Updated List of Transport Proteins in *Plasmodium falciparum*

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Malaria remains a leading cause of death and disease in many tropical and subtropical regions of the world. Due to the alarming spread of resistance to almost all available antimalarial drugs, novel therapeutic strategies are urgently needed. As the intracellular human malaria parasite *Plasmodium falciparum* depends entirely on the host to meet its nutrient requirements and the majority of its transmembrane transporters are essential and lack human orthologs, these have often been suggested as potential targets of novel antimalarial drugs. However, membrane proteins are less amenable to proteomic tools compared to soluble parasite proteins, and have thus not been characterised as well. While it had been proposed that *P. falciparum* had a lower number of transporters (2.5% of its predicted proteome) in comparison to most reference genomes, manual curation of information from various sources led to the identification of 197 known and putative transporter genes, representing almost 4% of all parasite genes, a proportion that is comparable to well-studied metazoan species. This transporter list presented here was compiled by collating data from several databases along with extensive literature searches, and includes parasite-encoded membrane-resident/associated channels, carriers, and pumps that are located within the parasite or exported to the host cell. It provides updated information on the substrates, subcellular localisation, class, predicted essentiality, and the presence or absence of human orthologs of *P. falciparum* transporters to quickly identify essential proteins without human orthologs for further functional characterisation and potential exploitation as novel drug targets.

**Keywords:** *Plasmodium falciparum*, malaria, drug target, transport pathway, transporters and channels, systems biology, calcium homeostasis, nutrient uptake

**INTRODUCTION**

To sustain rapid growth within human red blood cells, *Plasmodium falciparum* requires sufficient nutrients and electrolytes for its active metabolism. Therefore, the parasite expresses a wide range of transport proteins to acquire substrates and efflux metabolites. As the majority of these carriers, channels, and pumps are predicted to be essential during intraerythrocytic stages (Martin, 2020) and have no identified human orthologs, these could be exploited as targets of novel drugs (Ludin et al., 2012). Due to the emergence of parasite resistance to most available antimalariais, new therapeutic strategies are urgently needed (Plowe, 2022). There are many reports on transporters associated with drug resistance (Cowell and Winzeler, 2019; Martin, 2020; Murithi et al., 2021;...
Shafik et al., 2022), and advances in the development of drugs that target solute transporters were recently reviewed (Belete, 2020; Monteiro Júnior et al., 2022). Here, an extended list of P. falciparum transport proteins is presented with many new additions and updated information on transporter localisation and essentiality based on experimental evidence and orthology inference.

The last two transporter lists were published in 2020 and 2016 and contained 117 (Martin, 2020) and 139 (Weiner and Kooij, 2016) proteins, corresponding to 2.2% and 2.6% of the predicted P. falciparum proteome, respectively. The localisation within the parasite-infected host cell was not indicated for all of these, as microscopic examination after endogenous tagging with fluorescent proteins or staining using specific antibodies was not conducted for all transporters. However, precise knowledge of the location of a transport protein and its orientation in the membrane is paramount for understanding its function and the dynamics of solute transport processes between cellular compartments. Therefore, the list presented here contains new information on subcellular localisation and function based on results from recent microscopy experiments (Edaye and Georges, 2015; Haase et al., 2021; Murithi et al., 2021; Wichers et al., 2021; Ahiya et al., 2022; Wichers et al., 2022), solubility assays, immunoprecipitation, proximity-dependent biotinylation or subcellular fractionation followed by immunoblot or proteomic analyses (Boucher et al., 2018; Balestra et al., 2021; Bullen et al., 2022), functional and structural studies (Shafik et al., 2020; Beck and Ho, 2021), the presence of targeting signals (Sayers et al., 2018; van Esveld et al., 2021), and Gene Ontology (GO) annotations (Blake et al., 2015). In addition, data on essentiality of P. falciparum genes are usually based on a large piggyBac screen (Zhang et al., 2018) that is known to contain some false-positive and false-negative results (Martin, 2020), highlighting the need for verification by other studies. Thus, results from the latest publications (Jiang et al., 2020; Swift et al., 2020; Oberstaller et al., 2021; Wichers et al., 2022) were included in the list along with information on the presence or absence of human orthologs, as this is important for therapeutic development and was not systematically specified previously. Of note, this mini review focuses mainly on asexual blood-stage parasites and also contains recent data on other stages, as transporters are likely important throughout the life cycle.

Plasmodium gene annotations are still incomplete with a large proportion of genes completely lacking characterisation of their function and localisation or only having sparse functional annotation deduced by orthology (Böhme et al., 2019). The lower number of genes representing the malaria transportome reported in earlier studies may be due to the lack of conventional transmembrane domains in some P. falciparum transporters (Desai, 2012) and difficult analysis by mass spectrometry. The reduced number of detected peptides (Lu et al., 2021) stems both from the typically low protein amounts extracted from parasite culture that are subjected to subcellular fractionation or immunoprecipitation and from the fact that membrane proteins such as transporters are less amenable to proteomics compared to soluble proteins. This has resulted in the conclusion that P. falciparum may have a reduced set of transporters compared to metazoan reference genomes (Weiner and Kooij, 2016; Martin, 2020).

Here, additional putative transporters were detected by compiling data from several databases (Aurrecoechea et al., 2009; Blake et al., 2015; Saier et al., 2016; Elbourne et al., 2017) and the literature. This mini review also covers newly identified putative calcium transporters (Balestra et al., 2021; Gupta et al., 2022), as calcium homeostasis is thought to be critical for all parasite stages (Brochet and Billker, 2016) and likely a promising drug target (Gupta et al., 2022). However, the molecular identity of most of the transporters involved in calcium transport has remained unclear (Lourido and Moreno, 2015), with contrasting results and conclusions regarding their substrates and subcellular localisation as well as the cellular compartment used for calcium storage (Brochet and Billker, 2016). The manually curated list of 197 transporter genes presented here represents almost 4% of 5720 P. falciparum 3D7 genes, of which 5318 are protein-coding (Aurrecoechea et al., 2009), a proportion that is comparable to the 3 – 5% reported for well-studied metazoan species (Elbourne et al., 2017). It includes the most recent published data and provides an updated overview on the substrates, localisation, function, classification, essentiality, and human orthologs of P. falciparum transporters and may serve as a basis for improved annotations of transporter genes and further functional characterisation of potential drug targets.

**APPRAOCHES FOR TRANSPORT PROTEIN IDENTIFICATION AND COMPIILATION OF A COMPREHENSIVE LIST**

Whole-genome sequencing, genome-wide searches and comparative genomics enabled the detection and fast annotation of many P. falciparum transporter genes by assigning functions that are computationally inferred from orthology across hundreds of species, facilitating functional characterisation at a large scale. However, molecular pathways and mechanisms that occur in parasites can differ tremendously from model organisms (Woo et al., 2015), and some known Plasmodium transporters are genus-specific and/or lack conventional transmembrane domains (Desai, 2012). Thus, function predictions based on the presence of protein features and on orthology inference harbour the possibility of incomplete or incorrect annotations. For example, PF3D7_1368200 was annotated as “ABC transporter E family member 1, putative (ABCE1)” due to its ATP-binding cassette that similar to that of ABC transporters (Koenderink et al., 2010). However, it is unlikely to be a transporter because of its function in RNA processing (Mather et al., 2007; Sinha et al., 2021), demonstrating the need for manual curation of GO terms and gene annotations.
The existing transporter list published in 2020 (Martin, 2020) was extended by collating data from various sources. Therefore, a table of 123 transport proteins from the *P. falciparum* strain 3D7 (genome version 3.0) with information on substrates, transporter classes and families was downloaded from http://www.membranetransport.org/transportDB2/index.html (Elbourne et al., 2017). Additional transporters associated with the GO term “transmembrane transporter activity” (GO:0022857) (Blake et al., 2015), mentioned on Malaria Parasite Metabolic Pathways (https://mpmp.huji.ac.il/maps/transporters.html) (Ginsburg and Tilley, 2011) or in research articles were included. For example, PTMCO1 (transmembrane and coiled-coil domain-containing protein, PF3D7_1362300), identified based on orthology to proteins in other protozoan parasites (Gupta et al., 2022), was added. In contrast, glideosome-associated protein 40 (PGAP40, PF3D7_0515700) and rhoptry protein PfROP14 (PF3D7_0613300) were removed, as new data on their function and localisation suggest that these are not transporters (Anantharaman et al., 2007; Zuccala et al., 2012; Ferreira et al., 2020).

As different names were sometimes used for the same protein (Weiner and Kooij, 2016; Staines et al., 2017; Martin, 2020), all alternative names found in the literature are mentioned in the table for clarification (Table 1). Transporter localisation, substrates and functions are indicated as in Martin (2020) and predicted gene essentiality according to Zhang et al. (2018), unless stated otherwise. Transporter classes were assigned according to the Transport Classiﬁcation Database (TCDB) (Saier et al., 2016) and if the transporter family was unknown, it was assigned according to the top TCDB blast hit (http://www.tcdb.org/progs/blast.php) based on sequence similarity to known transport proteins (Altschul et al., 1997). Data on the presence of human orthologs was retrieved from https://mpmp.huji.ac.il/maps/orth_hsap.html (Ginsburg and Tilley, 2011), a list compiled using recent publications. The existence of human orthologs was further verified using the TCDB protein blast.

In total, 197 transport proteins were identiﬁed (Table 1), with some of these forming a complex, e.g. the *Plasmodium* Translocon of Exported proteins (PTEX), consisting of three core components (de Koning-Ward et al., 2009; Beck and Ho, 2021). Protein complex components residing in or associated with the respective membrane that are required for substrate translocation were included, whereas accessory and auxiliary subunits were excluded. For clarity, only the likely site of active transport is indicated for each protein, although it might be detectable in other subcellular compartments during trafficking.

**CALCIUM TRANSPORT PROTEINS AS POTENTIAL DRUG TARGETS**

Calcium homeostasis was chosen as an example for illustrating transport pathways in the *P. falciparum*-infected erythrocyte (Figure 1), as Ca$^{2+}$ signalling is known to be critical throughout the parasite life cycle (Brochet and Billker, 2016) and a link between Ca$^{2+}$ uptake and virulence has been proposed in the related parasite *Toxoplasma gondii* (Pace et al., 2014). In fact, Ca$^{2+}$ transporters such as PfATP6 (PF3D7_0106300) are currently under investigation as novel antimalarial drug targets (Gupta et al., 2022; Monteiro Júnior et al., 2022). While the concentration of free Ca$^{2+}$ is ~1.8 mM in the blood plasma, mature erythrocytes only contain 30 – 60 nM Ca$^{2+}$ (Brochet and Billker, 2016) due to active ion extrusion by the P-type plasma membrane Ca$^{2+}$ ATPases (PMCA) 1 and 4 and slow Ca$^{2+}$ uptake via several channels such as Piezo1, the erythroid N-methyl-d-aspartate (NMDA) receptor, and the voltage-dependent anion channel (VDAC) (Kaestner et al., 2020).

A malaria parasite that resides within an erythrocyte maintains a cytosolic calcium level of approximately 100 nM by permeabilising its host cell and using a regulatory Ca$^{2+}$ pool (Garcia et al., 1996). Extracellular Ca$^{2+}$ is thought to first pass through a parasite-encoded channel in the erythrocyte plasma membrane (EMP) that is independent of PSAC (plasmodial surface anion channel), thereby increasing the intracellular Ca$^{2+}$ concentration of the infected red blood cell (Zippier et al., 2014). One candidate for this channel is hemolysin III (PfHlyIII, PF3D7_1455400), which forms an ion-porous pore of approximately 3.2 nm in EMPS after its release from the parasite digestive vacuole (DV) upon merozoite egress (Moonah et al., 2014). Another potential route of Ca$^{2+}$ entry into the infected erythrocyte is via enhanced activity of a host channel induced by the parasite, as suggested for VDAC (Bouyer et al., 2011).

Passage through the parasitophorous vacuole membrane (PVM) likely occurs via a nutrient pore for solutes < 1.4 kDa formed by PfEXP1 (PF3D7_1121600) and PfEXP2 (PF3D7_1471100) (Garten et al., 2018; Mesén-Ramírez et al., 2019). The ion may then enter the parasite cytosol via a parasite-encoded channel, one candidate being the calcium-permeable stress-gated cation channel PfCSC (PF3D7_1250200) that is activated by high external calcium levels (Martin, 2020). The localisation of this transporter at the PPM was inferred from an ancestral gene (Gaudet et al., 2011) and although this remains to be confirmed experimentally, it seems plausible due to the identification of this protein as an immunoreactive antigen with high serodominance in exposed individuals (Doolan et al., 2008). PfCSC is highly expressed in sporozoites (Le Roch et al., 2003), its exposure to the immune system may occur at this parasite stage.

Calcium can then be stored in the endoplasmic reticulum upon active import by the SERCA-type Ca$^{2+}$-ATPase PfATP6 (Lourido and Moreno, 2015; Martin, 2020). In case of Ca$^{2+}$ overload of the ER, the putative calcium load-activated calcium channel PFMCO1 (Gupta et al., 2022) may become active and release ions into the cytosol (Lourido and Moreno, 2015; Wang et al., 2016). Ca$^{2+}$ efflux from the mitochondrion is likely mediated by the cation/H$^+$ antiporters PfLETM1 (PF3D7_0417300) (Martin, 2020) and PfCAX/PfCHA (PF3D7_0603500) in exchange for protons that travel along the H$^+$ gradient across the inner mitochondrial membrane (Rotmann et al., 2010).
| Gene ID         | Product | Substrate and function                                  | Family | Localisation | Essential | Human ortholog |
|----------------|---------|--------------------------------------------------------|--------|--------------|-----------|----------------|
| PF3D7_1227200  | K1, Kch1| voltage-gated potassium channel                        | 1.A.1  | e - EPM      | b - yes   | yes            |
| PF3D7_1465500  | K2, Kch2| voltage-gated potassium channel                        | 1.A.1  | e - PPM      | b - no    | yes            |
| PF3D7_1436100  | NIC     | putative K+ channel (Ginsburg and Tilley, 2011)         | 1.A.1  | c - PPM      | b - no    | no             |
| PF3D7_1132800  | AQP     | channel for water, glycerol and polyols                | 1.A.8  | e - PPM      | b - yes   | no             |
| PF3D7_1438100  | SEC62   | protein import in complex with Sec61 (Marapana et al., 2018) | 1.A.15 | e - ER       | b - yes   | yes            |
| PF3D7_1250200  | CSC, CSC1| calcium-activated stress-gated channel for Ca2+, K+ and Na+ | 1.A.17 | c - PPM      | b - yes   | yes            |
| PF3D7_1107900  | MSOS    | putative mechanosensitive anion channel                | 1.A.23 | c - PPM?     | b - no    | no             |
| PF3D7_1120300  | MIT1    | magnesium/nickel/cobalt ion channel (Ginsburg and Tilley, 2011) | 1.A.35 | c - mitochondrion (van Esveld et al., 2021) | b - no    | yes            |
| PF3D7_1304200  | MIT2    | magnesium/nickel/cobalt ion channel (Ginsburg and Tilley, 2011) | 1.A.35 | c - mitochondrion (Blake et al., 2015) | b - no    | no             |
| PF3D7_1427600  | MIT3    | magnesium/nickel/cobalt ion channel (Ginsburg and Tilley, 2011) | 1.A.35 | c - mitochondrion (Blake et al., 2015) | b - no    | yes            |
| PF3D7_1333800  | IQn     | anion channel                                          | 1.A.47 | c - PPM      | b - no    | no             |
| PF3D7_1439000  | CTR1    | copper channel                                         | 1.A.56 | e - EPM, PPM | b - yes   | no             |
| PF3D7_1421900  | CTR2    | copper channel                                         | 1.A.56 | e - PPM      | b - no    | no             |
| PF3D7_0306700  | MMgT, EMC5| solute channel                                        | 1.A.67 | c - apicoplast | b - yes   | no             |
| PF3D7_0302500  | CLAG3.1, CLAG3.2, RhopH1, RhopH2, RhopH3 | PSAC/RhopH complex components for nutrient uptake (anions/organic cations) | 1.A.91.1.1 | e - EPM     | b - no    | no             |
| PF3D7_0302200  | CLAG3.1, CLAG3.2, RhopH1, RhopH2, RhopH3 | PSAC/RhopH complex components for nutrient uptake (anions/organic cations) | 1.A.91.1.1 | e - EPM     | b - no    | no             |
| PF3D7_0208000  | CLAG2   | PSAC/RhopH complex components for nutrient uptake (anions/organic cations) | 1.A.91.1.1 | e - EPM     | b - no    | no             |
| PF3D7_0331800  | CLAG8   | PSAC/RhopH complex components for nutrient uptake (anions/organic cations) | 1.A.91.1.1 | e - EPM     | b - no    | no             |
| PF3D7_0335800  | CLAG9   | PSAC/RhopH complex components for nutrient uptake (anions/organic cations) | 1.A.91.1.1 | e - EPM     | b - no    | no             |
| PF3D7_0934900  | RhopH2  | PSAC/RhopH complex components for nutrient uptake (anions/organic cations) | 1.A.91.1.1 | e - EPM     | b - no    | no             |
| PF3D7_0929000  | RhopH3  | PSAC/RhopH complex components for nutrient uptake (anions/organic cations) | 1.A.91.1.1 | e - EPM     | b - no    | no             |
| PF3D7_1362300  | TMCO1   | Ca2+ channel, prevents ER overfilling? (Wang et al., 2016) | 1.A.106 | c - ER? (Blake et al., 2015) | unknown | yes            |
| PF3D7_1432100  | OMP1, VDAC, TOM7 | solute channel                                    | 1.B.8.5.2 | c - mitochondrion (Blake et al., 2015) | unknown | no             |
| PF3D7_0823700  | TOM7    | components of TOM complex for protein import across outer membrane (Sheiner and Soldati-Favre, 2008; Schmidt et al., 2010) | 1.B.8 | c - mitochondrion (Blake et al., 2015) | b - yes   | no             |
| PF3D7_0524700  | TOM22   | components of TOM complex for protein import across outer membrane (Sheiner and Soldati-Favre, 2008; Schmidt et al., 2010) | 1.B.8 | c - mitochondrion (van Dooren et al., 2006) | b - yes   | no             |
| PF3D7_0617000  | TOM40   | components of TOM complex for protein import across outer membrane (Sheiner and Soldati-Favre, 2008; Schmidt et al., 2010) | 1.B.8 | c - mitochondrion (van Dooren et al., 2006) | b - yes   | no             |
| PF3D7_0408700  | PLP1, PPLP1 | erythrocyte permeabilisation and rupture (Jarg et al., 2013) | 1.C.39 | e - EPM (Garg et al., 2013) | b - no, s - yes | no (Yang et al., 2017) |
| PF3D7_1216700  | PLP2, PPLP2 | erythrocyte permeabilisation and rupture (Wirth et al., 2014) | 1.C.39 | e - EPM (Wirth et al., 2014) | b - no, g - yes | no |
| PF3D7_0923300  | PLP3, PPLP3 | erythrocyte permeabilisation and rupture (Wirth et al., 2014) | 1.C.39 | c - host cell membrane (Sassmannshausen et al., 2020) | unknown | no |
| PF3D7_0819400  | PLP4, PPLP4 | erythrocyte permeabilisation and rupture (Wirth et al., 2014) | 1.C.39 | c - host cell membrane (Sassmannshausen et al., 2020) | unknown | no |
|              |         | rupture of mosquito midgut epithelial cells (Wirth et al., 2015) | 1.C.39 | c - host cell membrane (Sassmannshausen et al., 2020) | unknown | no |

(Continued)
| Gene ID     | Product | Substrate and function                                                                 | Family     | Localisation          | Essential | Human ortholog |
|------------|---------|---------------------------------------------------------------------------------------|------------|-----------------------|-----------|----------------|
| PF3D7_0819200 | PLP5, PPLP5 | host cell permeabilisation and rupture (Sassmannshausen et al., 2020)                 | 1.C.39     | c - host cell membrane (Sassmannshausen et al., 2020) | b - yes   | no             |
| PF3D7_1331500 |         | putative calcium channel (Gupta et al., 2022)                                          | 1.C.105    | c - PPM? (Blake et al., 2015) | unknown   | yes            |
| PF3D7_1234600 | TOC75   | protein import across 2nd inner membrane (Agrawal and Striepen, 2010)                 | 1.C.105    | c - apicoplast (Boucher et al., 2018) | b - yes   | no             |
| PF3D7_0104100 | E140, MPMP |                                                                                       | 1.C.105    | c - PPM? (Blake et al., 2015) | b - yes   | no             |
| PF3D7_1455400 | HylI    | forms pore (~3.2 nm) for solutes and ions                                               | 1.C.113    | e - EPM               | b - yes   | no             |
| PF3D7_0204700 | HT1     | imports glucose and fructose                                                               | 2.A.1.1    | e - PPM               | b - yes   | yes            |
| PF3D7_0516500 | MFS1, MT | putative metabolite/drug transporter                                                       | 2.A.1.2    | unknown               | b - no    | yes            |
| PF3D7_0916000 | MFS2    | putative sugar transporter                                                                 | 2.A.1.1    | unknown               | b - no    | yes            |
| PF3D7_0919500 | MFS3    | putative sugar transporter                                                                 | 2.A.1.1    | e - PPM? (Swearingen et al., 2016), c - mitochondrion (Blake et al., 2015) | b - no    | yes            |
| PF3D7_1203400 | MFS4    | putative transporter                                                                       | 2.A.1      | unknown               | b - no    | no             |
| PF3D7_1428200 | MFS5    | putative metabolite transporter                                                           | 2.A.1      | unknown               | b - no    | no             |
| PF3D7_1440800 | MFS6    | H+ import, metabolite/drug export                                                        | 2.A.1      | e - apicoplast        | b - no    | no             |
| PF3D7_1107000 | P115    |                                                                                           | 2.A.1      | c - PPM (Blake et al., 2015) | b - no    | no             |
| PF3D7_0614300 | MFR1    | putative organic anion transporter                                                        | 2.A.1.2    | unknown               | b - no    | no             |
| PF3D7_0104700 | MFR2    | putative amino acid transporter                                                           | 2.A.1      | e - PPM (Wichers et al., 2021) | b - no    | no             |
| PF3D7_0312500 | MFR3    | putative amino acid transporter                                                           | 2.A.1      | e - PPM (Wichers et al., 2021) | b - no    | no             |
| PF3D7_0914700 | MFR4    | putative amino acid transporter                                                           | 2.A.1      | e - PPM (Wichers et al., 2021) | b - no    | no             |
| PF3D7_1129900 | MFR5    | putative amino acid transporter                                                           | 2.A.1      | e - PPM (Wichers et al., 2021) | b - no    | no             |
| PF3D7_0104800 | NPT1    | putative amino acid transporter                                                           | 2.A.1      | e - PPM (Wichers et al., 2021) | b - no    | no             |
| PF3D7_0201300 | MCT1    | exports monocarboxylate                                                                   | 2.A.1      | c - PPM               | b - yes   | yes            |
| PF3D7_0926400 | MCT2    | exports organic solutes, imports H+                                                      | 2.A.1      | e - apicoplast        | b - no    | no             |
| PF3D7_1038800 | ACT, AT, AT1 | imports acetyl-CoA, exports CoA                                                         | 2.A.1.25   | e - ER                | b - no    | yes            |
| PF3D7_1104800 | UMF     | pantothenate:H+ import                                                                    | 2.A.1.63   | c - PPM               | b - yes   | no             |
| PF3D7_0206200 | TFP1, PAT | pantothenate:H+ import (Ginsburg and Tilley, 2011)                                       | 2.A.1.66   | e - PPM               | b - no    | yes            |
| PF3D7_0529200 | GPH     | putative sucrgarction symporter                                                          | 2.A.2      | unknown               | b - no    | no             |
| PF3D7_0715900 | CDF, ZIP3 |                                                                                         | 2.A.4      | e - cytoplasmic vesicle (Wichers et al., 2022) | b - no    | yes            |
| PF3D7_0609100 | ZIP1    | Zn2+ import? (Ginsburg and Tilley, 2011)                                                | 2.A.5      | e - PPM (Wichers et al., 2022) | b - no    | yes            |
| PF3D7_1022300 | ZIPCO, ZIP2 | Zn2+/Fe2+ import into cytosol                                                          | 2.A.5      | c - PPM? (Blake et al., 2015) | b - no    | yes            |
| PF3D7_0107500 | NCR1, NPC1R | cholesterol/sterol/lipid export, H+ import                                               | 2.A.6.6    | e - PPM               | b - yes   | yes            |
| PF3D7_0715800 | DMT1    | organic solute transport                                                                 | 2.A.7.3    | c - apicoplast        | b - no    | no             |
| PF3D7_0716900 | DMT2    | IPP export                                                                               | 2.A.7      | e - apicoplast        | b - yes   | no             |
| PF3D7_0709800 | CRT     | drug:peptide:H+ export                                                                   | 2.A.7.3    | e - DV                | b - no    | yes            |
| PF3D7_0508300 | TPT, TPT, aPT | PEP/3GP import, P, export                                                          | 2.A.7.9    | e - apicoplast        | b - yes   | yes            |
| PF3D7_0530200 | PPT, PPT, aPT | PEP/3GP import, P, export                                                          | 2.A.7.9    | e - apicoplast        | b - yes   | yes            |
| PF3D7_1218400 | TPT3    | putative organic phosphate ester,P, antiporter                                           | 2.A.7.9    | unknown               | b - no    | yes            |

(Continued)
| Gene ID     | Product | Substrate and function | Family | Localisation | Essential | Human ortholog |
|------------|---------|------------------------|--------|--------------|----------|----------------|
| PF3D7_0505300 | NGT     | UDP-N-acetylglucosamine import, UMP export | 2.A.7.10 | c - Golgi     | b - no   | yes            |
| PF3D7_1113300 | UGT     | UDP-galactose/UDP-glucose import, UMP export | 2.A.7.11 | e - ER       | b - yes  | yes            |
| PF3D7_0212000 | GFT     | GDP-tucose import, GMP export | 2.A.7.16 | c - Golgi     | b - yes  | yes            |
| PF3D7_0522500 | NPA     | Mg²⁺ import | 2.A.7.25 | e - PPM      | b - yes  | yes            |
| PF3D7_0629500 | AT1     | transports Ile, Leu, Met | 2.A.18  | c - PPM, DV  | b - yes  | yes            |
| PF3D7_1231400 | AAT2    | transports amino acids, GABA | 2.A.18  | c - PPM      | b - no   | yes            |
| PF3D7_1231400 | AAT3    | transports Ile, Leu, Met or Ca²⁺ (Buikstra et al., 2021) | 2.A.18 | unknown | b - yes | no             |
| PF3D7_0603500 | CAX, CHA| imports H⁺, exports Ca²⁺/Mg²⁺/Mn²⁺ | 2.19    | e - mitochondrion | b - no   | no             |
| PF3D7_1340900 | PT      | imports phosphate and Na⁺ into cytosol | 2.20    | e - PPM      | b - yes  | yes            |
| PF3D7_0209800 | NSS1    | putative amino acid transporter | 2.22    | e - PPM (Blake et al., 2015) | b - yes  | yes            |
| PF3D7_0515500 | GEP1, NSS2 | neurotransmitter:Na⁺ symport (Ginsburg and Tilley, 2011) | 2.22    | c - cytoplasmic vesicle (Jiang et al., 2020) | b - no   | no             |
| PF3D7_1132500 | NSS3    | amino acid/GABA transport | 2.22    | c - PPM      | b - no   | yes            |
| PF3D7_0714100 | MAATS1  | export of H⁺ and amino acids (Ginsburg and Tilley, 2011) | 2.22    | unknown | b - no | yes            |
| PF3D7_1368700 | TPC, DNC | thiamine pyrophosphate import, nucleotide export | 2.29    | c - mitochondrion | b - yes  | yes            |
| PF3D7_0905200 | MRS3, MC5 | putative Fe²⁺/Mn²⁺ import (Blake et al., 2015) | 2.29    | c - mitochondrion | b - yes  | yes            |
| PF3D7_0407500 | MTA1, MC3 | unknown | 2.29    | c - mitochondrion | b - yes  | yes            |
| PF3D7_1214600 | SAMC, PET8 | imports S-adenosylmethionine, exports S-adenosylhomocysteine | 2.29    | e - mitochondrion | b - yes  | yes            |
| PF3D7_0108400 | MEM1, MC1 | unknown | 2.29    | c - mitochondrion | b - no   | yes            |
| PF3D7_0108800 | AMC1, MC2 | unknown | 2.29    | c - mitochondrion | b - yes  | no             |
| PF3D7_0811100 | AMC2, MC4 | unknown | 2.29    | c - mitochondrion | b - no   | yes            |
| PF3D7_0908800 | AMC3, MC6 | unknown | 2.29    | c - mitochondrion | b - yes  | yes            |
| PF3D7_1037300 | AAC1, ADT | ADP/ATP antiporter (Blake et al., 2015) | 2.29    | e - mitochondrion | b - yes  | yes            |
| PF3D7_1004800 | AAC2, PAAC | ADP/ATP antiporter (Blake et al., 2015) | 2.29    | c - mitochondrion | b - yes  | yes            |
| PF3D7_1223800 | COC, YHM2 | imports oxoglutarate, exports citrate | 2.29    | c - mitochondrion | b - no   | yes            |
| PF3D7_0825900 | DTC, CMT | imports dicarboxylate, exports tricarboxylate | 2.29    | e - mitochondrion | b - yes  | yes            |
| PF3D7_1302500 | MPC, PIC, PIC2 | P₁H⁺ import | 2.29    | c - mitochondrion | b - no   | yes            |
| PF3D7_1303500 | NHE | H⁺ import into cytosol in exchange for Na⁺ | 2.36    | c - PPM (Blake et al., 2015) | b - no   | yes            |
| PF3D7_0904500 | MR1, MC5 | putative Na⁺:H⁺ exchanger (Saier et al., 2016) | 2.36    | unknown | b - yes | yes            |
| PF3D7_0827700 | MGT1 | Mg²⁺:H⁺ antiporter (Blake et al., 2015) | 2.36    | unknown | b - no | yes            |
| PF3D7_1135000 | unknown | unknown | 2.43    | c - apicoplast | unknown | no             |
| PF3D7_0316600 | FNT | lactate/formate and H⁺ release from cytosol | 2.44    | e - PPM, DV | b - no | no             |
| PF3D7_1471200 | SuLP | inorganic anion antiporter | 2.53    | e - PPM      | b - yes  | yes            |
| PF3D7_0523800 | NRAMP2, NRAMP, VRVT1 | Fe²⁺/Mn²⁺:H⁺ export | 2.55    | e - DV (Wichers et al., 2022) | b - yes | yes            |
| PF3D7_1347200 | NT1, ENT1 | purine base import | 2.57    | e - PPM      | b - yes  | no             |
| PF3D7_0824400 | NT2, ENT2 | nucleoside/nucleobase import | 2.57    | e - ER       | b - no   | no             |
| PF3D7_1469400 | NT3, ENT3 | putative nucleoside transporter | 2.57    | unknown | b - no | no             |
| PF3D7_0103500 | NT4, ENT4 | adenosine/adenosine import | 2.57    | c - PPM      | b - yes  | yes            |
| PF3D7_0212800 | MATE | putative organic solute:Na⁺/H⁺ antiporter | 2.66    | unknown | b - no | yes            |
| PF3D7_0826800 | FT1 | imports pABA and folates | 2.71    | e - PPM      | b - no   | no             |
| PF3D7_1116500 | FT2 | imports pABA, folates, 5-methyltetrahydrofolate | 2.71    | e - PPM      | b - no   | no             |
| PF3D7_1223700 | VT | imports Fe³⁺ for detoxification, exports H⁺ | 2.89    | unknown | b - no | yes            |
| PF3D7_0417300 | LETM1 | imports H⁺, exports Ca²⁺/K⁺ | 2.97    | c - mitochondrion | b - yes  | yes            |
| PF3D7_1340800 | MIP1 | pyruvate:H⁺ importer | 2.105   | c - mitochondrion | b - yes | yes            |
| Gene ID  | Product | Substrate and function | Family  | Localisation  | Essential | Human ortholog |
|---------|---------|------------------------|---------|---------------|-----------|----------------|
| PF3D7_1470400 | MPC2 | pyruvate:H+ importer | 2.A.105 | c - mitochondrion | unknown | yes |
| PF3D7_1033000 | HPR1, AMC4 | unknown | 2.A.123 | c - mitochondrion? | (van Esved et al., 2021) | b - yes | no |
| PF3D7_0216600 | SWEET | putative glucose/galactose transporter | 2.A.123 | c - ER/Golgi | unknown | b - yes | yes |
| PF3D7_0523000 | MDR1, ABCB1, Pgh1 | active drug and solute import (Friedrich et al., 2014) | 3.A.1.201 | e - DV (Papalexis et al., 2001) | b - yes | yes |
| PF3D7_1447900 | MDR2, ABCB2 | active Cd^2+ extrusion from cytosol | 3.A.1.210 | e - PPM, DV | b - no (van der Velden et al., 2015) | yes |
| PF3D7_1145500 | MDR3, ABCB3 | active peptide efflux | 3.A.1.209 | e - apicoplast | b - no | yes |
| PF3D7_0302600 | MDR4, ABCB4 | active peptide/heavy metal cation transport | 3.A.1.209 | e - apicoplast | b - no | yes |
| PF3D7_1339900 | MDR5, ABCB5 | active solute export | 3.A.1.201 | e - PPM | b - no | yes |
| PF3D7_1352100 | MDR6, ABCB6, Atm1 | active glutathione trisulfide efflux | 3.A.1.210 | c - mitochondrion, apicoplast | b - yes | yes |
| PF3D7_1209900 | MDR7, ABCB7 | active peptide efflux | 3.A.1.209 | c - mitochondrion | b - no | yes |
| PF3D7_0112200 | MRP1, ABCB1 | active export of drugs and glutathione conjugates | 3.A.1.208 | e - PPM | b - no | yes |
| PF3D7_1229100 | MRP2, ABCB2 | active export of glutathione conjugates | 3.A.1.208 | e - PPM | b - no | yes |
| PF3D7_0813700 | ABCF1 | heme import? (Blake et al., 2015) | 3.A.1 | e - cytoplasmic vesicle (Murithi et al., 2021) | unknown | yes |
| PF3D7_1426500 | ABCG3, ABCG1, ABCG2 | putative cell metabolite exporter (Edaye and Georges, 2015) | 3.A.1.204 | e - PPM (Edaye and Georges, 2015) | b - no | yes |
| PF3D7_0319700 | ABCB3 | active solute transport (Murithi et al., 2021) | 3.A.1 | e - cytoplasmic vesicle (Murithi et al., 2021) | unknown | yes |
| PF3D7_0810200 | ABCK1 | active peptide efflux (Ginsburg and Tilley, 2011) | 3.A.1 | c - mitochondrion (van Esved et al., 2021) | b - yes | yes |
| PF3D7_1004600 | drug transport? (Park et al., 2012) | unknown | 3.A.1 | unknown | b - no | no |
| PF3D7_0812900 | drug transport? (Park et al., 2012) | unknown | 3.A.1 | unknown | b - no | no |
| PF3D7_1434000 | CAF16 | putative ABC transporter (Blake et al., 2015) | 3.A.1 | unknown | b - yes | yes |
| PF3D7_0614900 | unknown | | 3.A.1 | c - PPM (Blake et al., 2015) | b - yes | no |
| PF3D7_1144700 | Tic20 | protein import across innermost membrane (Agrawal and Striepen, 2010) | 3.A.1 | c - apicoplast (Boucher et al., 2018) | b - yes | no |
| PF3D7_1121600 | EXP1 | pore for solutes < 1.4 kDa with EXP2 (Mesén-Ramírez et al., 2019) | 3.A.1 | e - PVM (Mesén-Ramírez et al., 2019) | b - yes (Maier et al., 2008) | no |
| PF3D7_0217100 | ATPα, F₁, α | H^+-importing ATP synthase subunits | 3.A.2 | e - mitochondrion | b - yes | yes |
| PF3D7_1235700 | ATPβ, F₁, β | | 3.A.2 | unknown | b - no | yes |
| PF3D7_1311300 | ATPγ, F₁, γ | | 3.A.2 | unknown | b - yes | yes |
| PF3D7_1147700 | ATPδ, F₁, δ | | 3.A.2 | unknown | b - no | no |
| PF3D7_0715500 | ATPε, F₁, ε | | 3.A.2 | unknown | b - no | no |
| PF3D7_1310000 | OSCP | | 3.A.2 | b - yes | yes |
| PF3D7_0719100 | Fₐ | | 3.A.2 | b - yes | no |
| PF3D7_1125100 | Fₐ | | 3.A.2 | b - yes | no |
| PF3D7_0705900 | Fₐ | | 3.A.2 | b - yes | yes |
| PF3D7_0311800 | Fₐ | | 3.A.2 | b - yes | no |
| Gene ID    | Product | Substrate and function                                                                 | Family | Localisation           | Essential | Human ortholog |
|------------|---------|---------------------------------------------------------------------------------------|--------|------------------------|-----------|-----------------|
| PF3D7_1311900 vapA, V1 subunit A | V-ATPase subunits: active H⁺ export from cytosol | 3.A.2  | e - PPM, DV, cytoplasmic vesicle (Hayashi et al., 2000) | b - yes  | yes             |
| PF3D7_0406100 vapB, V1 subunit B |                                              |        |                        | b - yes  | yes             |
| PF3D7_0106100 vapC, V1 subunit C |                                              |        |                        | b - yes  | yes             |
| PF3D7_1341900 vapD, V1 subunit D |                                              |        |                        | b - yes  | yes             |
| PF3D7_0934500 vapE, V1 subunit E |                                              |        |                        | b - yes  | yes             |
| PF3D7_1140100 vapF, V1 subunit F |                                              |        |                        | b - no   | yes             |
| PF3D7_1323200 vapG, V1 subunit G |                                              |        |                        | b - yes  | no              |
| PF3D7_1306000 vapH, V1 subunit H |                                              |        |                        | b - yes  | yes             |
| PF3D7_0806800 Ṽ subunit a | extrusion of inorganic cations from cytosol | 3.A.3  | e - PPM, DV | b - yes  | no              |
| PF3D7_0519200 Ṽ subunit c, 16-kDa proteolipid | putative phospholipid flippase | 3.A.3  | c - apicoplast | b - yes  | yes             |
| PF3D7_1354400 Ṽ subunit c*, 21-kDa proteolipid | putative phospholipid flippase | 3.A.3  | c - PPM (Blake et al., 2015) | b - no   | yes             |
| PF3D7_1468600 Ṽ subunit d, C/AC39 | putative phospholipid flippase | 3.A.3  | c - cytoplasmic vesicle (Jiang et al., 2020) | b - yes  | yes             |
| PF3D7_0904900 CuTP | active Cu²⁺ export | 3.A.3  | e - EPM, PPM | b - no   | yes             |
| PF3D7_1360500 GCb | phospholipid flippase | 3.A.3  | c - PPM | b - no  | yes             |
| PF3D7_0319000 ATP4 | active Mr²⁺ transport | 3.A.3  | c - ER | b - yes  | yes             |
| PF3D7_1348800 ATP7 | putative phospholipid flippase | 3.A.3  | c - PPM | b - no  | yes             |
| PF3D7_0821800 SECo | active Ca²⁺ transport | 3.A.3  | e - ER (Marapana et al., 2018) | b - no  | yes             |
| PF3D7_1234400 SECo | putative phospholipid flippase | 3.A.3  | c - PPM (Blake et al., 2015) | b - no  | yes             |
| PF3D7_1346100 SECo | putative phospholipid flippase | 3.A.3  | c - cytoplasmic vesicle (Jiang et al., 2020) | b - yes  | yes             |
| PF3D7_0721900 Ṽ subunit e | protein import across inner membrane (Sheiner and Soldati-Favre, 2008; Schmidt et al., 2010) | 3.A.8  | c - mitochondrion (van Esved et al., 2021) | unknown  | no              |
| PF3D7_0512000 VP1 | active H⁺ export | 3.A.10 | e - PPM | b - yes  | no              |
| PF3D7_1352200 VP2 | putative Ca²⁺-dependent H⁺ export from cytosol | 3.A.10 | e - PPM, cytoplasmic | b - no  | no              |

(Continued)
Another putative intracellular Ca\textsuperscript{2+} pool may consist of acidocalcisomes – small electron-dense vesicles that are conserved from bacteria to humans and contain high concentrations of Ca\textsuperscript{2+}, pyrophosphate, polyphosphate, iron, and zinc (Huang et al., 2014). Accordingly, acidocalcisome membranes contain a variety of specific transporters for these substrates across the tree of life (Huang et al., 2014). While many transporters were shown to reside in the acidocalcisome membrane in Trypanosoma brucei through proteomic studies and microscopy (Huang et al., 2014), no protein has been definitely localised to these organelles in P. falciparum (Magowan et al., 1997; Ruiz et al., 2004). Their low internal pH is likely required for the secondary active import of various ions and thought to be established and maintained by the plant-like H\textsuperscript{+}-pump V-ATPase (Wunderlich et al., 2012; de Oliveira et al., 2021). This has yet to be verified experimentally, and there may be differences between parasite species. For example, PfVP1 (PF3D7_1456800), an orthologue of the acidocalcisome marker in T. brucei (Huang et al., 2014) and T. gondii (Rohloff et al., 2011), was previously suggested to localise to the parasite plasma membrane (PPM), DV and acidocalcisomes in P. falciparum, but could only be detected at the PPM by microscopy (Ahiya et al., 2022).

Other proteins that may translocate calcium and whose subcellular localisation has not yet been confirmed are PfATP9 (PF3D7_1348800), the putative calcium channel PF3D7_1331500, and PfICM1 (PF3D7_1231400). Elucidating their location and function is an important knowledge gap to be addressed (Kustatscher et al., 2022). Of the aforementioned putative Ca\textsuperscript{2+} transport proteins, PfICM1 and PfHlyIII may be worth exploring as drug targets due to their predicted essentiality and the absence of human counterparts.

### TABLE 1 | Continued

| Gene ID   | Product | Substrate and function | Family   | Localisation | Essential | Human ortholog |
|-----------|---------|------------------------|----------|--------------|-----------|----------------|
| PF3D7_0810400 AQP2 | water channel (Blake et al., 2015) | 3.A.16 | c - PPM (Blake et al., 2015) | b - no | no |
| PF3D7_0314300 Der1-1 | protein import across periplastid membrane (Spork et al., 2009) | 3.A.25.2.1 | e - apicoplast (Spork et al., 2009) | b - yes | no |
| PF3D7_1452300 Der1-2 | protein import across periplastid membrane (Spork et al., 2009) | 3.A.25.2.1 | e - apicoplast (Spork et al., 2009) | unknown | yes |
| PF3D7_0216800 | unknown | 3.A.25 | unknown | b - no | no |
| PF3D7_015700 | unknown | 3.A.25 | unknown | b - no | no |
| PF3D7_1471100 EXP2 | PTEX core components for protein export (Beck and Ho, 2021), EXP2 | 3.A.26.1.1 | e - PVM (de Koning-Ward et al., 2009) | b - yes | no |
| PF3D7_1436300 PTEX150 | putative transporter | 3.A.26 | c - PPM (Blake et al., 2015) | b - yes | no |
| PF3D7_1116800 HSP101 | putative transporter | 3.A.26 | unknown | b - no | no |
| PF3D7_1404600 ACo | phospholipid scramblase (Jose et al., 2021) | 3.A.26 | e - parasite periphery (Jose et al., 2021) | b - no | no |
| PF3D7_1022700 PLSCK | putative transporter | 3.A.26 | unknown | b - no | no |
| PF3D7_1332100 | putative transporter | 3.A.26 | unknown | b - no | no |
| PF3D7_0530500 | putative transporter | 3.A.26 | unknown | b - no | no |
| PF3D7_0628400 | putative transporter | 3.A.26 | unknown | b - no | no |
| PF3D7_1135300 PMRT1 | unknown | 3.A.26 | unknown | b - no | no |
| PF3D7_1022200 FBT | putative metabolite/vitamin transporter (Ginsburg and Tilley, 2011) | 3.A.26 | e - cis-Golgi (Jose et al., 2021) | b - no | no |
| PF3D7_0314300 Der1-1 | protein import across periplastid membrane (Spork et al., 2009) | 3.A.26 | unknown | b - no | no |
| PF3D7_1135300 PMRT1 | putative transporter | 3.A.26 | unknown | b - no | no |
| PF3D7_0810400 AQP2 | water channel (Blake et al., 2015) | 3.A.16 | c - PPM (Blake et al., 2015) | b - no | no |

Substrates, functions, and localisations are indicated as in Martin (2020), unless stated otherwise. Known or putative localisation refers to the site of active function of the transport protein regardless of its trafficking route, as evidenced either by experimental data (e) or computational analysis (c). DV: digestive vacuole, EPM, erythrocyte plasma membrane; PPM, parasite plasma membrane; PVM, parasitophorous vacuole membrane. Transporter families were assigned according to the Transport Classification Database (Saier et al., 2016). 1: channels and pores, 1.A: α-type channels, 1.B: β-barrel pores, 1.C: pore-forming toxins. 2: electrochemical potential-driven transporters, 2.A: porters (uniporters, symporters, antiporters), 3: primary active transporters, 3.A: P-B-barrel-hydrolase-driven transporters, 8: accessory factors involved in transport, 9: incompletely characterised transport systems, 9.A: recognised transporters of unknown biochemical mechanism, 9.B: putative transport proteins. Predicted gene essentiality refers to Zhang et al. (2018), unless another reference is given. The tested life cycle stages are indicated as b, asexual blood stage; g, gametocytes; o, ookinetes; s, sporozoites. Information on the presence of human orthologs is listed according to https://mpmp.huji.ac.il/maps/orth_hsap.html (Ginsburg and Tilley, 2011).
CONCLUSIONS AND FUTURE PERSPECTIVES

This mini review consolidates data from various databases and provides an up-to-date overview of the subcellular localisation, function, predicted essentiality, and human orthologs of *P. falciparum* transporters for the fast identification of essential parasite transporters without human orthologs that may be promising novel targets for therapeutic development. Many of these candidates localise to the apicoplast, the mitochondrion, or the digestive vacuole, which are known to be “druggable” (Wunderlich et al., 2012; Oberstaller et al., 2021).

Moreover, the new transporter list will improve gene annotations and serve as a basis for further functional characterisation of the proteins. It will also be useful for systems biology approaches as it allows more reliable screening of e.g. genomic, transcriptomic, and proteomic data for *P. falciparum* transporters. The low coverage of the *P. falciparum* membrane proteome that complicates target profiling (Lu et al., 2021) may be overcome by large-scale culturing (Dalton et al., 2012) and more sensitive mass spectrometry techniques (McClure and Williams, 2018). Chemogenomic and transcriptional profiling of mutant-parasite libraries with altered drug sensitivities will further guide the determination of the mechanisms of drug action (Adjalley et al., 2015; Pradhan et al., 2015).

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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