Ion channels are involved in a large variety of cellular processes including stem cell differentiation. Numerous families of ion channels are present in the organism which can be distinguished by means of, for example, ion selectivity, gating mechanism, composition, or cell biological function. To characterize the distinct expression of this group of ion channels we have compared the mRNA expression levels of ion channel genes between human keratinocyte-derived induced pluripotent stem cells (hiPSCs) and their somatic cell source, keratinocytes from plucked human hair. This comparison revealed that 26% of the analyzed probes showed an upregulation of ion channels in hiPSCs while just 6% were downregulated. Additionally, iPSCs express a much higher number of ion channels compared to keratinocytes. Further, to narrow down specificity of ion channel expression in iPS cells we compared their expression patterns with differentiated progeny, namely, neurons and cardiomyocytes derived from iPSC cells. To conclude, hiPSCs exhibit a very considerable and diverse ion channel expression pattern. Their detailed analysis could give an insight into their contribution to many cellular processes and even disease mechanisms.

1. Introduction

Ion channels are comprised of a large variety of differing families of pore proteins. Initially, ion channels were mostly known for their role in the nervous system where they play a crucial role in the signal transmission over neurites and synapses. But in fact they are involved in numerous other cellular processes including cell size regulation, muscle contractions, immune system activation [1], or hormone release [2]. Distinct ion channels are furthermore recognized to be of high importance for excitable cells of the heart: cardiomyocytes of the working myocardium as well as cells of the cardiac conduction system. In the heart, specific ion channels are responsible, for example, for the regulated generation of action potentials and for cardiac muscle contraction strength and time [3]. Additionally, ion channels play an important role in several differentiation and maturation processes [4–6]. The presented study aims to take a closer look at ion channel expression in human-induced pluripotent stem cells (hiPSCs) to give a start point for further analyses of their distinct roles at an early developmental cell state and differentiation processes.

hiPSCs are generated from somatic cells by timed overexpression of specific transcription factors and strongly resemble pluripotent embryonic stem cells [7, 8]. Pluripotency is amongst others defined by the ability to differentiate into cells of all three germ layers and unlimited symmetrical cell division. This cell system is widely utilized for studies investigating developmental processes or disease mechanisms [9, 10]. Although it has become clear that differentiation processes influence ion channel expression [11], the distinct role of ion channels during these processes is so far only poorly
understood. Nevertheless, it became evident that certain ion channels play a pivotal role in stem cell biology, including cell fate determination, cell cycle regulation, or cytoskeletal reorganization [6, 12–15].

The possibilities of iPSCs include the generation of individual or patient-specific pluripotent cells, which can be subsequently differentiated into the affected cell types. This is already utilized to study pathomechanisms in a variety of tissues and cell types [9, 16–18]. The so-called channelopathies which are based on mutations in ion channels are the cause of developmental disorders and are the subject of various studies [19, 20]. To elucidate the role of ion channels in cell differentiation, maturation or their role in pathomechanisms a well-founded knowledge of ion channel distribution in pluripotent cells, representing one of the earliest stages of development, is indispensable. In that respect, we compared the expression levels of several ion channels in human keratinocytes with their reprogrammed progeny, hiPSCs. Keratinocytes derived from plucked human hair [21, 22] represent one of the most promising cell sources for the generation of the investigated hiPSCs [23]. We have elucidated ion channel regulation for various channel families and their subtypes. Additionally, we compared the expression levels of ion channel families and subtypes, found to be regulated during reprogramming, with iPSC-differentiated progeny, namely, neurons and cardiomyocytes. These comparisons could be a start point to evaluate the contribution and function of different ion channels, for example, for self-renewal and differentiation processes in stem cells.

2. Material and Methods

2.1. Ethical Statement and Donor Information. After informed consent was given by the donors (ethical agreement by the University of Ulm, number 88/12) hair with intact hair roots was gathered by plucking from the scalp after disinfection. We used hair from healthy volunteers (age between 24 to 45 and both male and female gender).

2.2. hiPSC Generation and Cell Culture. Keratinocytes were obtained from plucked human scalp hair as already described [22]. Keratinocytes were propagated in EpiLife medium with HKGS supplement (both Invitrogen, Carlsbad, CA, USA). hiPSCs were generated from keratinocytes by lentiviral transduction of four reprogramming factors (Oct4, Sox2, Klf4, and cMyc) as described earlier [23]. After the reprogramming on rat embryonic fibroblasts they were maintained feeder-free on Matrigel (BD Biosciences, Franklin Lakes, NJ, USA) coated dishes in mTeSR1 medium (Stemcell Technologies, Vancouver, CA, USA).

2.3. Gene Expression Microarrays. Gene expression microarrays were performed for 6 keratinocyte samples and 9 hiPSC samples with the Agilent Whole Human Genome Microarray Kit (4x44k microarray kit G4122F, Agilent Technologies, Santa Clara, CA, USA). 500 ng of total RNA was used to produce Cy3-CTP-labeled cRNA with the Agilent Low RNA Input Liner Amplification Kit. The cRNA was purified and 1,650 µg per array was hybridized for 17 h at 65 °C and 10 r.p.m. Afterwards, the arrays were washed with Agilent Gene Expression Wash Buffers one and two and finally with acetonitrile for 1 min. The slides were scanned using Scan Control 7.0 software with a resolution of 5 µm. Scan data was extracted with the Feature Extraction 9.1 software. Expression levels were background adjusted and quantile normalized with the GeneSpring GX 12 software. Differential expression between keratinocytes and hiPSCs was analyzed using student’s t-test. A fold change > 2 and a P value < 0.05 was considered significant and highlighted bold (upregulation) or italic (downregulation) in the results table. For comparisons of iPSCs with iPSC-derived neurons published data from GSE34879 (GSM856936, GSM856937, GSM856915, GSM856916) and for cardiomyocytes GSE17579 (GSM438022, GSM438026, GSM438034, GSM438021, GSM438032, GSM438036) were used (both from NCBI Gene Expression Omnibus, http://www.ncbi.nlm.nih.gov/geo/). Fold change is shown if > 2.

3. Results

3.1. Differential Expression of Ion Channels in hiPSCs Compared to Keratinocytes. We first compared the expression of various ion channel families from keratinocytes to hiPSCs and from hiPSCs to cardiomyocytes and neurons, respectively. From the 387 probes (Table 1) binding in ion channel genes from parental keratinocytes to hiPSCs, 101 (26%) showed a significant increase in expression (fold change > 2, P < 0.05; labeled in bold) while 23 (6%) showed a significant decrease (fold change > −2, P < 0.05; labeled in italic). In a second step differentially regulated ion channels from hiPSCs to hiPSC-derived neurons were investigated and we found 29 ion channel transcripts to be upregulated (fold change > 2; labeled in bold) while 6 showed a significant decrease (fold change > −2; labeled in italic). For cardiomyocytes, mRNA levels of only 7 ion channel members were upregulated (fold change > 2; labeled in bold) and 10 mRNA levels showed a significant decrease (fold change > −2; labeled in italic).

3.2. Voltage-Gated Calcium Channels. Voltage-gated calcium channels are crucially involved in the Ca2+ influx thereby playing an important role in calcium signaling of virtually all cells. High-voltage-gated calcium channels include the neural N-type channel, the poorly defined brain-specific R-type channel, the closely related P/Q-type channel, and the dihydropyridine-sensitive L-type channels responsible for excitation-contraction coupling of skeletal, smooth, and cardiac muscles as well as for hormone secretion in endocrine cells (reviewed in [24]). While mainly permeable for calcium ions they also show a low permeability for sodium ions. Upon depolarization of the cell they mediate a calcium influx into the cell. The channels consist of the main alpha subunit as well as regulatory beta, alpha 2/delta, and gamma subunits. The α1 subunit forms the ion conducting pore while the associated subunits have several functions including modulation of gating [25]. CACNA1A mutations are for example involved in ataxia [26]. We have analyzed their expression with 42 probes.
Table 1: The expression levels for ion channel genes were compared in hiPSCs (9 samples) and keratinocytes (6 samples) via microarray. Gene names, accession numbers, and gene symbols are shown together with the corresponding fold change and $P$ values. Significant changes (defined as fold change $> 2$, $P < 0.05$) are labeled in bold for upregulation or italic for downregulation. Accession numbers refer to the NCBI or Ensembl (numbers starting with ENST) databases. Analyses of hiPSC-derived neurons or hiPSC-derived cardiomyocytes were performed using published data sets from GSE34879 (neurons) and GSE17579 (cardiomyocytes). These data sets already contain both iPSCs and differentiated progeny. Fold changes $> 2$ (marked bold) and $< −2$ (marked italic) are shown in the respective columns.

**(a) Voltage-gated calcium channels**

| Gene name                                                                 | Accession number | Gene symbol | $P$    | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|--------------------------------------------------------------------------|------------------|-------------|-------|------------------------------------|----------------------------------------|-----------------------------------|
| Calcium channel, voltage-dependent, P/Q type, alpha 1A subunit, transcript variant 1 | NM_000068        | CACNA1A     | 2.26E−01 | −1.32                              |                                        |                                   |
| Calcium channel, voltage-dependent, N type, alpha 1B subunit             | NM_000718        | CACNA1B     | 7.27E−01 | −1.10                              |                                        |                                   |
| Calcium channel, voltage-dependent, N type, alpha 1B subunit [Source: HGNC Symbol; Acc: 1389] | ENST00000277550  | CACNA1B     | 7.15E−01 | −1.14                              |                                        |                                   |
| Calcium channel, voltage-dependent, N type, alpha 1B subunit             | NM_000718        | CACNA1B     | 6.32E−09 | 6.82                               |                                        |                                   |
| Calcium channel, voltage-dependent, N type, alpha 1B subunit [Source: HGNC Symbol; Acc: 1389] | ENST00000277551  | CACNA1B     | 3.32E−02 | −1.57                              |                                        |                                   |
| Calcium channel, voltage-dependent, L type, alpha 1C subunit, transcript variant 18 | NM_000719        | CACNA1C     | 6.77E−02 | −1.37                              |                                        |                                   |
| Calcium channel, voltage-dependent, L type, alpha 1C subunit, transcript variant 18 | NM_000719        | CACNA1C     | 5.72E−03 | 2.37                               | 2.94                                   |                                   |
| Calcium channel, voltage-dependent, L type, alpha 1D subunit, transcript variant 1   | NM_000720        | CACNA1D     | 3.83E−01 | 1.58                               |                                        |                                   |
| Calcium channel, voltage-dependent, R type, alpha 1E subunit, transcript variant 3 | NM_000721        | CACNA1E     | 3.10E−02 | −4.48                              | 2.08                                   |                                   |
| Calcium channel, voltage-dependent, R type, alpha 1E subunit [Source: HGNC Symbol; Acc: 1392] | ENST00000524607  | CACNA1E     | 8.83E−01 | 1.05                               |                                        |                                   |
| Calcium channel, voltage-dependent, L type, alpha 1F subunit             | NM_005183        | CACNA1F     | 8.92E−01 | 1.02                               |                                        |                                   |
| Calcium channel, voltage-dependent, T type, alpha 1G subunit, transcript variant 15 | NM_198397        | CACNA1G     | 6.42E−01 | −1.12                              | 4.60                                   |                                   |
| Calcium channel, voltage-dependent, T type, alpha 1G subunit, transcript variant 1   | NM_018896        | CACNA1G     | 5.37E−07 | 6.96                               |                                        |                                   |
| Calcium channel, voltage-dependent, T type, alpha 1H subunit, transcript variant 1 | NM_021098        | CACNA1H     | 7.38E−10 | 6.78                               |                                        |                                   |
| Calcium channel, voltage-dependent, T type, alpha 1I subunit, transcript variant 1 | NM_021096        | CACNA1I     | 2.22E−11 | 37.25                              |                                        |                                   |
| Calcium channel, voltage-dependent, T type, alpha 1I subunit, transcript variant 1 | NM_021096        | CACNA1I     | 4.30E−07 | 62.50                              | 2.02                                   |                                   |
| Calcium channel, voltage-dependent, alpha 2/delta subunit 1              | NM_000069        | CACNA1S     | 5.22E−02 | −1.97                              |                                        |                                   |
| Calcium channel, voltage-dependent, alpha 2/delta subunit 2, transcript variant 1 | NM_001005505     | CACNA2D1    | 1.38E−09 | 9.65                               |                                        |                                   |
| Calcium channel, voltage-dependent, alpha 2/delta subunit 3              | NM_018398        | CACNA2D3    | 5.14E−05 | 5.42                               | 2.55                                   |                                   |
(a) Continued.

| Gene name                                                                 | Accession number | Gene symbol | P       | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|--------------------------------------------------------------------------|------------------|-------------|--------|------------------------------------|--------------------------------------|----------------------------------|
| Calcium channel, voltage-dependent, alpha 2/delta subunit 3             | AF516696         | CACNA2D3    | $4.68E-11$ | 33.67                              |                                      |                                  |
| Calcium channel, voltage-dependent, alpha 2/delta subunit 4             | NM_172364        | CACNA2D4    | $2.95E-01$ | -1.41                              |                                      |                                  |
| Calcium channel, voltage-dependent, beta 1 subunit, transcript variant 3| NM_199248        | CACNB1      | $4.31E-01$ | -1.14                              |                                      |                                  |
| Calcium channel, voltage-dependent, beta 1 subunit, transcript variant 1| NM_000723        | CACNB1      | $8.02E-01$ | -1.02                              |                                      |                                  |
| Calcium channel, voltage-dependent, beta 1 subunit, transcript variant 1| NM_000723        | CACNB1      | $6.22E-01$ | 1.04                               |                                      |                                  |
| cDNA FLJ45229 fis, clone BRCAN2020972,                                  | AK128769         | CACNB2      | $9.78E-01$ | 1.02                               |                                      |                                  |
| Calcium channel, voltage-dependent, beta 2 subunit, transcript variant 1| NM_000724        | CACNB2      | $4.71E-02$ | 3.45                               |                                      |                                  |
| Calcium channel, voltage-dependent, beta 3 subunit, transcript variant 1| NM_000725        | CACNB3      | $3.55E-02$ | -1.93                              |                                      | 9.56                             |
| Calcium channel, voltage-dependent, beta 3 subunit, transcript variant 1| NM_000725        | CACNB3      | $6.61E-01$ | 1.09                               |                                      |                                  |
| Calcium channel, voltage-dependent, beta 4 subunit, transcript variant 1| NM_001005747     | CACNB4      | $1.33E-03$ | 4.43                               |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 1                     | NM_000727        | CACNG1      | $9.46E-01$ | 1.02                               |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 2                     | NM_006078        | CACNG2      | $4.19E-01$ | -1.29                              |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 2                     | NM_006078        | CACNG2      | $7.91E-01$ | 1.09                               |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 3                     | NM_006539        | CACNG3      | $2.21E-01$ | -1.95                              |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 4                     | NM_014405        | CACNG4      | $4.93E-01$ | 1.14                               |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 5                     | NM_145811        | CACNG5      | $7.49E-01$ | -1.13                              |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 5 [Source: HGNCSymbol; Acc: 1409] | ENST00000169565  | CACNG5      | $2.19E-01$ | -1.56                              |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 6, transcript variant 1| NM_145814        | CACNG6      | $5.56E-11$ | 46.40                              |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 7                     | NM_031896        | CACNG7      | $3.54E-13$ | 1439.36                            |                                      | 3.37                             |
| Calcium channel, voltage-dependent, gamma subunit 7                     | NM_031896        | CACNG7      | $1.82E-01$ | 1.26                               |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 8                     | NM_031895        | CACNG8      | $2.01E-01$ | 1.43                               |                                      |                                  |
| Calcium channel, voltage-dependent, gamma subunit 8                     | NM_031895        | CACNG8      | $1.18E-09$ | 9.70                               |                                      |                                  |

(b) Sperm-associated cation channels

| Gene name                                                 | Accession number | Gene symbol | P       | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|-----------------------------------------------------------|------------------|-------------|--------|------------------------------------|--------------------------------------|----------------------------------|
| Cation channel, sperm associated 1                        | NM_053054        | CATSPER1    | $3.26E-01$ | 1.51                              |                                      |                                  |
| Cation channel, sperm associated 2, transcript variant 2  | NM_172095        | CATSPER2    | $1.32E-04$ | -2.78                             |                                      |                                  |
(b) Continued.

| Gene name                                                                 | Accession number | Gene symbol | P             | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|---------------|--------------------------|---------------------------|------------------------|
| Cation channel, sperm associated 2, transcript variant 4                 | NM_172097        | CATSPER2    | 3.12E−02      | −1.78                    |                           |                        |
| Cation channel, sperm associated 3                                        | NM_178019        | CATSPER3    | 1.50E−03      | 1.93                     |                           |                        |
| Cation channel, sperm associated 4                                        | NM_198137        | CATSPER4    | 2.51E−01      | 1.48                     |                           |                        |
| Cation channel, sperm-associated, beta                                    | NM_024764        | CATSPERB    | 4.38E−01      | −1.25                    |                           |                        |
| Cation channel, sperm-associated, gamma                                   | NM_021185        | CATSPERG    | 3.56E−01      | 1.34                     |                           |                        |

(c) Nicotinic acetylcholine receptors

| Gene name                                                                 | Accession number | Gene symbol | P             | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|---------------|--------------------------|---------------------------|------------------------|
| Cholinergic receptor, nicotinic, alpha 1 (muscle), transcript variant 1  | NM_001039523     | CHRNA1      | 8.06E−01      | −1.10                    |                           |                        |
| Cholinergic receptor, nicotinic, alpha 1 (muscle), (cDNA clone IMAGE: 4124038), with apparent retained intron | BC006314         | CHRNA1      | 4.64E−01      | 1.47                     |                           |                        |
| Cholinergic receptor, nicotinic, alpha 2 (neuronal)                        | NM_000742        | CHRNA2      | 6.05E−01      | −1.30                    |                           |                        |
| Cholinergic receptor, nicotinic, alpha 3, transcript variant 1             | NM_000743        | CHRNA3      | 1.84E−10      | 34.22                    |                           |                        |
| Cholinergic receptor, nicotinic, alpha 4                                  | NM_000744        | CHRNA4      | 6.79E−01      | 1.15                     |                           |                        |
| Cholinergic receptor, nicotinic, alpha 4 (neuronal), exon 1               | X89741           | CHRNA4      | 2.79E−02      | −2.53                    |                           |                        |
| Cholinergic receptor, nicotinic, alpha 5                                  | NM_000745        | CHRNA5      | 4.03E−05      | 3.41                     |                           |                        |
| Cholinergic receptor, nicotinic, alpha 6, transcript variant 1             | NM_004198        | CHRNA6      | 2.23E−01      | −1.27                    |                           | 2.21                   |
| Cholinergic receptor, nicotinic, alpha 7, transcript variant 1             | NM_000746        | CHRNA7      | 4.61E−04      | 1.86                     |                           |                        |
| Cholinergic receptor, nicotinic, alpha 7, transcript variant 2             | NM_001190455     | CHRNA7      | 1.56E−11      | 13.24                    |                           |                        |
| Cholinergic receptor, nicotinic, alpha 9                                  | NM_017581        | CHRNA9      | 6.30E−06      | 6.15                     |                           |                        |
| Cholinergic receptor, nicotinic, alpha 10                                 | NM_020402        | CHRNA10     | 1.57E−02      | 1.57                     |                           |                        |
| Cholinergic receptor, nicotinic, beta 1 (muscle)                          | NM_000747        | CHRN1B      | 8.07E−04      | −2.47                    |                           |                        |
| Cholinergic receptor, nicotinic, beta 1 (muscle)                          | NM_000747        | CHRN1B      | 8.87E−03      | −1.92                    |                           |                        |
| Cholinergic receptor, nicotinic, beta 2 (neuronal)                        | NM_000748        | CHRN2B      | 6.03E−04      | −3.01                    |                           |                        |
| Cholinergic receptor, nicotinic, beta 2 (neuronal) [Source: HGNC Symbol; Acc: 1962] | ENST00000368476  | CHRB2       | 2.98E−09      | 32.05                    |                           |                        |
| Cholinergic receptor, nicotinic, beta 3                                  | NM_000749        | CHRN3B      | 5.91E−01      | 1.12                     |                           |                        |
| Cholinergic receptor, nicotinic, beta 4                                   | NM_000750        | CHRN4B      | 1.76E−02      | 4.20                     |                           |                        |
| Cholinergic receptor, nicotinic, delta                                    | NM_000751        | CHRN2D      | 9.84E−01      | 1.01                     |                           |                        |
| Cholinergic receptor, nicotinic, epsilon                                  | NM_000080        | CHRN5E      | 3.66E−01      | −1.20                    |                           |                        |
| Cholinergic receptor, nicotinic, gamma                                    | NM_005199        | CHRNG       | 6.70E−01      | 1.14                     |                           |                        |

(d) Cyclic nucleotide-gated channels

| Gene name                                                                 | Accession number | Gene symbol | P             | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|---------------|--------------------------|---------------------------|------------------------|
| Cyclic nucleotide-gated channel alpha 1, transcript variant 2             | NM_000087        | CNGA1       | 7.14E−01      | 1.15                     |                           |                        |
(d) Continued.

| Gene name                                                                 | Accession number | Gene symbol | $P$                     | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|---------------------------------------------------------------------------|------------------|-------------|-------------------------|---------------------------------------|----------------------------------------|----------------------------------|
| Cyclic nucleotide-gated channel alpha 1, transcript variant 2            | NM_000087        | CNGA1       | $1.18E-02$              | 2.00                                  |                                        |                                  |
| Cyclic nucleotide-gated channel alpha 3, transcript variant 1            | NM_001298        | CNGA3       | $2.00E-01$              | 1.21                                  |                                        |                                  |
| Cyclic nucleotide-gated channel alpha 4                                   | NM_001037329     | CNGA4       | $2.78E-01$              | 1.82                                  |                                        |                                  |
| Cyclic nucleotide-gated channel beta 1, transcript variant 1             | NM_001297        | CNGB1       | $9.22E-03$              | -2.05                                 |                                        |                                  |
| Cyclic nucleotide-gated channel beta 1, transcript variant 1             | NM_001297        | CNGB1       | $6.36E-01$              | -1.13                                 |                                        |                                  |
| Cyclic nucleotide-gated channel beta 3                                   | NM_019098        | CNGB3       | $2.93E-01$              | 1.78                                  |                                        |                                  |

(e) GABA receptors

| Gene name                                                                 | Accession number | Gene symbol | $P$                     | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|---------------------------------------------------------------------------|------------------|-------------|-------------------------|---------------------------------------|----------------------------------------|----------------------------------|
| Gamma-aminobutyric acid (GABA) A receptor, alpha 1, transcript variant 1  | NM_000806        | GABRA1      | $1.26E-01$              | 1.41                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, alpha 1, transcript variant 1  | NM_000806        | GABRA1      | $8.87E-01$              | 1.05                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, alpha 2, transcript variant 1  | NM_000807        | GABRA2      | $9.70E-02$              | 1.70                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, alpha 2, transcript variant 1  | NM_000807        | GABRA2      | $4.49E-01$              | 1.48                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, alpha 3                         | NM_000808        | GABRA3      | $2.10E-01$              | 1.43                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, alpha 4, transcript variant 1   | NM_000809        | GABRA4      | $3.76E-01$              | 1.43                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, alpha 4, transcript variant 1   | NM_000809        | GABRA4      | $8.30E-01$              | 1.05                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, alpha 5, transcript variant 1   | NM_000810        | GABRA5      | $1.09E-08$              | 14.41                                 |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, alpha 6                         | NM_000811        | GABRA6      | $1.69E-01$              | 1.23                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, beta 1                         | NM_000812        | GABRB1      | $1.14E-01$              | 1.43                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, beta 2, transcript variant 2    | NM_000813        | GABRB2      | $1.27E-02$              | 1.94                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, beta 3, transcript variant 1    | NM_000814        | GABRB3      | $6.70E-10$              | 85.93                                 |                                        | -4.49                            |
| Gamma-aminobutyric acid (GABA) A receptor, beta 3, transcript variant 1    | NM_000814        | GABRB3      | $1.15E-09$              | 115.69                                |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, delta                         | NM_000815        | GABRD       | $6.26E-02$              | 3.02                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, epsilon                        | NM_004961        | GABRE       | $5.83E-05$              | -5.47                                 |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, Gamma 1                        | NM_J73536        | GABRG1      | $1.78E-01$              | 1.24                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, Gamma 1                        | NM_J73536        | GABRG1      | $1.70E-02$              | 2.19                                  |                                        |                                  |
| Gamma-aminobutyric acid (GABA) A receptor, Gamma 2, transcript variant 1  | NM_198904        | GABRG2      | $6.02E-01$              | 1.14                                  |                                        |                                  |
### (e) Continued.

| Gene name                                                                 | Accession number | Gene symbol | $P$       | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|---------------------------------------------------------------------------|------------------|-------------|----------|-------------------------------------|----------------------------------------|-----------------------------------|
| Gamma-aminobutyric acid (GABA) A receptor, Gamma 2, transcript variant 2 | NM_000816        | GABRG2      | $5.28E\rightarrow02$ | 1.72                                |                                        |                                   |
| Gamma-aminobutyric acid (GABA) A receptor, Gamma 2, transcript variant 2 | NM_000816        | GABRG2      | $9.47E\rightarrow09$ | 8.41                                |                                        |                                   |
| Gamma-aminobutyric acid (GABA) A receptor, Gamma 3                       | NM_033223        | GABRG3      | $1.99E\rightarrow01$ | 2.00                                |                                        |                                   |
| Gamma-aminobutyric acid (GABA) A receptor, Gamma 3                       | NM_033223        | GABRG3      | $1.04E\rightarrow01$ | 1.61                                |                                        |                                   |
| Gamma-aminobutyric acid (GABA) A receptor, pi                           | NM_014211        | GABRP       | $6.62E\rightarrow01$ | $-1.12$                             |                                        | 17.25                             |
| Gamma-aminobutyric acid (GABA) receptor, theta                          | NM_018558        | GABRQ       | $1.60E\rightarrow01$ | 1.56                                |                                        |                                   |
| Gamma-aminobutyric acid (GABA) receptor, theta                          | NM_018558        | GABRQ       | $4.76E\rightarrow01$ | $-1.27$                             |                                        |                                   |
| Gamma-aminobutyric acid (GABA) receptor, theta [Source: HGNC Symbol; Acc: 14454] | ENST00000370306 | GABRQ      | $8.22E\rightarrow09$ | 52.17                              |                                        |                                   |
| Gamma-aminobutyric acid (GABA) receptor, rho 1                          | NM_002042        | GABRR1      | $8.94E\rightarrow01$ | $-1.04$                             |                                        |                                   |
| Gamma-aminobutyric acid (GABA) receptor, rho 2                          | NM_002043        | GABRR2      | $2.83E\rightarrow01$ | 1.54                                |                                        |                                   |
| Gamma-aminobutyric acid (GABA) receptor, rho 3                          | NM_001105580     | GABRR3      | $3.05E\rightarrow01$ | $-1.34$                             |                                        |                                   |

### (f) Glycine receptors

| Gene name                                                                 | Accession number | Gene symbol | $P$       | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|---------------------------------------------------------------------------|------------------|-------------|----------|-------------------------------------|----------------------------------------|-----------------------------------|
| Glycine receptor, alpha 1, transcript variant 2                          | NM_000171        | GLRA1       | $5.47E\rightarrow01$ | $-1.29$                             |                                        |                                   |
| Glycine receptor, alpha 2, transcript variant 1                          | NM_002063        | GLRA2       | $1.17E\rightarrow01$ | 1.42                                |                                        | 11.41                             |
| Glycine receptor, alpha 3, transcript variant 1                          | NM_006529        | GLRA3       | $5.16E\rightarrow01$ | $-1.26$                             |                                        |                                   |
| Glycine receptor, alpha 3 [Source: HGNC Symbol; Acc: 4328]               | ENST00000274093  | GLRA3       | $8.33E\rightarrow02$ | 1.64                                |                                        |                                   |
| Glycine receptor, alpha 3, transcript variant 1                          | NM_006529        | GLRA3       | $1.46E\rightarrow01$ | 1.41                                |                                        |                                   |
| Glycine receptor, alpha 4, transcript variant 1                          | NM_001024452     | GLRA4       | $7.75E\rightarrow01$ | 1.17                                |                                        |                                   |
| Glycine receptor, beta, transcript variant 1                             | NM_000824        | GLRB        | $6.38E\rightarrow02$ | $-1.69$                             |                                        | 6.61                              |

### (g) Ionotropic glutamate receptors

| Gene name                                                                 | Accession number | Gene symbol | $P$       | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|---------------------------------------------------------------------------|------------------|-------------|----------|-------------------------------------|----------------------------------------|-----------------------------------|
| Glutamate receptor, ionotropic, AMPA 1, transcript variant 1              | NM_000827        | GRIA1       | $7.65E\rightarrow01$ | $-1.20$                             |                                        | 2.06                              |
| Glutamate receptor, ionotropic, AMPA 2, transcript variant 1              | NM_000826        | GRIA2       | $2.87E\rightarrow01$ | $-1.87$                             |                                        | 21.26                             |
| Glutamate receptor, ionotropic, AMPA 2, transcript variant 1              | NM_000826        | GRIA2       | $2.72E\rightarrow01$ | 1.33                                |                                        |                                   |
| Glutamate receptor, ionotropic, AMPA 2, transcript variant 1              | NM_000826        | GRIA2       | $6.54E\rightarrow01$ | 1.22                                |                                        |                                   |
| Gene name                                                                 | Accession number | Gene symbol | P         | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|-----------|-------------------------|----------------------------|------------------------|
| Glutamate receptor, ionotropic, AMPA 3, transcript variant 2             | NM_000828        | GRIA3       | 5.05E-01  | 1.26                    |                            |                        |
| Glutamate receptor, ionotropic, AMPA 3 [Source: HGNCSymbol; Acc: 4573]  | ENST00000371264  | GRIA3       | 1.14E-01  | 1.50                    |                            |                        |
| Glutamate receptor, ionotropic, AMPA 3, transcript variant 2             | NM_000828        | GRIA3       | 9.05E-01  | -1.05                   |                            |                        |
| Glutamate receptor, ionotropic, AMPA 4, transcript variant 1             | NM_000829        | GRIA4       | 2.30E-02  | 1.80                    | 3.73                       |                        |
| Glutamate receptor, ionotropic, delta 1                                  | NM_017551        | GRID1       | 1.82E-01  | 1.50                    |                            |                        |
| Glutamate receptor, ionotropic, delta 1                                  | NM_017551        | GRID1       | 5.08E-05  | 3.63                    |                            |                        |
| Glutamate receptor, ionotropic, delta 2                                  | NM_001510        | GRID2       | 7.64E-01  | -1.11                   |                            |                        |
| Glutamate receptor, ionotropic, delta 2                                  | NM_001510        | GRID2       | 5.55E-09  | 55.66                   |                            |                        |
| Glutamate receptor, ionotropic, kainate 1, transcript variant 1          | NM_000830        | GRIK1       | 1.64E-01  | 1.29                    | 2.58                       |                        |
| Glutamate receptor, ionotropic, kainate 2, transcript variant 3          | NM_00166247      | GRIK2       | 1.42E-01  | 1.56                    | 2.53                       |                        |
| Glutamate receptor, ionotropic, kainate 2, transcript variant 1          | NM_021956        | GRIK2       | 1.14E-01  | -2.01                   |                            |                        |
| Glutamate receptor, ionotropic, kainate 2, transcript variant 2          | NM_175768        | GRIK2       | 7.80E-01  | 1.08                    |                            |                        |
| Glutamate receptor, ionotropic, kainate 3                                | NM_000831        | GRIK3       | 1.58E-01  | 1.64                    |                            |                        |
| Glutamate receptor, ionotropic, kainate 3                                | NM_000831        | GRIK3       | 6.15E-10  | 22.64                   |                            |                        |
| Glutamate receptor, ionotropic, kainate 4 [Source: HGNCSymbol; Acc: 4582] | ENST00000527524  | GRIK4       | 1.77E-11  | 18.10                   |                            |                        |
| Glutamate receptor, ionotropic, kainate 4                                | NM_014619        | GRIK4       | 5.73E-02  | 2.54                    |                            |                        |
| Glutamate receptor, ionotropic, kainate 5                                | NM_002088        | GRIK5       | 2.65E-03  | 1.79                    | -2.41                      |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 1, transcript variant NRI-3 | NM_007327       | GRIN1       | 1.93E-02  | -3.02                   | 2.69                       |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 1, transcript variant NRI-3 | NM_007327       | GRIN1       | 6.01E-02  | -2.45                   |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 1, transcript variant NRI-3 | NM_007327       | GRIN1       | 3.86E-01  | -1.65                   |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 2A, transcript variant 2 | NM_000833       | GRIN2A      | 6.54E-01  | 1.18                    |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 2A, transcript variant 2 | NM_000833       | GRIN2A      | 9.21E-01  | -1.02                   |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 2A, transcript variant 1 | NM_00134407     | GRIN2A      | 3.32E-10  | 29.85                   |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 2A, transcript variant 2 | NM_000833       | GRIN2A      | 2.63E-01  | 1.55                    |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 2B                   | NM_000834        | GRIN2B      | 6.64E-01  | -1.26                   |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 2C                   | NM_000835        | GRIN2C      | 8.01E-01  | -1.08                   |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 2C                   | NM_000835        | GRIN2C      | 5.01E-01  | 1.13                    |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 2D                   | NM_000836        | GRIN2D      | 4.69E-02  | -1.82                   |                            |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate 3A                   | NM_133445        | GRIN3A      | 3.28E-01  | -1.41                   |                            |                        |
### (g) Continued.

| Gene name                                                                 | Accession number | Gene symbol | P          | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|------------|-------------------------|---------------------------|------------------------|
| Glutamate receptor, ionotropic, N-methyl-D-aspartate 3B                   | NM_138690        | GRIN3B      | $9.36E-01$ | $-1.02$                 |                           |                        |
| Glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1 (glutamate binding), transcript variant 1 | NM_000837        | GRINA       | $3.68E-04$ | $-2.05$ $2.05$         |                           |                        |
| NMDA receptor glutamate-binding chain (hnrgw), partial                   | U44954           | GRINA       | $3.06E-04$ | $-1.81$                 |                           |                        |

### (h) Hyperpolarization-activated cyclic nucleotide-gated channels

| Gene name                                                                 | Accession number | Gene symbol | P          | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|------------|-------------------------|---------------------------|------------------------|
| Hyperpolarization-activated cyclic nucleotide-gated potassium channel 1  | NM_021072        | HCN1        | $3.47E-11$ | $52.85$                 |                           |                        |
| Hyperpolarization-activated cyclic nucleotide-gated potassium channel 1  | NM_021072        | HCN1        | $1.01E-08$ | $9.91$                  |                           |                        |
| Hyperpolarization-activated cyclic nucleotide-gated potassium channel 2  | NM_001194        | HCN2        | $5.36E-02$ | $1.63$                  |                           |                        |
| Hyperpolarization-activated cyclic nucleotide-gated potassium channel 3  | NM_020897        | HCN3        | $1.98E-02$ | $2.12$ $6.56$           |                           |                        |
| Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4  | NM_005477        | HCN4        | $1.01E-01$ | $-1.66$                 |                           |                        |

### (i) Serotonin receptors

| Gene name                                                                 | Accession number | Gene symbol | P          | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|------------|-------------------------|---------------------------|------------------------|
| 5-hydroxytryptamine (serotonin) receptor 3A, transcript variant 1          | NM_213621        | HTR3A       | $1.99E-03$ | $2.77$ $-2.20$          |                           |                        |
| 5-hydroxytryptamine (serotonin) receptor 3A, transcript variant 1          | NM_213621        | HTR3A       | $2.63E-11$ | $11.11$                 |                           |                        |
| 5-hydroxytryptamine (serotonin) receptor 3B, family member C              | NM_006028        | HTR3B       | $1.99E-01$ | $-1.54$                 |                           |                        |
| 5-hydroxytryptamine (serotonin) receptor 3, family member D, transcript variant 2 | NM_130770        | HTR3C       | $4.81E-01$ | $1.34$                  |                           |                        |
| 5-hydroxytryptamine (serotonin) receptor 3, family member D, transcript variant 2 | NM_182537        | HTR3D       | $4.75E-01$ | $-1.37$                 |                           |                        |
| 5-hydroxytryptamine (serotonin) receptor 3, family member E               | NM_182589        | HTR3E       | $1.52E-01$ | $-1.44$                 |                           |                        |

### (j) Voltage-gated potassium channels

| Gene name                                                                 | Accession number | Gene symbol | P          | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|------------|-------------------------|---------------------------|------------------------|
| Potassium voltage-gated channel, shaker-related subfamily, member 1 (episodic ataxia with myokymia) | NM_000217        | KCNA1       | $1.64E-01$ | $2.00$                  |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, member 1 (episodic ataxia with myokymia) | NM_000217        | KCNA1       | $1.31E-01$ | $1.87$                  |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, member 2, transcript variant 2          | NM_001204269     | KCNA2       | $8.55E-02$ | $1.33$                  |                           |                        |
(j) Continued.

| Gene name                                                                 | Accession number | Gene symbol | P        | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|----------|-------------------------|---------------------------|------------------------|
| Potassium voltage-gated channel, shaker-related subfamily, member 2, transcript variant 1 | NM_004974        | KCNA2       | 8.33E−01 | 1.06                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, member 3       | NM_002232        | KCNA3       | 2.43E−01 | 1.76                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, member 4       | NM_002233        | KCNA4       | 5.75E−01 | 1.11                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, member 5       | NM_002234        | KCNA5       | 7.6E−04  | 4.11                    | 5.63                      |                        |
| Potassium voltage-gated channel, shaker-related subfamily, member 6       | NM_002235        | KCNA6       | 7.20E−02 | 2.28                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, member 7       | NM_031866        | KCNA7       | 8.53E−03 | 3.67                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, member 7       | NM_031866        | KCNA7       | 1.04E−01 | 2.39                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, member 10      | NM_005549        | KCNA10      | 3.32E−01 | −1.62                   |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, beta member 1, transcript variant 2 | NM_003471        | KCNAB1      | 2.70E−01 | 1.46                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, beta member 1, transcript variant 2 | NM_003471        | KCNAB1      | 3.60E−02 | 2.42                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, beta member 1, transcript variant 2 | NM_003471        | KCNAB1      | 7.87E−02 | 3.06                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, beta member 2, transcript variant 1 | NM_003636        | KCNAB2      | 5.35E−01 | −1.35                   |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, beta member 2, transcript variant 1 | NM_003636        | KCNAB2      | 2.20E−01 | 1.26                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, beta member 3 [Source: HGNC Symbol; Acc: 6230] | ENST00000303790  | KCNAB3      | 8.14E−02 | 1.62                    |                           |                        |
| Potassium voltage-gated channel, shaker-related subfamily, beta member 3 | NM_004732        | KCNAB3      | 3.66E−01 | 1.35                    |                           |                        |
| Potassium voltage-gated channel, Shab-related subfamily, member 1         | NM_004975        | KCNB1       | 7.42E−08 | 16.32                   | 2.59                      |                        |
| Potassium voltage-gated channel, Shab-related subfamily, member 2         | NM_004770        | KCNB2       | 1.54E−05 | 4.58                    |                           |                        |
| Potassium voltage-gated channel, Shab-related subfamily, member 1, transcript variant A | NM_00112741      | KCNC1       | 1.47E−01 | 1.75                    |                           |                        |
| Potassium voltage-gated channel, Shab-related subfamily, member 1, transcript variant B | NM_00112741      | KCNC1       | 4.86E−08 | 13.97                   |                           |                        |
| Potassium voltage-gated channel, Shab-related subfamily, member 1, transcript variant A | NM_00112741      | KCNC1       | 2.17E−01 | 1.56                    |                           |                        |
| Potassium voltage-gated channel, Shab-related subfamily, member 2, transcript variant 1 | NM_139136        | KCNC2       | 8.53E−01 | 1.06                    |                           |                        |
| Potassium voltage-gated channel, Shab-related subfamily, member 2, transcript variant 2 | NM_139137        | KCNC2       | 4.04E−01 | 1.34                    |                           |                        |
| Potassium voltage-gated channel, Shab-related subfamily, member 3         | NM_004977        | KCNC3       | 3.56E−01 | 1.20                    |                           |                        |
| Potassium voltage-gated channel, Shab-related subfamily, member 4, transcript variant 3 | NM_001039574     | KCNC4       | 7.70E−02 | −1.40                   |                           |                        |
| Potassium voltage-gated channel, Shal-related subfamily, member 1         | NM_004979        | KCND1       | 1.48E−04 | 7.11                    |                           |                        |
| Potassium voltage-gated channel, Shal-related subfamily, member 2         | NM_012281        | KCND2       | 1.62E−12 | 91.08                   | 2.76                      | −2.57                  |
| Gene name                                                                 | Accession number | Gene symbol | P         | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|--------------------------------------------------------------------------|------------------|-------------|-----------|-----------------------------------|--------------------------------------|-----------------------------------|
| Potassium voltage-gated channel, Shal-related subfamily, member 2       | NM_012281        | KCND2       | 2.76E–09  | 21.83                             |                                      |                                  |
| Potassium voltage-gated channel, Shal-related subfamily, member 3 [Source: HGNC Symbol; Acc: 6239] | ENST00000369697  | KCND3       | 5.36E–01  | –1.36                             |                                      |                                  |
| Potassium voltage-gated channel, Shal-related subfamily, member 3, transcript variant 1 | NM_004980        | KCND3       | 1.05E–01  | 1.55                              |                                      |                                  |
| Potassium voltage-gated channel, Shal-related subfamily, member 3, transcript variant 1 | NM_004980        | KCND3       | 4.41E–01  | 1.37                              |                                      |                                  |
| Potassium voltage-gated channel, Shal-related subfamily, member 3 [Source: HGNC Symbol; Acc: 6239] | ENST00000369697  | KCND3       | 3.86E–04  | –1.84                             |                                      |                                  |
| Potassium voltage-gated channel, Isk-related family, member 1, transcript variant 2 | NM_000219        | KCNE1       | 3.53E–01  | –1.45                             |                                      |                                  |
| Potassium voltage-gated channel, Isk-related family, member 1, transcript variant 2 | NM_000219        | KCNE1       | 3.59E–01  | 1.25                              |                                      |                                  |
| KCNE1-like                                                                | NM_012282        | KCNE1L      | 1.34E–08  | 4.44                              | –2.18                               |                                  |
| KCNE1-like                                                                | NM_012282        | KCNE1L      | 1.11E–08  | 3.65                              |                                      |                                  |
| KCNE1-like                                                                | NM_012282        | KCNE1L      | 6.41E–03  | 1.88                              |                                      |                                  |
| Potassium voltage-gated channel, Isk-related family, member 2            | NM_172201        | KCNE2       | 1.41E–04  | 3.93                              |                                      |                                  |
| Potassium voltage-gated channel, Isk-related family, member 3            | NM_005472        | KCNE3       | 8.65E–15  | 52.36                             |                                      |                                  |
| Potassium voltage-gated channel, Isk-related family, member 4            | NM_080671        | KCNE4       | 5.04E–01  | 1.20                              |                                      |                                  |
| Potassium voltage-gated channel, subfamily F, member 1                   | NM_002236        | KCNF1       | 2.25E–05  | 6.48                              | 2.84                                |                                  |
| Potassium voltage-gated channel, subfamily G, member 1                   | NM_002237        | KCNG1       | 8.51E–03  | –1.82                             |                                      |                                  |
| Potassium voltage-gated channel, subfamily G, member 1                   | NM_002237        | KCNG1       | 1.55E–01  | –1.65                             |                                      |                                  |
| Potassium voltage-gated channel, subfamily G, member 2                   | NM_012283        | KCNG2       | 6.21E–02  | 1.32                              |                                      |                                  |
| Potassium voltage-gated channel, subfamily G, member 3, transcript variant 1 | NM_133329        | KCNG3       | 3.74E–11  | 58.95                             | –2.93                               |                                  |
| Potassium voltage-gated channel, subfamily G, member 4                   | NM_172347        | KCNG4       | 3.36E–03  | –3.33                             |                                      |                                  |
| Potassium voltage-gated channel, subfamily G, member 4, (cDNA clone IMAGE: 3028985) | BC008969         | KCNG4       | 2.24E–04  | –3.29                             |                                      |                                  |
| Potassium voltage-gated channel, subfamily H (eag-related), member 1, transcript variant 1 | NM_172362        | KCNH1       | 8.05E–01  | –1.15                             |                                      |                                  |
| Potassium voltage-gated channel, subfamily H (eag-related), member 2, transcript variant 1 | NM_000238        | KCNH2       | 5.94E–04  | 37.53                             |                                      |                                  |
| Potassium voltage-gated channel, subfamily H (eag-related), member 2, transcript variant 2 | NM_172056        | KCNH2       | 5.70E–03  | 1.73                              |                                      |                                  |
| Potassium voltage-gated channel, subfamily H (eag-related), member 3     | NM_012284        | KCNH3       | 9.65E–01  | 1.01                              |                                      |                                  |
| Potassium voltage-gated channel, subfamily H (eag-related), member 4     | NM_012285        | KCNH4       | 3.18E–01  | –1.24                             |                                      |                                  |
| Gene name                                                                 | Accession number | Gene symbol | P          | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|--------------------------------------------------------------------------|------------------|-------------|------------|-------------------------|---------------------------|------------------------|
| Potassium voltage-gated channel, subfamily H (eag-related), member 5, transcript variant 2 | NM_172376        | KCNH5       | 3.04E−03   | 2.96                    |                           |                        |
| Potassium voltage-gated channel, subfamily H (eag-related), member 5, transcript variant 1 | NM_139318        | KCNH5       | 5.41E−01   | 1.47                    |                           |                        |
| Potassium voltage-gated channel, subfamily H (eag-related), member 6, transcript variant 2 | NM_173092        | KCNH6       | 2.93E−02   | 3.04                    |                           |                        |
| cDNA FLJ33650 fis, clone BRAMY2024514, highly similar to Rattus norvegicus Potassium channel (erg2) | AK090969         | KCNH6       | 2.08E−05   | 12.42                   |                           |                        |
| Potassium voltage-gated channel, subfamily H (eag-related), member 6, transcript variant 2 | NM_173092        | KCNH6       | 2.55E−02   | 2.29                    |                           |                        |
| Potassium voltage-gated channel, subfamily H (eag-related), member 7, transcript variant 2 | NM_173162        | KCNH7       | 4.63E−01   | −1.40                   |                           |                        |
| Potassium voltage-gated channel, subfamily H (eag-related), member 7, transcript variant 1 | NM_033272        | KCNH7       | 7.58E−01   | −1.09                   |                           |                        |
| Potassium voltage-gated channel, subfamily H (eag-related), member 8 | NM_144633        | KCNH8       | 3.00E−09   | 24.57                   | 2.97                      |                        |
| Kv channel interacting protein 1, transcript variant 1                   | NM_001034837     | KCNIP1      | 8.33E−02   | 1.96                    | 4.24                      |                        |
| Kv channel interacting protein 2, transcript variant 7                  | NM_173197        | KCNIP2      | 6.43E−01   | 1.21                    |                           |                        |
| Kv channel interacting protein 2, transcript variant 1                  | NM_014591        | KCNIP2      | 2.53E−03   | 1.96                    |                           |                        |
| Kv channel interacting protein 3, calsenilin, transcript variant 1       | NM_013434        | KCNIP3      | 1.15E−03   | −3.47                   |                           |                        |
| Kv channel interacting protein 4, transcript variant 5                  | NM_001035003     | KCNIP4      | 6.73E−01   | 1.16                    | 2.01                      |                        |
| Kv channel interacting protein 4, transcript variant 5                  | NM_001035003     | KCNIP4      | 9.26E−01   | 1.05                    |                           |                        |
| Potassium voltage-gated channel, KQT-like subfamily, member 1, transcript variant 1 | NM_000218        | KCNQ1       | 3.31E−09   | 79.52                   |                           |                        |
| Potassium voltage-gated channel, KQT-like subfamily, member 2, transcript variant 5 | NM_172109        | KCNQ2       | 5.68E−19   | 3408.43                 |                           |                        |
| Potassium voltage-gated channel, KQT-like subfamily, member 2, transcript variant 3 | NM_004518        | KCNQ2       | 1.29E−02   | 1.82                    |                           |                        |
| Potassium voltage-gated channel, KQT-like subfamily, member 2, (cDNA clone IMAGE: 4154700) | BC020384         | KCNQ2       | 1.09E−08   | 37.12                   |                           |                        |
| Potassium voltage-gated channel, KQT-like subfamily, member 3, transcript variant 1 | NM_004519        | KCNQ3       | 1.10E−04   | −1.69                   |                           |                        |
| Potassium voltage-gated channel, KQT-like subfamily, member 4, transcript variant 1 | NM_004700        | KCNQ4       | 9.77E−01   | 1.02                    |                           |                        |
| Potassium voltage-gated channel, KQT-like subfamily, member 5, transcript variant 1 | NM_019842        | KCNQ5       | 9.81E−02   | −1.79                   |                           |                        |
| Potassium voltage-gated channel, delayed-rectifier, subfamily S, member 1 | NM_002251        | KCNS1       | 3.39E−01   | −1.27                   | −2.64                     |                        |
| Potassium voltage-gated channel, delayed-rectifier, subfamily S, member 2 | NM_020697        | KCNS2       | 6.19E−02   | −2.45                   | 2.11                      |                        |
| Potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3 | NM_002252        | KCNS3       | 1.04E−04   | 2.22                    | −2.61                     | −2.39                  |
| Potassium channel, subfamily T, member 1 (sodium activated)              | NM_020822        | KCNT1       | 8.51E−02   | −2.17                   |                           |                        |
(j) Continued.

| Gene name                                             | Accession number | Gene symbol | P       | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|-------------------------------------------------------|------------------|-------------|---------|-------------------------|--------------------------|------------------------|
| Potassium channel, subfamily V, member 1              | NM_014379        | KCNV1       | 7.84E−02 | 1.58                    |                          |                        |
| Potassium channel, subfamily V, member 2              | NM_133497        | KCNV2       | 7.63E−01 | −1.16                   |                          |                        |

(k) Inwardly rectifying potassium channels

| Gene name                                                                 | Accession number | Gene symbol | P       | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|---------------------------------------------------------------------------|------------------|-------------|---------|-------------------------|--------------------------|------------------------|
| Potassium inwardly-rectifying channel, subfamily J, member 1, transcript variant rom-k5 | NM_153767        | KCNJ1       | 2.54E−02 | 2.66                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 1, transcript variant rom-k5 | NM_153767        | KCNJ1       | 8.51E−01 | −1.05                   |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 2              | NM_000891        | KCNJ2       | 5.14E−04 | 4.38                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 3              | NM_002239        | KCNJ3       | 4.56E−01 | 1.34                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 4, transcript variant 1 | NM_152868        | KCNJ4       | 4.80E−02 | 2.30                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 5              | NM_000890        | KCNJ5       | 1.88E−08 | −45.40                  |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 6              | NM_002240        | KCNJ6       | 3.29E−05 | 6.75                    | 5.54                     |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 8              | NM_004982        | KCNJ8       | 1.98E−04 | 5.97                    | 2.74                     |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 9 [Source: HGNC Symbol; Acc: 6270] | ENST00000368088  | KCNJ9       | 3.17E−01 | 1.49                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 9              | NM_004983        | KCNJ9       | 3.07E−01 | 1.79                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 10             | NM_002241        | KCNJ10      | 8.85E−04 | 4.14                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 10             | NM_002241        | KCNJ10      | 9.56E−01 | 1.01                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 11, transcript variant 1 | NM_000525        | KCNJ11      | 4.00E−04 | 2.93                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 12             | NM_021012        | KCNJ12      | 1.00E−01 | 1.47                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 12             | NM_021012        | KCNJ12      | 3.53E−06 | 5.81                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 13, transcript variant 1 | NM_002242        | KCNJ13      | 7.75E−01 | 1.20                    |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 14, transcript variant 2 | NM_170720        | KCNJ14      | 9.05E−02 | −1.40                   |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 15, transcript variant 1 | NM_170736        | KCNJ15      | 3.41E−08 | −150.95                 |                          |                        |
| Potassium inwardly-rectifying channel, subfamily J, member 16, transcript variant 2 | NM_170741        | KCNJ16      | 2.22E−01 | −1.93                   |                          |                        |
### (l) Two-P potassium channels

| Gene name                                                                 | Accession number | Gene symbol | \(P\)       | Fold change Ker \(\rightarrow\) hiPSC | Fold change hiPSC \(\rightarrow\) Neuron | Fold change hiPSC \(\rightarrow\) CM |
|--------------------------------------------------------------------------|------------------|-------------|------------|--------------------------------------|----------------------------------------|-----------------------------------|
| Potassium channel, subfamily K, member 1                                  | NM_002245        | KCNK1       | 3.02E−04  | −1.68                                |                                        |                                   |
| Potassium channel, subfamily K, member 2, transcript variant 1            | NM_00107424      | KCNK2       | 3.46E−01  | 1.57                                 |                                        |                                   |
| Potassium channel, subfamily K, member 3                                  | NM_002246        | KCNK3       | 9.98E−01  | 1.00                                 | 2.36                                   |                                   |
| Potassium channel, subfamily K, member 3                                  | NM_002246        | KCNK3       | 8.75E−01  | −1.10                                |                                        |                                   |
| Potassium channel, subfamily K, member 3                                  | NM_002246        | KCNK3       | 5.34E−01  | −1.30                                |                                        |                                   |
| Potassium channel, subfamily K, member 3 [Source: HGNC Symbol; Acc: 6278] | ENST00000302909  | KCNK3       | 2.53E−01  | 1.52                                 |                                        |                                   |
| Potassium channel, subfamily K, member 4                                  | NM_033310        | KCNK4       | 6.21E−01  | −1.14                                | 2.05                                   |                                   |
| Potassium channel, subfamily K, member 5                                  | NM_003740        | KCNK5       | 1.16E−14  | 29.46                                | −2.35                                  | −2.03                             |
| Potassium channel, subfamily K, member 6                                  | NM_004823        | KCNK6       | 1.22E−06  | −3.48                                | −5.11                                  |                                   |
| Potassium channel, subfamily K, member 6                                  | NM_004823        | KCNK6       | 2.05E−08  | −5.22                                |                                        |                                   |
| Potassium channel, subfamily K, member 7, transcript variant A            | NM_033347        | KCNK7       | 1.17E−01  | −1.52                                |                                        |                                   |
| Potassium channel, subfamily K, member 9                                  | NM_016601        | KCNK9       | 6.67E−01  | −1.29                                |                                        |                                   |
| Potassium channel, subfamily K, member 10, transcript variant 1           | NM_021161        | KCNK10      | 2.63E−01  | −1.30                                |                                        |                                   |
| Potassium channel, subfamily K, member 10, transcript variant 2           | NM_138317        | KCNK10      | 1.41E−02  | 1.43                                 |                                        |                                   |
| Potassium channel, subfamily K, member 12                                 | NM_022055        | KCNK12      | 4.58E−10  | 23.40                                | −5.58                                  |                                   |
| Potassium channel, subfamily K, member 13                                 | NM_022054        | KCNK13      | 7.65E−01  | −1.10                                |                                        |                                   |
| Potassium channel, subfamily K, member 15                                 | NM_022358        | KCNK15      | 4.96E−02  | −1.50                                |                                        |                                   |
| Potassium channel, subfamily K, member 15                                 | NM_022358        | KCNK15      | 9.10E−01  | −1.09                                |                                        |                                   |
| Pancreatic potassium channel TALK-1d; alternatively spliced               | AY253147         | KCNK16      | 2.17E−02  | −2.43                                |                                        |                                   |
| Potassium channel, subfamily K, member 17, transcript variant 1           | NM_031460        | KCNK17      | 1.87E−11  | 28.60                                |                                        |                                   |
| Potassium channel, subfamily K, member 17, transcript variant 1           | NM_031460        | KCNK17      | 1.52E−05  | 19.62                                |                                        |                                   |
| Potassium channel, subfamily K, member 18                                 | NM_181840        | KCNK18      | 1.77E−01  | 1.61                                 |                                        |                                   |

### (m) Calcium-activated potassium channels

| Gene name                                                                 | Accession number | Gene symbol | \(P\)       | Fold change Ker \(\rightarrow\) hiPSC | Fold change hiPSC \(\rightarrow\) Neuron | Fold change hiPSC \(\rightarrow\) CM |
|--------------------------------------------------------------------------|------------------|-------------|------------|--------------------------------------|----------------------------------------|-----------------------------------|
| Potassium large conductance calcium-activated channel, subfamily M, alpha member 1, transcript variant 2 | NM_002247        | KCNMA1      | 1.01E−02  | 1.84                                 | 2.01                                   |                                   |
| Potassium large conductance calcium-activated channel, subfamily M, alpha member 1, transcript variant 1  | NM_00104797      | KCNMA1      | 3.19E−01  | 1.32                                 |                                        |                                   |
| Potassium large conductance calcium-activated channel, subfamily M, alpha member 1, transcript variant 2 | NM_002247        | KCNMA1      | 3.67E−03  | 2.27                                 |                                        |                                   |
| Potassium large conductance calcium-activated channel, subfamily M, alpha member 1, transcript variant 2 | NM_002247        | KCNMA1      | 8.53E−02  | 1.44                                 |                                        |                                   |
| Maxi-K channel HSLO                                                      | AF349445         | KCNMA1      | 3.04E−01  | 1.44                                 |                                        |                                   |
| Gene name                                                                 | Accession number | Gene symbol | P       | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
|--------------------------------------------------------------------------|------------------|-------------|---------|-------------------------|---------------------------|------------------------|
| Potassium large conductance calcium-activated channel, subfamily M, alpha member 1, transcript variant 2 | NM_002247        | KCNMA1      | $2.15E-01$ | -1.23                   |                           |                        |
| Potassium large conductance calcium-activated channel, subfamily M, beta member 1 | NM_004137        | KCNMB1      | $7.12E-02$ | -1.41                   |                           |                        |
| Potassium large conductance calcium-activated channel, subfamily M, beta member 1 | NM_004137        | KCNMB1      | $2.23E-06$ | 7.82                    |                           |                        |
| Potassium large conductance calcium-activated channel, subfamily M, beta member 2, transcript variant 1 | NM_181361        | KCNMB2      | $3.36E-01$ | 1.56                    |                           |                        |
| Potassium large conductance calcium-activated channel, subfamily M, beta member 2, transcript variant 1 | NM_181361        | KCNMB2      | $1.17E-01$ | 1.47                    |                           |                        |
| Potassium large conductance calcium-activated channel, subfamily M beta member 3, transcript variant 1 | NM_171828        | KCNMB3      | $1.41E-05$ | 2.63                    |                           |                        |
| Potassium large conductance calcium-activated channel, subfamily M, beta member 4 | NM_014505        | KCNMB4      | $8.85E-12$ | 103.99                  |                           |                        |
| Potassium large conductance calcium-activated channel, subfamily M, beta member 4 [Source: HGNCSymbol; Acc: 6289] | ENST00000258111  | KCNMB4      | $9.22E-10$ | 18.40                   |                           |                        |
| Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 1 | NM_002248        | KCNN1       | $3.40E-05$ | 4.67                    |                           |                        |
| Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2, transcript variant 1 | NM_021614        | KCNN2       | $1.88E-13$ | 22.23                   | -3.63                     |                        |
| Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3, transcript variant 1 | NM_002249        | KCNN3       | $2.58E-06$ | 8.25                    |                           |                        |
| Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3, transcript variant 3 | NM_001204087     | KCNN3       | $1.11E-07$ | 15.29                   |                           |                        |
| Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4 | NM_002250        | KCNN4       | $1.06E-02$ | -1.84                   |                           |                        |

| n) P2X receptors                                                                 |
|-------------------------------------------------------------------------------|
| Gene name                                                                 | Accession number | Gene symbol | P       | Fold change Ker → hiPSC | Fold change hiPSC → Neuron | Fold change hiPSC → CM |
| Purinergic receptor P2X, ligand-gated ion channel, 1                          | NM_002558        | P2X1        | $7.71E-01$ | 1.14                    |                           |                        |
| Purinergic receptor P2X, ligand-gated ion channel, 2, transcript variant 4    | NM_170683        | P2X2        | $5.25E-02$ | -1.66                   |                           |                        |
| Purinergic receptor P2X, ligand-gated ion channel, 3                          | NM_002559        | P2X3        | $2.43E-02$ | -1.76                   |                           |                        |
| Purinergic receptor P2X, ligand-gated ion channel, 4                          | NM_002560        | P2X4        | $8.68E-01$ | -1.03                   |                           |                        |
| Purinergic receptor P2X, ligand-gated ion channel, 5, transcript variant 1    | NM_002561        | P2X5        | $7.68E-08$ | 6.97                    |                           |                        |
### (n) Continued.

| Gene name                                                                 | Accession number | Gene symbol | P       | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|---------------------------------------------------------------------------|------------------|-------------|---------|------------------------------------|---------------------------------------|-----------------------------------|
| Purinergic receptor P2X, ligand-gated ion channel, 5, transcript variant 2 | NM_175080        | P2RX5       | 6.13E−02 | 1.54                                |                                       |                                   |
| Purinergic receptor P2X, ligand-gated ion channel, 6 [Source: HGNC Symbol; Acc: 8538] | ENST00000413302  | P2RX6       | 4.13E−01 | 1.68                                |                                       |                                   |
| Purinergic receptor P2X, ligand-gated ion channel, 7, transcript variant 1 | NM_002562        | P2RX7       | 6.13E−01 | 1.23                                |                                       |                                   |
| Purinergic receptor P2X, ligand-gated ion channel, 7, transcript variant 1 | NM_002562        | P2RX7       | 9.17E−01 | 1.04                                |                                       |                                   |

### (o) Transient receptor potential channels

| Gene name                                                                 | Accession number | Gene symbol | P       | Fold change Ker $\rightarrow$ hiPSC | Fold change hiPSC $\rightarrow$ Neuron | Fold change hiPSC $\rightarrow$ CM |
|---------------------------------------------------------------------------|------------------|-------------|---------|------------------------------------|---------------------------------------|-----------------------------------|
| Polycystic kidney disease 2 (autosomal dominant)                          | NM_000297        | PKD2        | 7.48E−07 | 1.79                                |                                       |                                   |
| Polycystic kidney disease 2 (autosomal dominant)                          | NM_000297        | PKD2        | 2.38E−05 | 1.98                                |                                       |                                   |
| Polycystic kidney disease 2-like 1                                        | NM_016112        | PKD2L1      | 1.29E−03 | 4.66                                |                                       |                                   |
| Polycystic kidney disease 2-like 2                                        | NM_014386        | PKD2L2      | 1.94E−01 | 1.49                                |                                       |                                   |
| Polycystic kidney disease 2-like 2                                        | NM_014386        | PKD2L2      | 7.43E−01 | 1.19                                |                                       |                                   |
| Polycystic kidney disease 2-like 2                                        | NM_014386        | PKD2L2      | 6.74E−01 | 1.09                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily A, member 1        | NM_007332        | TRPA1       | 2.99E−01 | 1.74                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily A, member 1        | NM_007332        | TRPA1       | 5.64E−02 | 2.70                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily C, member 1        | NM_003304        | TRPC1       | 4.30E−06 | 2.01                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily C, member 3, transcript variant 2 | NM_003305        | TRPC3       | 1.12E−07 | 5.78                                |                                       | 2.45                             |
| Transient receptor potential cation channel, subfamily C, member 4, transcript variant alpha | NM_016179        | TRPC4       | 3.25E−07 | 25.38                               |                                       |                                   |
| Transient receptor potential cation channel, subfamily C, member 5        | NM_012471        | TRPC5       | 1.20E−01 | 1.28                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily C, member 6        | NM_004621        | TRPC6       | 1.21E−01 | 2.33                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily C, member 7, transcript variant 1 | NM_020389        | TRPC7       | 6.18E−01 | −1.36                               |                                       |                                   |
| Transient receptor potential cation channel, subfamily M, member 1        | NM_002420        | TRPM1       | 2.29E−01 | 1.31                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily M, member 2, transcript variant 1 | NM_003307        | TRPM2       | 1.22E−01 | 1.97                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily M, member 2, transcript variant 1 | NM_003307        | TRPM2       | 5.04E−02 | 2.53                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily M, member 3, transcript variant 7 | NM_206948        | TRPM3       | 3.04E−09 | 10.69                               |                                       |                                   |
| Transient receptor potential cation channel, subfamily M, member 3 [Source: HGNC Symbol; Acc: 17992] | ENST00000354500  | TRPM3       | 2.34E−03 | 3.74                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily M, member 3, transcript variant 7 | NM_206948        | TRPM3       | 3.41E−06 | 6.23                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily M, member 3, transcript variant 9 | NM_001007471     | TRPM3       | 7.23E−01 | 1.13                                |                                       |                                   |
| Transient receptor potential cation channel, subfamily M, member 3, transcript variant 9 | NM_001007471     | TRPM3       | 1.54E−05 | 2.60                                |                                       |                                   |
Continued.

| Gene name                                                                 | Accession number | Gene symbol | $P$       | Fold change $\text{Ker} \rightarrow \text{hiPSC}$ | Fold change $\text{hiPSC} \rightarrow \text{Neuron}$ | Fold change $\text{hiPSC} \rightarrow \text{CM}$ |
|--------------------------------------------------------------------------|------------------|-------------|-----------|-----------------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Transient receptor potential cation channel, subfamily M, member 4, transcript variant 1 | NM_017636        | TRPM4       | $3.72 E-02$ | $-1.89$                                       |                                                 |                                               |
| Transient receptor potential cation channel, subfamily M, member 5       | NM_014555        | TRPM5       | $8.21 E-01$ | $-1.08$                                       |                                                 |                                               |
| Transient receptor potential cation channel, subfamily M, member 6, transcript variant a | NM_017662        | TRPM6       | $3.80 E-01$ | $1.64$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily M, member 6, transcript variant a | NM_017662        | TRPM6       | $9.10 E-01$ | $1.05$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily M, member 6, transcript variant a | NM_017662        | TRPM6       | $5.32 E-07$ | $5.59$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily M, member 7       | NM_017672        | TRPM7       | $2.16 E-02$ | $-1.25$                                       |                                                 |                                               |
| Transient receptor potential cation channel, subfamily M, member 7       | NM_017672        | TRPM7       | $3.64 E-03$ | $-1.38$                                       |                                                 |                                               |
| Transient receptor potential cation channel, subfamily M, member 8       | NM_024080        | TRPM8       | $2.04 E-01$ | $1.89$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily V, member 1, transcript variant 3 | NM_080706        | TRPV1       | $3.59 E-05$ | $1.92$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily V, member 1, transcript variant 3 | NM_080706        | TRPV1       | $4.14 E-05$ | $2.25$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily V, member 2       | NM_16113         | TRPV2       | $8.02 E-08$ | $4.68$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily V, member 3       | NM_145068        | TRPV3       | $4.64 E-01$ | $1.35$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily V, member 3       | NM_145068        | TRPV3       | $1.35 E-01$ | $-2.39$                                       |                                                 |                                               |
| Transient receptor potential cation channel, subfamily V, member 4, transcript variant 2 | NM_147204        | TRPV4       | $4.33 E-01$ | $1.39$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily V, member 5, (cDNA clone MGC: 34269 IMAGE: 5186668) | BC034740         | TRPV5       | $1.00 E-01$ | $1.38$                                        |                                                 |                                               |
| Transient receptor potential cation channel, subfamily V, member 5       | NM_019841        | TRPV5       | $3.14 E-01$ | $-1.40$                                       |                                                 |                                               |
| Transient receptor potential cation channel, subfamily V, member 6       | NM_018646        | TRPV6       | $1.57 E-01$ | $-1.38$                                       |                                                 |                                               |

(p) Voltage-gated sodium channels

| Gene name                                                                 | Accession number | Gene symbol | $P$       | Fold change $\text{Ker} \rightarrow \text{hiPSC}$ | Fold change $\text{hiPSC} \rightarrow \text{Neuron}$ | Fold change $\text{hiPSC} \rightarrow \text{CM}$ |
|--------------------------------------------------------------------------|------------------|-------------|-----------|-----------------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Sodium channel, voltage-gated, type I, alpha subunit, transcript variant 2 | NM_006920        | SCN1A       | $1.98 E-01$ | $1.54$                                        |                                                 |                                               |
| Sodium channel, voltage-gated, type I, beta, transcript variant b        | NM_199037        | SCN1B       | $9.95 E-01$ | $-1.00$                                       |                                                 |                                               |
| Sodium channel, voltage-gated, type II, alpha subunit, transcript variant 1 | NM_021007        | SCN2A       | $4.16 E-01$ | $1.62$                                        |                                                 | $5.00$                                        |
| Sodium channel, voltage-gated, type II, beta                            | NM_004588        | SCN2B       | $3.61 E-01$ | $-1.58$                                       |                                                 |                                               |
| Sodium channel, voltage-gated, type II, beta                            | NM_004588        | SCN2B       | $8.16 E-04$ | $-2.41$                                       |                                                 |                                               |
### (p) Continued.

| Gene name                                                      | Accession number | Gene symbol | \( P \)  | Fold change \( \text{Ker} \rightarrow \text{hiPSC} \) | Fold change \( \text{hiPSC} \rightarrow \text{Neuron} \) | Fold change \( \text{hiPSC} \rightarrow \text{CM} \) |
|---------------------------------------------------------------|------------------|-------------|---------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| Sodium channel, voltage-gated, type III, alpha subunit, transcript variant 1 | NM_006922        | SCN3A       | \( 2.87E \rightarrow 01 \) | 2.00                                                | 2.85                                                |                                                     |
| Sodium channel, voltage-gated, type III, alpha subunit, transcript variant 1 | NM_006922        | SCN3A       | \( 1.89E \rightarrow 01 \) | 1.49                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type III, beta, transcript variant 1 | NM_018400        | SCN3B       | \( 8.74E \rightarrow 01 \) | 1.06                                                | 4.70                                                |                                                     |
| Sodium channel, voltage-gated, type III, beta, transcript variant 1 | NM_018400        | SCN3B       | \( 1.57E \rightarrow 01 \) | 1.46                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type III, beta, transcript variant 1 | NM_018400        | SCN3B       | \( 1.56E \rightarrow 01 \) | 1.96                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type IV, alpha subunit         | NM_000334        | SCN4A       | \( 1.62E \rightarrow 08 \) | 9.91                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type IV, beta, transcript variant 1 | NM_174934        | SCN4B       | \( 3.25E \rightarrow 04 \) | 3.66                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type V, alpha subunit, transcript variant 1 | NM_198056        | SCN5A       | \( 2.43E \rightarrow 08 \) | 14.10                                               |                                                     |                                                     |
| Sodium channel, voltage-gated, type V, alpha subunit, transcript variant 2 | NM_000335        | SCN5A       | \( 4.93E \rightarrow 02 \) | 1.95                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type VII, alpha                | NM_002976        | SCN7A       | \( 4.49E \rightarrow 03 \) | 1.63                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type VII, alpha                | NM_002976        | SCN7A       | \( 2.07E \rightarrow 01 \) | 1.72                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type VIII, alpha subunit, transcript variant 1 | NM_014191        | SCN8A       | \( 1.89E \rightarrow 09 \) | 15.61                                               |                                                     |                                                     |
| Sodium channel, voltage-gated, type VIII, alpha subunit, transcript variant 1 | NM_014191        | SCN8A       | \( 4.06E \rightarrow 07 \) | 11.23                                               |                                                     |                                                     |
| Sodium channel, voltage-gated, type IX, alpha subunit         | NM_002977        | SCN9A       | \( 4.08E \rightarrow 08 \) | 11.51                                               |                                                     |                                                     |
| Sodium channel, voltage-gated, type IX, alpha subunit         | NM_002977        | SCN9A       | \( 1.62E \rightarrow 01 \) | 1.66                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type IX, alpha subunit         | NM_002977        | SCN9A       | \( 3.38E \rightarrow 03 \) | 2.57                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type X, alpha subunit          | NM_006514        | SCN10A      | \( 4.06E \rightarrow 01 \) | 1.35                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type XI, alpha subunit         | NM_014139        | SCN11A      | \( 3.02E \rightarrow 01 \) | 1.57                                                |                                                     |                                                     |
| Sodium channel, voltage-gated, type XI, alpha subunit         | ENST00000444237  | SCN11A      | \( 8.83E \rightarrow 03 \) | 1.94                                                |                                                     |                                                     |

(q) Nonvoltage-gated sodium channels

| Gene name                                                      | Accession number | Gene symbol | \( P \)  | Fold change \( \text{Ker} \rightarrow \text{hiPSC} \) | Fold change \( \text{hiPSC} \rightarrow \text{Neuron} \) | Fold change \( \text{hiPSC} \rightarrow \text{CM} \) |
|---------------------------------------------------------------|------------------|-------------|---------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| Sodium channel, nonvoltage-gated 1 alpha, transcript variant 1 | NM_001038        | SCNN1A      | \( 1.33E \rightarrow 09 \) | 51.49                                               | -21.13                                              | -10.71                                              |
| Sodium channel, nonvoltage-gated 1, beta                      | NM_000336        | SCNN1B      | \( 2.11E \rightarrow 01 \) | 1.64                                                |                                                     |                                                     |
| Sodium channel, nonvoltage-gated 1, beta                      | NM_000336        | SCNN1B      | \( 5.52E \rightarrow 01 \) | 1.09                                                |                                                     |                                                     |
| Sodium channel, nonvoltage-gated 1, delta, transcript variant 1 | NM_00130413      | SCNN1D      | \( 8.43E \rightarrow 02 \) | 1.49                                                |                                                     |                                                     |
| Sodium channel, nonvoltage-gated 1, gamma                     | NM_001039        | SCNN1G      | \( 2.33E \rightarrow 01 \) | 1.59                                                |                                                     |                                                     |
| Gamma subunit of epithelial amiloride-sensitive sodium channel | X87160           | SCNN1G      | \( 3.99E \rightarrow 01 \) | 1.27                                                |                                                     |                                                     |
During reprogramming 14 (33%) of them are significantly upregulated while only 1 (2%) is significantly downregulated. From iPSCs to neurons, as expected, neuronal alpha-subunits CACNAID, CACNAIE are upregulated together with several neuronal channel subunits (α, δ, β, and γ). In cardiomyocytes, solely the alpha subunit of the cardiac CACNAIC is upregulated. Of note, none of the differentiated progeny downregulated any voltage-gated calcium channels.

3.3. Sperm-Associated Cation Channels. Sperm-associated cation channels or CatSper channels are calcium ion channels. They are flagellar proteins involved in sperm motility and therefore affect fertility [27]. During reprogramming to iPSCs, from seven used probes just one showed a significant downregulation and none had a significant upregulation. We observed nothing noteworthy in the differentiated progeny.

3.4. Nicotinic Acetylcholine Receptors. Nicotinic acetylcholine receptors play a role in interneuronal synapses and neuromuscular junctions. They are composed of five subunits as homomeric or heteromeric receptors. They are located at the postsynaptic site and upon binding of acetylcholine they allow the transmission of cations, especially sodium and potassium ions, in some versions also calcium ions. This leads to a depolarization of the membrane and triggers further signaling pathways [28]. Several acetylcholine receptors and subunits are thought to play roles in a variety of pathomechanisms, for example, psychiatric disorders, cardiovascular diseases, or cancer [29–31]. From 21 probes, 5 (24%) showed a significant upregulation while 3 (14%) showed a significant downregulation from keratinocytes to iPSCs. In neurons, solely the neuronal nicotinic acetylcholine receptor CHRNA6 alpha subunit was upregulated, none in cardiomyocytes.

3.5. Cyclic Nucleotide-Gated Channels. Cyclic nucleotide-gated channels form tetrameric channels which—upon binding of cGMP—allow a flow of cations. For that, these channels track the intracellular concentration of cNMPs to produce a voltage response [32]. Their major role is the depolarization of rod photoreceptors, but they are also found in other tissues like olfactory sensory neurons [33], testis, kidney, or heart [34] and play a role in cellular development such as neuronal growth cone guidance [35]. Defects in these genes are reported to cause retinitis pigmentosa [36]. From 7 used probes one showed a significant upregulation and one showed a significant downregulation (both 14%) during reprogramming, while none was differentially regulated in differentiated neurons or cardiomyocytes.

3.6. GABA Receptors. GABA (γ-aminobutyric acid) receptors are ligand-gated chloride channels. Since GABA is the main inhibitory neurotransmitter in the central nervous system GABA receptors play an important role for the brain function. The receptors are composed of five subunits which form heteromers. The GABA receptors are a drug target for anesthetics and other psychoactive drugs. We have analyzed 29 probes within GABA receptor subunits. From keratinocytes to iPSCs, 6 (21%) of them are significantly upregulated while just one (3%) is significantly downregulated. Interestingly, none was up- or downregulated in differentiated neurons, while GABRB3 was downregulated and GABRP was upregulated in cardiomyocytes. Up to now, more or less nothing is known about GABA receptors or their subunits in cardiac cells.

3.7. Glycine Receptors. Glycine receptors are inhibitory receptors of the postsynaptic site. They are activated by glycine and mediate an influx of chloride ions. Accordingly, GlyRs regulate not only the excitability of motor and sensory neurons but are also essential for the processing of photoreceptor signals, neuronal development, and inflammatory pain sensitization [37]. The heteromeric pore is formed by five subunits. Concerning their role in pathomechanisms, it was reported that mutations are causing hyperekplexia (also known as startle disease) [38]. We have analyzed 7 probes and none of them was significantly altered in hiPSCs.
Transcript levels for the alpha2 subunit and the beta subunit were highly upregulated in differentiated neurons, pointing to their functional role in the nervous system.

3.8. Ionotropic Glutamate Receptors. Glutamate is the predominant excitatory neurotransmitter in the central nervous system. Therefore, ionotropic glutamate receptors play a key role for learning and memory processes. They are located in the postsynaptic membrane and are composed of several heteromeric subunits. Ionotropic glutamate receptors are further divided into AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate), NMDA (N-Methyl-D-aspartate) or kainate receptors depending on their sensitivity for the agonists. From 36 probes, 5 (14%) showed a significantly increased expression and 2 (6%) showed a decreased expression in iPSCs compared to keratinocytes. As expected, several subunits were upregulated in neurons (none downregulated). None was upregulated in cardiomyocytes, while the kainate subtype GRIK5 was downregulated.

3.9. Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels. Hyperpolarization-activated cyclic nucleotide-gated channels are homodimers or heterodimers and form a hyperpolarization-activated potassium channel. CNG channels display a very complex heteromeric structure with various subunits and domains that play a critical role in their function [39]. They contribute to pacemaker currents in the heart [40] but are also found in neurons [41]. We have analyzed 5 probes and 3 (60%) of them showed a significant upregulation while none was downregulated after reprogramming. In neurons the HCN3 channel transcript was upregulated, which plays a role in several neuronal functions including excitability of basal ganglia output neurons [42]. Although HCN4 for example plays a critical role in the conduction system of the heart, we did not observe a specific regulation in cardiomyocytes.

3.10. Serotonin Receptors. Serotonin (or 5-hydroxytryptamine) receptors are ligand-gated receptors mainly found presynaptically in neurons. The type 3 receptor is the only ion channel while the other serotonin receptors are G-protein-coupled receptors. It forms a heteropentameric pore which upon activation by serotonin allows the flow of sodium and potassium, leading to a depolarization. Serotonin receptors modulate neuronal function and are therefore involved in various brain functions. The analysis of 6 probes for type 3 serotonin receptors showed a significant upregulation of 2 (33%, both for HTR3A) probes while none was downregulated in hiPSCs. Although we expected serotonin receptors to be upregulated during neuronal differentiation, no subunit was upregulated in neurons or cardiomyocytes, while only the receptor transcript for HTR3A was downregulated in neurons.

3.11. Voltage-Gated Potassium Channels. Voltage-gated potassium channels are composed of a large group of subunits with different characteristics concerning for example their inactivation speed. Functional channels are formed by heterotetramers. The channels are highly specific for potassium with a low affinity for sodium or other cations. Voltage-gated potassium channels are responsible for the repolarization of excitable cells following the sodium-mediated excitation of an action potential and are therefore found in neurons and other cells displaying action potentials. We have analyzed 81 probes. From keratinocytes to hiPSCs, 25 (31%) were significantly upregulated while only 3 (4%) were significantly downregulated. In neurons, several subunits were upregulated including KCNBI, coding for Kv2.1 and KCND2, both are better known for their role in cardiac cell excitability as well as KCNFI, KCNH8, and KCNIP1, all known for their contribution in neuronal excitability [43]. It should be noted that KCNT1 is actually sodium activated but is included in the alphabetical list for a better overview. Further, several “S” subunits were upregulated (KCNS2 in neurons) or downregulated (KCNS3 in neurons; KCNS1 and 3 in cardiomyocytes). These subunits are unable to form functional channels as homotetramers but instead heterotetramerize with other alpha-subunits to form conductive channels. These subunits are involved in modifying the channels response and conductivity [44]. Few is known about distinct roles in other tissues, but they were associated with for example, pain modulation [45] or airway responsiveness [46].

3.12. Inwardly Rectifying Potassium Channels. Inwardly rectifying potassium channels have a higher tendency to allow the flow of potassium ions into the cell rather than to the outside of the cell. Therefore, they play an important role in the maintenance of the resting membrane potential. Their activation is constitutive or controlled by ATP binding and G-proteins [47]. Functional channels are formed as homo- or heterotetramers. These channels can be found predominantly in neurons, cardiac myocytes, the pancreas, or the kidneys. From 20 analyzed probes in hiPSCs compared to keratinocytes, 8 (40%) showed a significant upregulation and 3 (15%) were significantly downregulated. The GIRK2 channel encoded by KCNJ6 is upregulated in neurons playing multiple roles in various tissues including the pancreas and brain [48, 49] and is associated with epileptic seizures in mice lacking the gene [50]. On the other hand, Kir6.1, encoded by KCNJ8, is upregulated in cardiomyocytes and has been reported to be involved in the pathogenesis of cardiac arrest in the early repolarization syndrome [51].

3.13. Two-P Potassium Channels. Two-P potassium channels contain two pore-forming P domains. After dimerization they form an outward rectifying potassium channel. They can be found in several tissues and are activated by various chemical or physical means (TRAALK channels). We have analyzed 23 probes. 4 (17%) of them were significantly upregulated while 4 (17%) were significantly downregulated. In neurons KCNK3, vital for setting the resting membrane potential and primary target for volatile anesthetics [52] as well as KCNK4, which is mechanically gated and contributes to axonal pathfinding, growth cone motility, and neurite elongation, as well as possibly having a role in touch or
pain detection [53, 54], were upregulated. KCNK5 and 6 were downregulated. In cardiomyocytes, downregulation of KCNK5 and 12 was observed.

### 3.14. Calcium-Activated Potassium Channels
Calcium-activated potassium channels are mostly activated by intracellular calcium; some family members are also voltage gated. The family consists of large, intermediate, and small conductance family members. Channels are formed by two units (KCNM family) or most commonly four units (KCNN family). They are involved in, for example, afterhyperpolarization following the action potential and are predominantly found in neurons. Additionally, they are known to play different roles in cellular mechanisms, including stem cell biology [4–6, 55]. We have analyzed 18 probes of which 9 (50%) were significantly upregulated and none was significantly downregulated after reprogramming. In neurons, solely KCNN2 was downregulated, while in cardiomyocytes KCNN1A, encoding the large conductance BK-channel, involved in heart rate regulation [56], was upregulated.

### 3.15. P2X Receptors
P2X receptors are receptors for extracellular ATP and upon activation open a channel for ions, predominantly calcium. The channel is formed by homo- or heterotrimers. They are found in several tissues, mainly in the nervous system and muscle tissue. They are involved in a range of physiological processes such as modulation of synaptic transmission, vascular tone, cardiac rhythm, and contractility and immune response [57–61]. In stem cells an influence of P2X receptors on embryonic stem cell proliferation was reported [62]. From the 9 analyzed probes 1 (11%) was significantly upregulated and none downregulated. None of these receptors/channels was regulated in differentiated progeny.

### 3.16. Transient Receptor Potential Channels
Transient receptor potential channels (TRP channels) are nonselective cation channels. They show different preferences for cations, as well as different activation mechanisms and functions. TRP channels are broadly expressed throughout the organism and mediate multiple functions. These include amongst others sensor activity for a wide range of hypertrophic stimuli and mutations in TRPM4 are now recognized as causes of human cardiac conduction disorders (reviewed in [63]). Furthermore, TRP channels are related to the onset or progression of several diseases, and defects in the genes encoding TRP channels (so-called “TRP channelopathies”) underlie certain neurodegenerative disorders due to their abnormal Ca$^{2+}$ signaling properties (reviewed in [64]). Additionally, TRP channels influence stem cell differentiation and survival [65, 66] and are involved in neuronal-stem-cell-derived development [67]. We have analyzed 40 probes. After reprogramming, 11 (28%) of them were significantly upregulated and none was significantly downregulated. In neurons, none of these channels was noteworthy regulated while solely TRPC3 was upregulated in cardiomyocytes, reported to be involved in conduction disturbances induced by adenosine receptor A1AR by enhanced Ca$^{2+}$ entry through the TRPC3 channel [68].

### 3.17. Voltage-Gated Sodium Channels
Voltage-gated sodium channels consist of a main alpha unit and some optional modulating or regulatory subunits. They are highly selective for sodium and are involved in a variety of cellular functions including action potential formation [69]. From 24 probes we have analyzed, 6 (25%) were significantly upregulated and two (8%) were significantly downregulated from keratinocytes to iPS cells. These channels seem to be expressed in different kinds of stem cells and during development [70–72]. It was further reported that, for example, SCN5A, highly upregulated in iPS cells, is involved in cancer stem cell invasion [73]. SCN2A, SCN3A, and SCN3B were upregulated in neurons, described to be involved in neuronal excitation and epilepsy pathogenesis [74]. Although voltage-gated sodium channels play multiple roles also in the cardiac system [70, 75, 76], we observed no changes of this channel family in cardiomyocytes.

### 3.18. Nonvoltage-Gated Sodium Channels
Epithelial nonvoltage-gated sodium channels are amiloride sensitive. They form heterotrimers and are involved in ion and fluid transport across epithelia in several organs. We have analyzed 6 probes and one (17%) of them was significantly upregulated while none was significantly downregulated. Interestingly, the upregulated SCNN1A in iPS cells was subsequently downregulated both in neurons and cardiomyocytes, pointing to a possible function in stem cells. Of note, it was shown already that repression of pluripotency by retinoic acid represses the SCNN1A gene together with several other pluripotency factors [77].

### 3.19. Two-Pore Channels
Two-pore channels are cation-selective ion channels activated by the second messenger nicotinic acid adenine dinucleotide phosphate (NAADP). Upon activation calcium is released from intracellular stores [78]. We have analyzed 5 probes and while none of them was significantly upregulated two (40%) were significantly downregulated from keratinocytes to iPS cells. None of these channels was regulated in neurons or cardiomyocytes.

### 3.20. Zinc-Activated Ligand-Gated Ion Channels
The zinc-activated ligand-gated ion channel is activated upon binding of zinc. Until now just one family member is known that is expressed in several tissues [79]. Its exact function is not known. The expression was not significantly altered as shown by one probe in all cells.

### 4. Discussion
Although ion channels are mainly known for their role in electrically excitable cells they can be found in almost all tissues and are additionally involved in various processes such as cell differentiation and maturation [3, 4, 6, 12, 24, 47, 70]. These large groups of channel proteins are still underestimated concerning their role during embryonic
development and cell fate determination. One of the most interesting in vitro models for the elucidation of both developmental processes and disease-specific cellular impairments is represented by pluripotent stem cells. Therefore we were interested in the set of ion channels expressed in hiPSCs after reprogramming and compared this set with iPSC-derived differentiated progeny, namely, neurons and cardiomyocytes. As little is known about ion channels in hiPSCs we aimed to start the analysis with gene expression microarray data. For a comparison, we chose the cells from which they were produced—namely, keratinocytes—as the reference cell type. The comparison of 6 keratinocyte samples with 9 hiPSC samples should minimize the often observed variances between hiPSC lines. We found out that almost a third (32%) of the ion channel probes we investigated showed a significant change in gene expression. Of note, this was mostly an upregulation. Additionally, while many ion channel genes were not expressed in keratinocytes they were present in hiPSCs. This indicates that several of the analyzed channel groups might play unknown roles in stem cell biology, for example, homeostasis, proliferation, or differentiation. Interestingly, after differentiation into neurons or cardiomyocytes, relatively small groups were subsequently regulated. This includes ion channel transcripts playing important roles in the respective tissues. Nevertheless, we compared already published sets of data from different experimental setups and additionally limited the analysis to a strong fold regulation. This might lead to high dropout rates of regulated genes during measurement. Still, various channel transcripts were “logically” up- or downregulated during differentiation into neurons or cardiomyocytes, following embryonic development. iPSC cells and especially patient-specific iPSC cells from persons suffering from genetic mutations leading to hereditary syndromes are a very valuable tool to investigate pathogenetic mechanisms and disease associated molecular and cellular changes [80–82]. As various channel subtypes are involved in multiple pathogenetic mechanisms it would be further interesting to analyze channel transcript regulation in patient specific iPSC cells and their differentiated progeny to elucidate possible disease-specific pathways.

Concerning the presented study it is clear that gene regulations on transcript level do not explicitly mimic either protein levels and posttranslational modifications or protein activity. This set of data is sought to describe a global overview on transcript regulation of ion channels during distinct steps of development. It should be noted that in cases where several probes bind within one gene they do not indicate the same upregulation. Sometimes they show the same trend but miss significance, but for some cases there are considerable differences. This could hint for some yet unknown splicing variants. More detailed studies of these hypothesized splice variants could give insights into their function and broaden the still scarce knowledge.

This work is intended to be a guide and start point for future work focusing on single channels and their composition, localization, and function in hiPSCs and their differentiated progeny. These studies could lead to better in vitro differentiation protocols but also explain some of the many disease pathomechanisms related to mutations in ion channel genes.

Conflict of Interests

There is no conflict of interests to declare.

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