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Association of the missense variant p.Arg203Trp in *PACS1* as a cause of intellectual disability and seizures

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Conflicts of Interest: Megan Cho, Rashmi Chikarmane, Rebecca Willaert, Kyle Retterer, Berivan Baskin, Maria Guillen Sacoto, Ingrid Wentzensen, Heather McLaughlin, and Dianalee McKnight are employees of GeneDx. Wendy Chung is a former employee of GeneDx and a member of the Scientific Advisory Board Regeneron Genetics Center. Dr. Schrier Vergano is a member of the Scientific Advisory Board for Ambry Genetics.

Ethical Statement: This study was approved by the Institutional Review Board of Columbia University.

Graphical abstract

Patient	1	2	3	4	5	6	7	8	Total with Feature n	Features of previous 23 individuals n
Gender	Female	Male	Male	Male	Female	Male	Male	Male	27, 6M	7 F, 12 M
Current Age	7 years	7 years	5 years	5 years	19 months	17 years	5 years	3 years	N/A	N/A
Growth parameters $\leq 10^{\text{th}}$ % or $\geq 90^{\text{th}}$ at birth	Unknown	No	Yes $< 10^{\text{th}}$ in Wt, Ht and OFC	Yes $< 10^{\text{th}}$ in OFC	Yes $< 90^{\text{th}}$ wt	Yes $> 90^{\text{th}}$ in Wt, Ht, and OFC	No	Yes $> 90^{\text{th}}$ in Height	N/A	N/A
Growth parameters $\leq 10^{\text{th}}$ % or $\geq 90^{\text{th}}$ currently	Unknown	Yes $< 10^{\text{th}}$ in wt	No	Yes $< 10^{\text{th}}$ OFC	Yes $< 10^{\text{th}}$ in Wt, Ht and OFC	No	No	No	N/A	N/A
DD/ID	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	15/19
Seizures	No	Yes	Yes	Yes	Yes	Yes	No	Uncertain	5/7	12/19
Abnormal Speech	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	15/19
Autism	Yes	No	No	Yes	N/A	No	No	No	3/7	6/19
Cardiac Defect	ASD/VSD/PDA	No	No	No	VSD/AFQ/ASD	Dilatation of main pulmonary artery	VSD	No	4/8	8/19 (ASD/VSD only)
Dysmorphic facial features	Hypertelorism, small teeth, narrow palate, finger and toe syndactyly, broad big toes	Downslanting palpebral fissures, bulbous nasal tip, flat philtrum, medial eyebrow flare, mild right ptosis, widely spaced teeth, upturned anterior hairline with a widow's peak	Downslanting palpebral fissures, long eyelashes, bulbous nasal tip, large single-corn, downturned corners of mouth	Round face, full eyebrows, eyes widely spaced, downslanting palpebral fissures	Almond eyes, mild upslanting palpebral fissures, tented mouth, overlapping toes	Epicanthal folds, short & broad nose, tented nasal bridge, camptodactyly of 1st toe, hyperlordosis of fingers	Triangular face, bushy eyebrows down slanting, nose, thin upper lip, micrognathia	Epicanthal folds, synophrys, low set ears, bulbous nose, thin upper lip, micrognathia	8/8	All

Graphical abstract key: Wt: weight, Ht: height, OFC: open fontanelle, DD: developmental delay, ID: intellectual disability, EEG: electroencephalogram, OCD: obsessive compulsive disorder, ADHD: attention deficit hyperactivity disorder, ASD: atrial septal defect, VSD: ventricular septal defect, PDA: patent ductus arteriosis, PFO: patent foramen ovale.

Keywords

de novo; intellectual disability; PACS1; seizures; whole exome sequencing

A recurrent *de novo* missense variant, p.Arg203Trp was identified within the binding domain of PACS1 in nineteen individuals [1-3] who all share an overlapping phenotype including intellectual disability (ID), delayed language development, dysmorphic craniofacial features, and seizures [1-3]. Using whole exome sequencing (WES), we identified eight additional individuals with the same p.Arg203Trp missense variant in *PACS1* that we demonstrated were *de novo* in seven individuals with available parental DNA. Consistent with the previous studies, all eight individuals of our series have ID, impaired language development, and similar dysmorphic facial features (Table 1)[3]. The dysmorphic features include hypertelorism, downslanting palpebral fissures, epicanthal folds, flat and long philtrum, and bulbous nasal tip. Speech and language in our cohort was universally delayed but developed in most, and three demonstrated dysarthria. Four individuals were unable to speak more than a few words within the first 3 years of life. Autism was diagnosed in two individuals, and four individuals have behavioral challenges including obsessive compulsive disorder, attention deficit hyperactivity disorder, self-injurious behaviors, outbursts, aggression, impulsivity, tactile aversions, and hand flapping. Seizures were observed in five individuals, which included Rolandic epilepsy, complex partial seizures, absence seizures, generalized and focal tonic-clonic seizures, and drop seizures. Cardiac defects were noted in four individuals, including two individuals with atrial septal defects, three with ventricular septal defects, and one individual with a dilated pulmonary artery. The majority of individuals in our series had gastroesophageal reflux, and constipation was common. Additionally, one individual required a gastrostomy-tube, and oral aversion was reported in two individuals. At their current ages, several individuals had lower than average height, weight, and/or head circumference.

The p.Arg203Trp allele is predicted to be damaging by prediction algorithms including PolyPhen2, SIFT, Mutation Taster, and CADD. *PACSI* is intolerant to variation and has a Residual Variance Intolerance Score (RVIS) score of 4.1% and subRVIS suggests that it falls within an intolerant region of *PACSI*. Additionally, ExAC gene-level constraint scores of $\text{misZ} = 4.32$ (4-sigma conservation against missense variations) and $\text{pLI} = 1.0$ (100% likelihood the gene is loss-of-function intolerant), based on ExACv0.3.1 non-TCGA data, indicating that *PACSI* is strongly constrained against both missense and loss-of-function variants.

PACS1 is responsible for trafficking proteins in the trans-Golgi-network [4]. PACS1 localizes proteins such as furin, and cation independent mannose-6-phosphate receptor (CI-MPR) by recognizing and binding to their acidic clusters detected by PACS1's furin-binding region (FBR) from amino acids 117 to 266 [2,4]. Within the FBR, there is a CK-2-binding motif from amino acids 196 to 200 [2]. The p.Arg203Trp missense variant is located within the FBR and three amino acid residues downstream from the CK2 binding motif [2]. The CK-2 binding motif is a target of CK-2 phosphorylation and PP2A dephosphorylation, which regulates cargo binding and PACS1 activation [5]. The close proximity of this important regulatory region and the p.Arg203Trp missense variant suggests that the variant could disrupt regulation leading to mislocalization of proteins [2, 3].

Due to the recurrence of the same specific p.Arg203Trp missense variant, similar phenotypes across the twenty seven patients, the intolerance of *PACSI* to genetic variation, and consistent in silico predictions of pathogenicity, Shuurs-Hoeijmakers' proposal that this variant is acting via a dominant-negative or a gain-of-function is likely correct [2, 3].

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