Darier’s disease (DD, OMIM#124200) is an autosomal dominant skin disorder characterized by multiple dark-brown keratotic plaques and warty papules covered by thick crusts. Most cases of DD are caused by mutations in \textit{ATP2A2}, which is expressed both in the skin and the brain (1). \textit{ATP2A2} encodes the cardiac muscle SERCA2a protein (997 amino acids) and the ubiquitously expressed SERCA2b (1042 amino acids), but no cardiac manifestations have been observed in patients with DD (2). DD sometimes shows neuropsychiatric manifestations, including schizophrenia (3). In a recent Swedish cohort study, 6 of 770 patients with DD (0.8%) were found to have schizophrenia (4). It was determined that individuals with DD had a 2.3 times higher risk of being diagnosed with schizophrenia than matched individuals from the general population, although the genotypes of \textit{ATP2A2} in the patients were not mentioned (4). Thus far, no genotype/phenotype correlations between \textit{ATP2A2} mutations and schizophrenia have been demonstrated.

In this report, we describe a novel mutation in \textit{ATP2A2}, p.Cys318Tyr, in a Japanese male with DD complicated by schizophrenia.

CASE REPORT

The proband is a 66-year-old Japanese man, with no apparent family history, who presented with multiple brown papules with itching on his entire body surface from one year earlier. Examination revealed multiple brown papules with crusts on the seborrhoeic areas of the head, face, neck, abdomen, back and legs (Fig. 1A and B). Partially exudative, hyperkeratotic lesions with odour were seen on the forehead, the nasal wings (Fig. 1A) and the intertriginous areas. His hair and nails were normal. He had been diagnosed with schizophrenia and intellectual disability, and had been treated with oral olanzapine since the age of 63 years. Light microscopy of a lesional skin biopsy from his neck revealed hyperkeratosis, acantholysis, clefts, grains and corpora ronds in the epidermis (Fig. 1C). Treatment with etretinate (0.2 mg/kg/day) effectively resolved the eruptions.

Ethical approval was obtained and all research was performed in accordance with the principles of the Declaration of Helsinki. Genomic DNA from the patient’s peripheral blood leukocytes was used for Sanger sequencing analysis, as described previously (5). Analysis of the data revealed a novel heterozygous missense mutation in \textit{ATP2A2}: c.953G>A (p.Cys318Tyr) (Fig. 1D). The mutation has not been described in the Human Genetic Variation Database, which includes 1,208 exome-sequencing data-sets of healthy Japanese controls (http://www.genome.med.kyoto-u.ac.jp/SnpDB/index.html). \textit{In silico} analysis with PolyPhen-2 predicts the mutation to be “probably damaging” (6), and Sorting Intolerant From Tolerant (SIFT) predicts it to...
be “damaging” (7); thus, the mutation is thought to be functionally relevant.

DISCUSSION

In DD, 2 mutations at the corresponding cysteine residue, Cys318, within the ATP2A2, p.Cys318Arg (8) and p.Cys318Phe (9), have been reported previously, and we detected a novel mutation, p.Cys318Tyr, the third mutation in the residue Cys318 (Fig. 1E). Members of the DD pedigree associated with p.Cys318Arg substitution show severe phenotypes, with early onset, oral lesions and erosive eruptions. However, they have no neuropsychiatric manifestations (8). By contrast, members of the reported family with p.Cys318Phe alteration show typical phenotypes of DD. It is of note that the elder brother of this patient had mild mental retardation and psychiatric abnormality (9). Table I summarizes reported patients with missense mutations affecting the cysteine residue Cys318 and their clinical features. The mutation p.Cys318Arg changes a hydrophobic amino acid into a basic one in the stalk 4 domain of the molecule (8). As for cysteine, both phenylalanine and tyrosine are hydrophobic amino acids, but phenylalanine and tyrosine are aromatic acids, differing from cysteine. In addition, mutation of the same residue to alanine was shown to have no effect on Ca$^{2+}$ transport in vitro (10). Thus, the change to aromatic acids from the corresponding cysteine might determine the occurrence of neuropsychiatric disorders.

Jacobsen et al. (11) reported that some missense mutations in ATP2A2 correlate with the presence of neuropsychiatric phenotypes and, more specifically, that missense mutations in the ATP-binding domain may have relevance in mood disorders. In contrast, Ruiz-Perez et al. (3) noted that neuropsychiatric features are not associated with a specific type of mutation in ATP2A2, but rather depend on concomitant genetic and environmental factors (3). In fact, there are several reports about neuropsychiatric complications in patients with DD having nonsense and frameshift mutations (8). With respect to schizophrenia, there have been few reports related to ATP2A2 genotypes. So far, there are no reported schizophrenia-associated mutation sites or domains within ATP2A2. A significant association between ATP2A2 and schizophrenia has been reported recently in a genome-wide association study (4). Further accumulation of schizophrenia cases with ATP2A2 mutations is needed to confirm the molecular pathogenesis of schizophrenia by ATP2A2 mutations.

ACKNOWLEDGEMENTS

The authors would like to thank Ms Haruka Ozeki and Ms Yuka Terashita for their technical help in analysing mutations of ATP2A2. This study was supported by JSPS KAKENHI Grant Numbers 15H04887, 15K15415, 15H04886, 15K15414, 15H06280. The work was also supported by the Japan Intractable Diseases Research Foundation.

REFERENCES

1. Sakuntabhai A, Ruiz-Perez V, Carter S, Jacobsen N, Burge S, Monk S, et al. Mutations in ATP2A2, encoding a Ca$^{2+}$ pump, cause Darier disease. Nat Genet 1999; 21: 271–277.
2. Dode L, Andersen JP, Leslie N, Dhitavat J, Vilsen B, Hovnanian A. Dissection of the functional differences between sarco(endo)plasmic reticulum Ca$^{2+}$-ATPase (SERCA) 1 and 2 isoforms and characterization of Darier disease (SERCA2) mutants by steady-state and transient kinetic analyses. J Biol Chem 2003; 278: 47877–47889.
3. Ruiz-Perez VL, Carter SA, Healy E, Todd C, Rees JL, Steijlen PM, et al. ATP2A2 mutations in Darier’s disease: variant cutaneous phenotypes are associated with missense mutations, but neuropsychiatric features are independent of mutation class. Hum Mol Genet 1999; 8: 1621–1630.
4. Cederlof M, Bergen SE, Langstrom N, Larsson H, Boman M, Craddock N, et al. The association between Darier disease, bipolar disorder, and schizophrenia revisited: a population-based family study. Bipolar Disord 2015; 17: 340–344.
5. Kaibuchi-Noda K, Sugiuira K, Takeichi T, Miura S, Kagami S, Takama H, et al. Darier’s disease: a novel ATP2A2 missense mutation at one of the calcium-binding residues. Acta Derm Venereol 2015; 95: 362–363.
6. Adzhubei IA, Schmidt M, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. Nat Methods 2010; 7: 248–249.
7. Ng PC, Henikoff S. SIFT: Predicting amino acid changes that affect protein function. Nucleic Acids Res 2003; 31: 3812–3814.
8. Sakuntabhai A, Burge S, Monk S, Hovnanian A. Spectrum of novel ATP2A2 mutations in patients with Darier’s disease. Hum Mol Genet 1999; 8: 1611–1619.
9. Wang PG, Gao M, Lin GS, Yang S, Lin D, Liang YH, et al. Genetic heterogeneity in acrokeratosis verruciformis of Hopf. Clin Exp Dermatol 2006; 31: 558–563.
10. Vilsen B, Andersen JP, MacLennan DH. Functional consequences of alterations to hydrophobic amino acids located at the M4S4 boundary of the Ca(2+) ATPase of sarcoplasmic reticulum. J Biol Chem 1991; 266: 18839–18845.
11. Jacobsen NJ, Lyons I, Hoogendoorn B, Burge S, Kwok PY, O’Donovan MC, et al. ATP2A2 mutations in Darier’s disease and their relationship to neuropsychiatric phenotypes. Hum Mol Genet 1999; 8: 1631–1636.