects primarily the development of the brain and eyes. It is characterized by typical craniofacial features and intellectual disability (ID) that ranges from mild (usually in those with normal brain structure) to profound (typically in those with a neuronal migration defect). Typical facial features include hypertelorism with ptosis, broad bulbous nose, ridged metopic suture, arched eyebrows and progressive coarsening of the face. Many affected individuals have iris or retinal coloboma, sensorineural deafness, and muscle wasting resulting in a peculiar stance with kyphosis, anteverted shoulders, and slightly flexed elbows and knees. Seizures, congenital heart defects, and renal malformations also are common. Differential diagnosis includes Noonan syndrome, Kabuki syndrome and hypertelorism, Teebi type. (https://www.ncbi.nlm.nih.gov/books/NBK327153/).

Recently Verloes et al. presented detailed phenotypic descriptions and neuroimaging on 36 patients analyzed by their group and six cases from the literature with a molecularly proven actinopathy (9 *ACTG1* and 33 *ACTB*). In conclusion, the major clinical anomalies were dysmorphic facial features with hypertelorism, broad nose with large tip and prominent root, congenital non-myopathic ptosis, ridged metopic suture and arched eyebrows. Iris or retinal coloboma and sensorineural deafness was present in many cases. Cleft lip and palate, hallux duplex, congenital heart defects and renal tract anomalies were seen in some cases. Microcephaly may develop with time. Nearly all patients with *ACTG1* mutations, and around 60% of those with *ACTB* mutations had some degree of pachygyria with anteroposterior severity gradient, rarely lissencephaly or neuronal heterotopia. Reduction of shoulder girdle muscle bulk and progressive joint stiffness was also common. Early muscular involvement, occasionally with congenital arthrogryposis, may be present in some patients. Progressive, severe dystonia was seen in one family. Intellectual disability and epilepsy was variable in severity and largely correlated with identified CNS anomalies. Based on the multifaceted role of actins in cell physiology, the authors hypothesized that some clinical manifestations may be partially mutation specific. (PubMed: 25052316).

Baraitser-Winter syndrome has been associated with heterozygous gain-of-function mutations in one of the two ubiquitous cytoplasmic actin-encoding genes ACTB and ACTG1 that encode β- and γ-actins. The known mutations in ACTB are missense mutations altering the function of β-actin, causing changes in the actin cytoskeleton that modify the structure and organization of cells and affect their ability to move. The most common mutation is the p.Arg196His. The variety of signs and symptoms associated with Baraitser-Winter syndrome are explained by the presence of β-actin in cells throughout the body and its involvement in many cell activities. To date, most affected individuals have had a de novo pathogenic variant according to GeneReviews. The risk to sibs is low but presumed to be greater than that of the general population because of the possibility of germline mosaicism. BWCFF syndrome is very rare and less than 50 individuals with a molecularly confirmed diagnosis have been reported to date. However, considering the phenotypic variability, it may be underdiagnosed. (https://www.ncbi.nlm.nih.gov/books/NBK327153/). Actb-/- is embryonically lethal in mice, whereas Actg1-/- shows reduced viability with some surviving to adulthood (PubMed: 22366783).

Mutation nomenclature is based on GenBank accession NM_001101.3 (*ACTB*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

CONCLUSION

Considering the current literature, the well-established role of *ACTB* c.587G>A, p.(Arg196His) as a disease causing mutation, and the clinical data available on the patient, we classify it as pathogenic. Unaffected parents do not carry the variant, and therefore the variant has occurred *de novo*, further supporting its pathogenicity. Genetic counseling is recommended. The recurrence risk for siblings is low but presumed to be greater than that of the general population because of the possibility of germline mosaicism. Disease caused by *ACTB* gene mutations is inherited in an autosomal dominant manner, thus each child of an affected individual has a 50% chance of inheriting the mutation. BpG offers mutation testing for the family if requested.

CONFIRMATION

The *ACTB* c.587G>A, p.(Arg196His) was confirmed by bidirectional Sanger sequencing.

On September 13, 2016 the statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results:

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