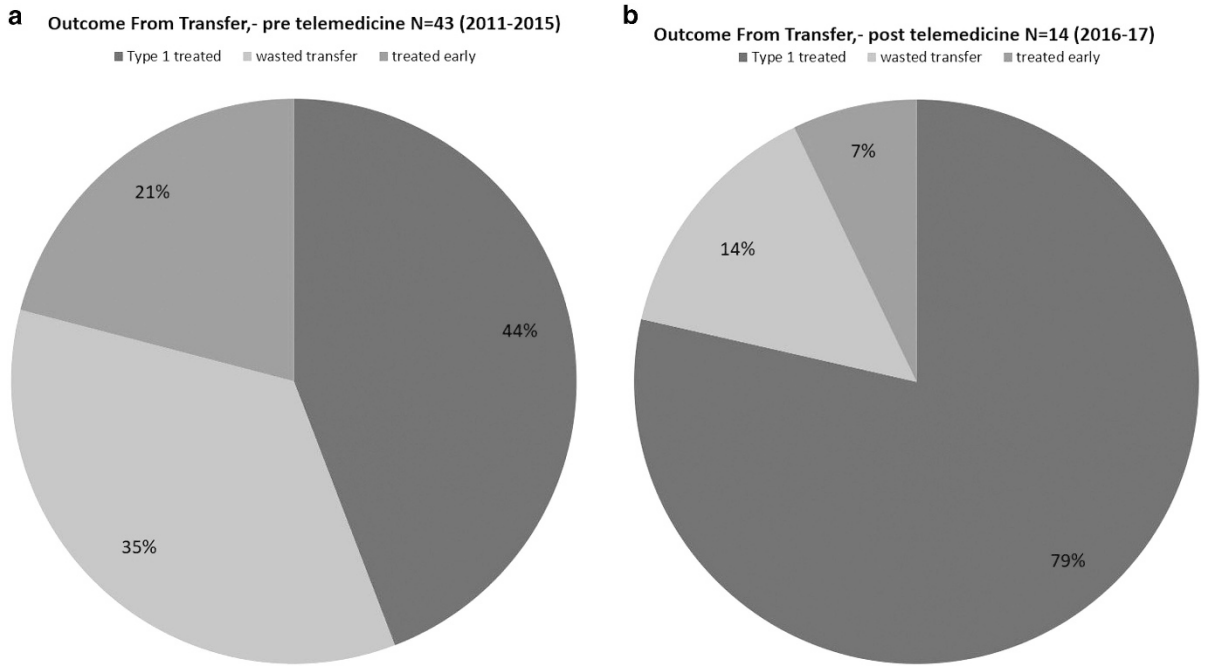

Figure 2 Pie charts showing outcome of transfer (a) pre and (b) post telemedicine service implementation.

Conflict of interest

The authors declare no conflict of interest.

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Sir,

A novel mutation (LEU396ARG) in OPA1 is associated with a severe phenotype in a large dominant optic atrophy pedigree

Dominant optic atrophy is a degenerative disease of the optic nerve, which causes decreased visual acuity in early childhood. Clinical signs include cecocentral scotomas, color blindness (blue-yellow dyschromatopsia), and temporal pallor of the optic nerve head. Visual acuity deficits are typically observed in the first decade of life and progress slowly. Visual acuity is highly variable, ranging from 20/20 to count fingers.

OPA1 is a nuclear gene that encodes a GTPase with key roles in mitochondial metabolism. Mutations in the *OPA1* gene cause the majority of dominant optic atrophy cases.[1,2] We previously reported features of a six-generation dominant optic atrophy family with a particularly severe phenotype. By the end of their second decade of life, visual acuities of family members with dominant optic atrophy ranged from 20/40 to 20/80, and most family members in their seventh decade of life or older were legally blind.[3] Here we report testing this

OPA1

Human:	L	Q	R	M	V	**L**	D	L	P	G	V
Rhesus:	L	Q	R	M	V	**L**	V	L	P	G	V
Mouse:	L	Q	R	M	V	**L**	V	L	P	G	V
Dog:	L	Q	R	M	V	**L**	V	L	P	G	V
Elephant:	L	Q	R	M	V	**L**	V	L	P	G	V
Chicken:	L	Q	R	M	V	**L**	V	L	P	G	V
Frog:	**I**	Q	R	M	V	**L**	V	L	P	G	V
Zebrafish:	**I**	Q	R	M	V	**L**	V	L	P	G	V
Lamprey:	L	Q	R	M	V	**L**	V	L	P	G	V

Figure 1 Conservation of OPA1 amino acid sequence. The leucine amino acid that is altered by the LEU396ARG mutation (indicated with a bold "L") is highly conserved in OPA1 across many species (indicated by the gray shading), which suggests that it may have a conserved role in the protein's function.

family for mutations in the *OPA1* gene using Sanger sequencing. We discovered a novel *OPA1* mutation (LEU396ARG) in all 34 members of this family with dominant optic atrophy available for testing, suggesting that this mutation causes their disease.

The LEU396ARG mutation has not been previously detected in dominant optic atrophy patients; however, a different mutation of the same amino acid, LEU396PRO, has been linked with this disease.[4] We evaluated the LEU396ARG mutation by testing large numbers of normal subjects. Disease-causing mutations should be absent or very rare in nomal individuals. First, we searched a cohort of 362 Iowans with normal eye exams for the LEU369ARG mutation in *OPA1*. No instances were detected in their exomes, which were previously sequenced as part of another project. Next, we searched the gnomAD database (http://gnomad.broadinstitute.org) of exome and genome sequences from 123,136 and 15,496 individuals, respectively. No instances of LEU396ARG were detected in these control populations, which further supports the pathogenicity of this mutation.

We also investigated the potential pathogenicity of the LEU396ARG mutation using mutation analysis algorithms. The LEU396ARG mutation produced a Blosum62 score of −2, a PolyPhen2 score of 1.000 (probably damaging), and a SIFT score of 0.00 (damaging). All three analyses suggested LEU396ARG is disease-causing. Additionaly, the hydrophobic leucine amino acid at position 396 in OPA1 is highly conserved across a range of diverse species (Figure 1). The LEU396ARG mutation places a polar arginine amino acid in this position and is likely harmful to OPA1 structure and function. These analyses suggest that LEU396ARG causes dominant optic atrophy.

Finally, we modeled the effects of the LEU396ARG mutation using a homology model of the OPA1 protein (residues 261–502) built from a structural template (PDB ID 4BEJ) with 35% sequence identity to OPA1.[5] This analysis shows that the LEU396ARG mutation places a charged amino acid, arginine, within the hydrophobic core of the GTPase domain (Figure 2). As a result, it is plausible that the LEU396ARG mutation destablizes this hydrophobic segment of OPA1 protein and alters its function. Together, these data indicate that the LEU396ARG mutation in *OPA1* is associated with severe dominant optic atrophy.

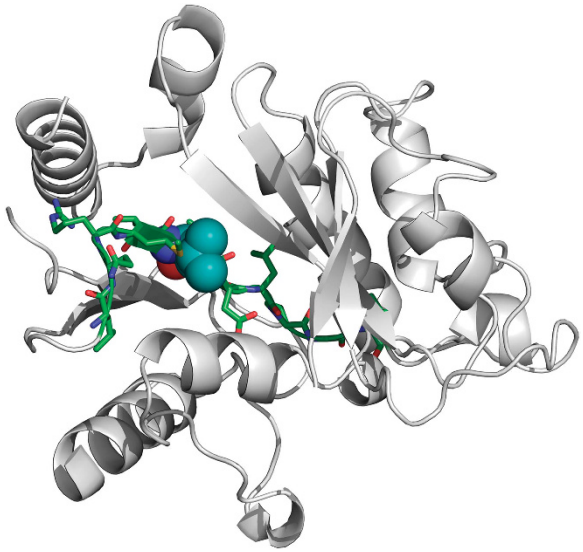

Figure 2 Modeling of the effects of the LEU396ARG mutation on OPA1 protein structure. The OPA1 homology model (residues 261 to 502) is shown with the wild-type amino acid (leucine) at position 396 highlighted in cyan, along with surrounding conserved residues shown in green (positions 391–402, see Figure 1). The LEU396ARG mutation places a charged amino (arginine) within a hydrophobic core of the GTPase domain, which likely alters both OPA1 folding stability and its function.

Conflict of interest

The authors declare no conflict of interest.

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