Supplementary Figure 1: Examples of gene deletions which result in misfolding or mis-localisation of the plasma membrane proteins Pdr5p and Mrh1p. Δhis3 is the “wild-type” positive control.
Supplementary Figure 2: Examples of gene deletions that prevented normal upregulation of Pdr5p-GFP and Yor1p-GFP reporters.

The images are of the Pdr5p-GFP reporter in the named gene deletion backgrounds. The images were adjusted so that fluorescence levels of DMSO control and drug treatment of each of the deletions (in 35µM atorvastatin) are directly comparable as to fluorescence intensity in each image filed.
Supplementary Figure 3: Examples of Spot Dilutions Assays and Western Blots. **Top panel:** Spot Dilution of different deletion strains in 1 and 0.5 µM ketoconazole, which allow Δpdr1Δpdr3 to grow. Deletion of SPT7 caused hypersensitivity to ketoconazole in both single deletion and in Δpdr1Δpdr3 background. Deletion of BMH1 caused hypersensitivity to ketoconazole in Δpdr1Δpdr3 background alone.

**Bottom panel:** Example of Western Blots of Pdr5p in different deletion backgrounds. Pma1p, another plasma membrane protein, was used as an internal control. It has two isoforms one of about the same size as Pdr5p and shows up as a background band after the Western Blot was exposed to both Pdr5p and Pma1p antibodies.
Supplementary Figure 4: The published genetic and physical interaction networks among our screen results and some of the known PDR-contributing genes.
## Supplementary Tables

### Supplementary Table 1: Gene Deletions that overlap between PDR screens and Mrh1p-GFP control screen

<table>
<thead>
<tr>
<th>Systematic Name</th>
<th>Standard Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>YJR033C</td>
<td>RAV1</td>
<td>Subunit of the RAVE complex, required for transport between the early and late endosome/PVC and for localization of TGN membrane proteins</td>
</tr>
<tr>
<td>YKL081W</td>
<td>TEF4</td>
<td>Gamma subunit of translational elongation factor eEF1B</td>
</tr>
<tr>
<td>YLR262C</td>
<td>YPT6</td>
<td>Rab family GTPase, Ras-like GTP binding protein involved in the secretory pathway; required for fusion of endosome-derived vesicles with the late Golgi</td>
</tr>
<tr>
<td>YLR386W</td>
<td>VAC14</td>
<td>Protein involved in regulated synthesis of PtdIns(3,5)P(2), in control of trafficking of some proteins to the vacuole lumen via the MVB</td>
</tr>
<tr>
<td>YPL154C</td>
<td>PEP4</td>
<td>Vacuolar aspartyl protease (proteinase A)</td>
</tr>
</tbody>
</table>

### Supplementary Table 2: List of gene deletions which cause insignificant change in PDR reporters upon atorvastatin treatment

<table>
<thead>
<tr>
<th>Systematic Name</th>
<th>Standard Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>YDR374C</td>
<td></td>
<td>Putative protein of unknown function</td>
</tr>
<tr>
<td>YFR018C</td>
<td></td>
<td>Putative protein of unknown function</td>
</tr>
<tr>
<td>YIL152W</td>
<td></td>
<td>Putative protein of unknown function</td>
</tr>
<tr>
<td>YNL315C</td>
<td>ATP11</td>
<td>Molecular chaperone, required for the assembly of alpha and beta subunits into the F1 sector of mitochondrial F1F0 ATP synthase</td>
</tr>
<tr>
<td>YER155C</td>
<td>BEM2</td>
<td>Rho GTPase activating protein (RhoGAP) involved in the control of cytoskeleton organization and cellular morphogenesis; required for bud emergence</td>
</tr>
<tr>
<td>YER177W</td>
<td>BMH1</td>
<td>14-3-3 protein, major isoform; controls proteome at post-transcriptional level, binds proteins and DNA, involved in regulation of many processes including exocytosis, vesicle transport, Ras/MAPK signaling, and rapamycin-sensitive signalling</td>
</tr>
<tr>
<td>YOR061W</td>
<td>CKA2</td>
<td>Alpha catalytic subunit of casein kinase 2 (CK2), a Ser/Thr protein kinase with roles in cell growth and proliferation; CK2, comprised of CKA1, CKA2, CKB1 and CKB2, has many substrates including transcription factors and all RNA polymerase</td>
</tr>
<tr>
<td>YDL155W</td>
<td>CLB3</td>
<td>B-type cyclin involved in cell cycle progression; activates Cdc28p to promote the G2/M transition; may be involved in DNA replication and spindle assembly; accumulates during S phase and G2, then targeted for ubiquitin-mediated degradation</td>
</tr>
<tr>
<td>YCR017C</td>
<td>CWH43</td>
<td>Putative sensor/transporter protein involved in cell wall biogenesis; contains 14-16 transmembrane segments and several putative glycosylation and phosphorylation sites; null mutation is synthetically lethal with pck1 deletion</td>
</tr>
<tr>
<td>YGL078C</td>
<td>DBP3</td>
<td>Putative ATP-dependent RNA helicase of the DEAD-box family involved in ribosomal biogenesis</td>
</tr>
<tr>
<td>YDR294C</td>
<td>DPL1</td>
<td>Dihydrophosphinosine phosphate lyase, regulates intracellular levels of sphingolipid long-chain base phosphates (LCBPs), degrades phosphorylated long chain bases, prefers C16 dihydrophosphinosine-l-phosphate as a substrate</td>
</tr>
</tbody>
</table>
YGR071C ENV11 Protein proposed to be involved in vacuolar functions; mutant shows defect in CPY processing and fragmented vacuoles; deletion mutant has increased glycogen accumulation and displays elongated buds; green fluorescent protein (GFP)-fusion protein localizes to the nucleus

YGL054C ERV14 Protein localized to COPII-coated vesicles, involved in vesicle formation and incorporation of specific secretory cargo; required for the delivery of bud-site selection protein Axl2p to cell surface; related to Drosophila cornichon

YIL065C FIS1 Protein involved in mitochondrial membrane fission and peroxisome abundance; required for localization of Dnm1p and Mdv1p during mitochondrial division; mediates ethanol-induced apoptosis and ethanol-induced mitochondrial fragmentation

YIL098C FMC1 Mitochondrial matrix protein, required for assembly or stability at high temperature of the F1 sector of mitochondrial F1F0 ATP synthase; null mutant temperature sensitivity growth on glycerol is suppressed by multicopy expression of Odc1p

YHR176W FMO1 Flavin-containing monooxygenase, localized to the cytoplasmic face of the ER membrane; catalyzes oxidation of biological thiols to maintain the ER redox buffer ratio for correct folding of disulfide-bonded proteins

YGR252W GCN5 Acetyltransferase, modifies N-terminal lysines on histones H2B and H3; acetylates Rsc4p, a subunit of the RSC chromatin-remodeling complex, altering replication stress tolerance; catalytic subunit of the ADA and SAGA histone acetyltransferase complexes; founding member of the Gcn5p-related N-acetyltransferase superfamily; mutant displays reduced transcription elongation in the G-less-based run-on (GLRO) assay

YGL020C GET1 (MDM39) Subunit of the GET complex; involved in insertion of proteins into the ER membrane; required for the retrieval of HDEL proteins from the Golgi to the ER in an ERD2 dependent fashion and for normal mitochondrial morphology and inheritance

YGR163W GTR2 Putative GTP binding protein that negatively regulates Ran/Te4 GTPase cycle; activates transcription; subunit of EGO and GSE complexes; required for sorting of Gap1p; localizes to cytoplasm and to chromatin; homolog of human RagC and RagD

YJR147W HMS2 Protein with similarity to heat shock transcription factors; overexpression suppresses the pseudohyphal filamentation defect of a diploid mep1 mep2 homozygous null mutant

YFR038W IRC5 Putative ATPase containing the DEAD/H helicase-related sequence motif; null mutant displays increased levels of spontaneous Rad52p foci

YER110C KAP123 Karyopherin beta, mediates nuclear import of ribosomal proteins prior to assembly into ribosomes and import of histones H3 and H4; localizes to the nuclear pore, nucleus, and cytoplasm; exhibits genetic interactions with RAII

YKL168C KKQ8 Putative serine/threonine protein kinase with unknown cellular role

YDR532C KRE28 Subunit of a kinetochore-microtubule binding complex with Spc105p that bridges centromeric heterochromatin and kinetochore MAPs and motors, and is also required for sister chromatid bi-orientation and kinetochore binding of SAC components

YCL061C MRC1 S-phase checkpoint protein required for DNA replication; interacts with and stabilizes Pol2p at stalled replication forks during stress, where it forms a pausing complex with Tof1p and is phosphorylated by Mec1p; protects uncapped telomeres

YDR192C NUP42 Subunit of the nuclear pore complex (NPC) that localizes exclusively to the cytoplasmic side; involved in RNA export, most likely at a terminal step; interacts with Gle1p

YJR073C OPI3 Phospholipid methyltransferase (methylene-fatty-acyl-phospholipid synthase), catalyzes the last two steps in phosphatidylcholine biosynthesis

YGL013C PDR1 Zinc cluster protein that is a master regulator involved in recruiting other zinc cluster proteins to pleiotropic drug response elements (PDREs) to fine tune the regulation of multidrug resistance genes
| YBL005W | PDR3 | Transcriptional activator of the pleiotropic drug resistance network, regulates expression of ATP-binding cassette (ABC) transporters through binding to cis-acting sites known as PDREs (PDR responsive elements); post-translationally upregulated in cells lacking a functional mitochondrial genome |
| YGL023C | PIB2 | Protein binding phosphatidylinositol 3-phosphate, involved in telomere-proximal repression of gene expression; similar to Fab1 and Vps27 |
| YBL051C | PIN4 | Protein involved in G2/M phase progression and response to DNA damage, interacts with Rad53p; contains an RNA recognition motif, a nuclear localization signal, and several SQ/TQ cluster domains; hyperphosphorylated in response to DNA damage |
| YHR075C | PPE1 | Protein with carboxyl methyl esterase activity that may have a role in demethylation of the phosphoprotein phosphatase catalytic subunit; also identified as a small subunit mitochondrial ribosomal protein |
| YNL169C | PSD1 | Phosphatidylserine decarboxylase of the mitochondrial inner membrane, converts phosphatidylserine to phosphatidylethanolamine |
| YAL017W | PSK1 | One of two (see also PSK2) PAS domain containing S/T protein kinases; coordinately regulates protein synthesis and carbohydrate metabolism and storage in response to a unknown metabolite that reflects nutritional status |
| YJR127C | RSF2 | Zinc-finger protein involved in transcriptional control of both nuclear and mitochondrial genes, many of which specify products required for glycerol-based growth, respiration, and other functions |
| YOL067C | RTG1 | Transcription factor (bHLH) involved in interorganelle communication between mitochondria, peroxisomes, and nucleus |
| YGR143W | SKN1 | Protein involved in sphingolipid biosynthesis; type II membrane protein with similarity to Kro6p |
| YHR206W | SKN7 | Nuclear response regulator and transcription factor; physically interacts with the Tup1-Cyc8 complex and recruits Tup1p to its targets; part of a branched two-component signaling system; required for optimal induction of heat-shock genes in response to oxidative stress; involved in osmoregulation |
| YGL115W | SNF4 | Activating gamma subunit of the AMP-activated Snf1p kinase complex (contains Snf1p and a Sip1p/Sip2p/Gal833p family member); activates glucose-repressed genes, represses glucose-induced genes; role in sporulation, and peroxisome biogenesis |
| YCR081W | SRB8 | Subunit of the RNA polymerase II mediator complex; associates with core polymerase subunits to form the RNA polymerase II holoenzyme; essential for transcriptional regulation; involved in glucose repression |
| YDR443C | SSN2 | Subunit of the RNA polymerase II mediator complex; associates with core polymerase subunits to form the RNA polymerase II holoenzyme; required for stable association of Srb10p-Srb11p kinase; essential for transcriptional regulation |
### Supplementary Table 3: Eleven Genes relating to RNA transcription were GO enriched as revealed in the PDR primary screens.

<table>
<thead>
<tr>
<th>GO-term</th>
<th>P-value</th>
<th>Gene(s) annotated to the term</th>
</tr>
</thead>
<tbody>
<tr>
<td>sequence-specific DNA binding transcription factor activity</td>
<td>0.00588</td>
<td>PDR3/YBL005W; UME6/YDR207C; SWI4/YER111C; PDR1/YGL013C; SKN7/YHR206W; RSF2/YJR127C; RTG1/YOL067C</td>
</tr>
<tr>
<td>nucleic acid binding transcription factor activity</td>
<td>0.00613</td>
<td>PDR3/YBL005W; UME6/YDR207C; SWI4/YER111C; PDR1/YGL013C; SKN7/YHR206W; RSF2/YJR127C; RTG1/YOL067C</td>
</tr>
<tr>
<td>transcription factor binding transcription factor activity</td>
<td>0.04211</td>
<td>ROX3/YBL093C; SRB8/YCR081W; UME6/YDR207C; SSN2/YDR443C; GCN5/YGR252W</td>
</tr>
<tr>
<td>transcription coactivator activity</td>
<td>0.04829</td>
<td>SRB8/YCR081W; SSN2/YDR443C; GCN5/YGR252W</td>
</tr>
</tbody>
</table>

### Supplementary Table 4: LOPAC compounds that activate PDR reporters and inhibit signalling-related pathways or molecules

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Mode-of-action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farnesylthiosalicylic acid</td>
<td>Non-toxic Ras inhibitor</td>
</tr>
<tr>
<td>3-alpha,21-dihydroxy-5-alpha-pregnan-20-one</td>
<td>Positive allosteric modulator of GABA-A receptors</td>
</tr>
<tr>
<td>Dequalinium analog, C-14 linker</td>
<td>Protein kinase C-alpha (PKC-alpha) inhibitor</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>N-phenylanthranilic acid</td>
<td>Cl- channel blocker</td>
</tr>
<tr>
<td>7-cyclopentyl-5-(4-phenoxy) phenyl-7H-pyrolo</td>
<td>Potent and selective Ick (src family tyrosine kinase) inhibitor.</td>
</tr>
<tr>
<td>DL-stearoylcarnitine chloride</td>
<td>Protein kinase C (PKC) inhibitor</td>
</tr>
<tr>
<td>SU 6656</td>
<td>Selective Src family kinase inhibitor</td>
</tr>
<tr>
<td>U0126</td>
<td>Specific inhibitor of MEK1 and MEK2 (MAP kinase kinase; MAPKK)</td>
</tr>
</tbody>
</table>