Supplemental Material

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Abbreviations: ATC, anatomical therapeutic chemical system; CI, confidence interval; cLQTS, congenital long QT syndrome; ICD-10, international classification of diseases system, 10th revision; ISCED, international standard classification of education; IQR, interquartile range; VT, ventricular tachycardia
**Supplemental Table 1**

**Title: Baseline characteristics, patients with cLQTS attached to the workforce (cases) and patients with cLQTS not attached to the workforce (not included)**

|                                | cLQTS patients attached to the workforce (n=298) | cLQTS patients not attached to the workforce (n=44) | p-value |
|--------------------------------|-------------------------------------------------|-------------------------------------------------|---------|
| Sex (female)                   | 192 (64.4)                                      | 29 (65.9)                                       | 0.98    |
| Age at diagnosis, years (median (IQR)) | 38.6 [28.0, 47.9]                                | 45.2 [39.8, 53.6]                                | 0.0001  |

**Social factors**

|                                |                                                |                                                |         |
|--------------------------------|-------------------------------------------------|-------------------------------------------------|---------|
| Education level                |                                                |                                                | 0.07    |
| - Basic school <10 years (ISCED 0-2) | 62 (22.3)                                       | 16 (36.4)                                       |         |
| - High school or vocational education (ISCED 3) | 130 (46.8)                                      | 20 (45.5)                                       |         |
| - Higher education (ISCED 5-8) | 86 (30.9)                                       | 8 (18.2)                                        |         |
| Living alone                   | 103 (35.0)                                      | 17 (38.6)                                       | 0.77    |
| Income                         |                                                |                                                | 0.002   |
| - 1. quartile (lowest)         | 75 (25.2)                                       | 5 (11.4)                                        |         |
| - 2. quartile                  | 74 (24.8)                                       | 23 (52.3)                                       |         |
| - 3. quartile                  | 74 (24.8)                                       | 8 (18.2)                                        |         |
| - 4. quartile (highest)        | 75 (25.2)                                       | 8 (18.2)                                        |         |

**Disease factors**

|                                |                                                |                                                | 0.25    |
|--------------------------------|-------------------------------------------------|-------------------------------------------------|---------|
| Disease manifestation          |                                                |                                                |         |
| - Aborted cardiac arrest       | 26 (8.7)                                       | 6 (13.6)                                        |         |
| - VT or syncope                | 59 (19.8)                                       | 12 (27.3)                                       |         |
| - Unspecified                  | 130 (43.6)                                      | 19 (43.2)                                       |         |
| - Asymptomatic                 | 83 (27.9)                                       | 7 (15.9)                                        |         |

**Comorbidities prior to date of diagnosis**

|                                |                                                |                                                |         |
|--------------------------------|-------------------------------------------------|-------------------------------------------------|---------|
| Diabetes                       | 12 (4.0)                                        | ≤3                                               | 1.00    |
| Hypertension                   | 31 (10.4)                                       | 14 (31.8)                                       | 0.0002  |
| Ischemic heart disease or prior myocardial infarction | 12 (4.0)                                       | 7 (15.9)                                        | 0.004   |
| Atrial fibrillation            | 7 (2.3)                                         | ≤3                                               | 0.24    |
| Epilepsy                       | 4 (1.3)                                         | ≤3                                               | 1.00    |
| Any psychiatric diagnosis      | 23 (7.7)                                        | 13 (29.5)                                       | < 0.0001|

**Concomitant pharmacotherapy, <90 days prior to date of diagnosis**

|                                |                                                |                                                |         |
|--------------------------------|-------------------------------------------------|-------------------------------------------------|---------|
| Beta-blockers                  | 89 (29.9)                                       | 20 (45.5)                                       | 0.06    |
| Calcium antagonists            | 7 (2.3)                                         | 6 (13.6)                                        | 0.001   |
| ACE inhibitors                 | 12 (4.0)                                        | 6 (13.6)                                        | 0.02    |
| Thiazides                      | 6 (2.0)                                         | ≤3                                               | 0.61    |
| Lipid lowering drugs           | 11 (3.7)                                        | 7 (15.9)                                        | 0.003   |
| Antiepileptica                 | 6 (2.0)                                         | 5 (11.4)                                        | 0.005   |
| Antidepressants                | 14 (4.7)                                        | 9 (20.5)                                        | 0.0004  |
| Anxiolytics                    | 10 (3.4)                                        | 9 (20.5)                                        | < 0.0001|
Supplemental Table 2

Title: Baseline characteristics, patients with cLQTS stratified by disease manifestation

|                                | Aborted cardiac arrest (n=27) | VT or syncope (n=58) | Unspecified (n=130) | Asymptomatic (n=83) | p-value |
|--------------------------------|-------------------------------|----------------------|---------------------|---------------------|---------|
| Sex (female)                   | 18 (66.7)                     | 45 (77.6)            | 82 (63.1)           | 47 (56.6)           | 0.08    |
| Age at diagnosis, years (median (IQR)) | 39.6 [26.6, 50.1]            | 39.1 [25.3, 49.8]    | 36.6 [28.8, 47.9]   | 38.5 [27.9, 45.9]   | 0.89    |

Social factors

Education level at diagnosis
- Basic school <10 years (ISCED 0-2) | 6 (26.1) | 13 (23.6) | 31 (25.6) | 12 (15.2) | 0.60 |
- High school or vocational education (ISCED 3) | 12 (52.2) | 26 (47.3) | 51 (42.1) | 41 (51.9) |
- Higher education (ISCED 5-8) | 5 (21.7) | 16 (29.1) | 39 (32.2) | 26 (32.9) |

Living alone | 13 (48.1) | 24 (42.1) | 47 (37.0) | 19 (22.9) | 0.03 |

Employment status at baseline
- Employed | 22 (81.5) | 43 (74.1) | 102 (78.5) | 63 (75.9) |
- Study, maternity leave, vacation | 9 (15.5) | 18 (31.0) | 14 (16.9) |
- Unemployed | 6 (10.3) | 10 (17.2) | 6 (7.2) |

Income
- 1. quartile (lowest) | 10 (37.0) | 17 (29.3) | 29 (22.3) | 19 (22.9) |
- 2. quartile | 6 (22.2) | 15 (25.9) | 35 (26.9) | 18 (21.7) |
- 3. quartile | 15 (25.9) | 31 (23.8) | 25 (30.1) |
- 4. quartile (highest) | 8 (29.6) | 11 (19.0) | 35 (26.9) | 21 (25.3) |

Comorbidities prior to date of diagnosis

|                               | ≤3 | ≤3 | ≤3 | ≤3 |
|-------------------------------|----|----|----|----|
| Diabetes                      | 6 (4.6) | 3 | 29 (22.3) | 19 (22.9) | 0.83 |
| Hypertension                  | 9 (15.5) | 15 (11.5) | 4 (4.8) | 0.20 |
| Ischemic heart disease or prior myocardial infarction | 8 (6.2) | 0 | 4 (4.8) | 0.12 |
| Atrial fibrillation           | 6 (4.6) | 3 | 29 (22.3) | 19 (22.9) | 0.83 |
| Epilepsy                      | 9 (15.5) | 15 (11.5) | 4 (4.8) | 0.20 |
| Any psychiatric diagnosis     | 8 (6.2) | 3 | 29 (22.3) | 19 (22.9) | 0.83 |

Concomitant pharmacotherapy, <90 days prior to date of diagnosis

|                               | ≤3 | ≤3 | ≤3 | ≤3 |
|-------------------------------|----|----|----|----|
| Beta blockers                 | 18 (31.0) | 47 (36.2) | 19 (22.9) | 0.11 |
| Calcium antagonists           | 0 | 4 (3.1) | ≤3 | 0.63 |
| ACE inhibitors                | 5 (8.6) | 4 (3.1) | ≤3 | 0.26 |
| Thiazides                     | 0 | 7 (5.4) | ≤3 | 0.56 |
| Lipid lowering drugs          | 8 (6.2) | 8 (6.2) | ≤3 | 0.64 |
| Antiepileptics                | 8 (6.2) | 8 (6.2) | ≤3 | 0.64 |
| Antidepressants               | 8 (6.2) | 8 (6.2) | ≤3 | 0.64 |
| Anxiolytics                   | 8 (6.2) | 8 (6.2) | ≤3 | 0.64 |
**Supplemental Table 3**

**Title:** *Findings in the patients with cLQTS with additional clinical information available*

|                       | Patients with cLQTS (n=156) |
|-----------------------|-------------------------------|
| **Sex (female)**      | 105 (67.3)                    |
| **Age at diagnosis, years** | 38.3 [25.3, 46.9]           |
| **Proband**           | 65 (41.7)                     |
| **Relative**          | 91 (58.3)                     |
| **Genetics**          |                               |
| KCNQ1                 | 41 (26.3)                     |
| KCNH2                 | 75 (48.1)                     |
| SCN5A                 | 11 (7.1)                      |
| Genonegative          | 18 (11.5)                     |
| Not tested            | 8 (5.1)                       |
| **Disease manifestation** |                             |
| ACA                   | 20 (12.8)                     |
| VT/syncope            | 44 (28.2)                     |
| Unspecified           | 9 (5.8)                       |
| Asymptomatic          | 82 (53.2)                     |
### Supplemental Table 4

**Title: Baseline characteristics, patients with cLQTS attached to the workforce and patients with cLQTS not attached to the workforce or dead six months after diagnosis**

|                                | Attached to the workforce (n=271) | Not attached to the workforce or dead (n=27) | p-value |
|--------------------------------|-----------------------------------|---------------------------------------------|---------|
| **Sex (female)**               | 174 (65.2)                        | 18 (66.6)                                   | 0.97    |
| **Age at diagnosis, years (median [IQR])** | 38.2 [28.0, 47.8]              | 40.5 [28.8, 49.5]                           | 0.63    |
| **Social factors**             |                                   |                                             |         |
| **Education level**            |                                   |                                             |         |
| - Basic school <10 years (ISCED 0-2) | 56 (22.0)                        | 6 (25.0)                                    | 0.87    |
| - High school or vocational education (ISCED 3) | 120 (47.2)                      | 10 (41.7)                                   |         |
| - Higher education (ISCED 5-8)  | 78 (30.7)                         | 8 (33.3)                                    |         |
| **Living alone**               | 94 (35.2)                         | 9 (33.3)                                    | 1       |
| **Employment status 30 days prior to date of diagnosis** |                                   |                                             |         |
| - Employed                     | 208 (76.8)                        | 22 (81.5)                                   |         |
| - Study, maternity leave, vacation | 42 (15.5)                        | ≤3                                           | 0.14    |
| - Unemployed                   | 21 (7.7)                          | 4 (14.8)                                    |         |
| **Income**                     |                                   |                                             |         |
| - 1. quartile (lowest)         | 66 (24.4)                         | 9 (33.3)                                    |         |
| - 2. quartile                  | 67 (24.7)                         | 7 (25.9)                                    |         |
| - 3. quartile                  | 69 (25.5)                         | 5 (18.5)                                    |         |
| - 4. quartile (highest)        | 69 (25.5)                         | 6 (22.2)                                    | 0.71    |
| **Disease factors**            |                                   |                                             |         |
| **Disease manifestation**      |                                   |                                             |         |
| - Aborted cardiac arrest       | 17 (6.3)                          | 10 (37.0)                                   |         |
| - VT or syncope                | 49 (18.1)                         | 9 (33.3)                                    |         |
| - Unspecified                  | 125 (46.1)                        | 5 (18.5)                                    |         |
| - Asymptomatic                 | 80 (29.5)                         | ≤3                                           | <0.0001 |
| **Comorbidities prior to date of diagnosis** |                                   |                                             |         |
| Diabetes                       | 9 (3.3)                           | ≤3                                           | 0.15    |
| Hypertension                   | 28 (10.3)                         | ≤3                                           | 1       |
| Ischemic heart disease or prior myocardial infarction | 10 (3.7)                        | ≤3                                           | 0.67    |
| Atrial fibrillation            | 6 (2.2)                           | ≤3                                           | 1       |
| Epilepsy                       | ≤3                                | ≤3                                           | 0.81    |
| Any psychiatric diagnosis      | 21 (7.7)                          | ≤3                                           | 1       |
| **Concomitant pharmacotherapy, <90 days prior to date of diagnosis** |                                   |                                             |         |
| Beta blockers                  | 80 (29.5)                         | 9 (33.3)                                    | 0.85    |
| Calcium antagonists            | 7 (2.6)                           | 0                                            | 0.86    |
| ACE inhibitors                 | 10 (3.7)                          | ≤3                                           | 0.67    |
| Tiazides                       | 5 (1.8)                           | ≤3                                           | 1       |
|                     | Count (Percentage) | ICD-10 Code | Frequency |
|---------------------|--------------------|-------------|-----------|
| Lipid lowering agents | 11 (4.1)           | 0           | 0.60      |
| Antiepileptics      | 4 (1.5)            | ≤3          | 0.17      |
| Anxiolytics         | 8 (3.0)            | ≤3          | 0.51      |
| Antidepressants     | 13 (4.8)           | ≤3          | 1         |
### Supplemental Table 5

**Title: Baseline characteristics, patients with cLQTS attached to the workforce and patients with cLQTS not attached to the workforce or dead one year after diagnosis**

|                                | Attached to the workforce (n=278) | Not attached to the workforce or dead (n=20) | p-value |
|--------------------------------|-----------------------------------|------------------------------------------|---------|
| **Sex (female)**               | 182 (65.5)                        | 10 (50.0)                                | 0.25    |
| **Age at diagnosis, years (median [IQR])** | 37.5 [27.9, 47.8]              | 44.5 [33.2, 50.4]                        | 0.13    |
| **Social factors**             |                                   |                                          |         |
| - Education level at diagnosis |                                   |                                          |         |
| - Basic school <10 years (ISCED 0-2) | 59 (22.5)                     | ≤3                                       |         |
| - High school or vocational education (ISCED 3) | 123 (46.9)                   | 7 (43.8)                                |         |
| - Higher education (ISCED 5-8)  | 80 (30.5)                        | 6 (37.5)                                | 0.83    |
| - Living alone                 | 95 (34.7)                        | 8 (40.0)                                | 0.81    |
| **Employment status 30 days prior to date of diagnosis** |                                   |                                          |         |
| - Employed                     | 213 (76.6)                      | 17 (85.0)                               |         |
| - Study, maternity leave, vacation | 43 (15.5)                  | 0                                       |         |
| - Unemployed                    | 22 (7.9)                        | ≤3                                      | 0.11    |
| **Income**                     |                                   |                                          |         |
| - 1. quartile (lowest)         | 70 (25.2)                       | 5 (25.0)                                |         |
| - 2. quartile                   | 66 (23.7)                       | 8 (40.0)                                |         |
| - 3. quartile                   | 71 (25.5)                       | ≤3                                      |         |
| - 4. quartile (highest)        | 71 (25.5)                       | 4 (20.0)                                | 0.38    |
| **Disease factors**            |                                   |                                          |         |
| - Disease manifestation        |                                   |                                          |         |
| - Aborted cardiac arrest       | 22 (7.9)                        | 5 (25.0)                                |         |
| - VT or syncope                | 51 (18.3)                       | 7 (35.0)                                |         |
| - Unspecified                  | 123 (44.2)                      | 7 (35.0)                                |         |
| - Asymptomatic                 | 82 (29.5)                       | ≤3                                      | 0.005   |
| **Comorbidities prior to date of diagnosis** |                                   |                                          |         |
| - Diabetes                     | 10 (3.6)                        | ≤3                                      | 0.41    |
| - Hypertension                 | 28 (10.1)                       | ≤3                                      | 0.75    |
| - Ischemic heart disease or prior myocardial infarction | 11 (4.0)                     | ≤3                                      | 1       |
| - Atrial fibrillation          | 6 (2.2)                         | ≤3                                      | 0.96    |
| - Epilepsy                     | 4 (1.4)                         | 0                                       | 1       |
| - Any psychiatric diagnosis    | 21 (7.6)                        | ≤3                                      | 1       |
| **Concomitant pharmacotherapy, <90 days prior to date of diagnosis** |                                   |                                          |         |
| - Beta blockers                | 81 (29.1)                       | 8 (40.0)                                | 0.44    |
| - Calcium antagonists          | 7 (2.5)                         | 0                                       | 1       |
| Drug Class          | Count (Average) | ≤3  | ≤3  | ≤3  |
|--------------------|-----------------|-----|-----|-----|
| ACE inhibitors     | 10 (3.6)        | ≤3  |      | 0.41|
| Tiazides           | 5 (1.8)         | ≤3  |      | 0.87|
| Lipid lowering agents | 11 (4.0)       | 0   |      | 0.77|
| Antiepileptics     | 5 (1.8)         | ≤3  |      | 0.87|
| Anxiolytics        | 8 (2.9)         | ≤3  |      | 0.29|
| Antidepressants    | 12 (4.3)        | ≤3  |      | 0.54|
**Supplemental Figure 1**

**Title: cLQTS disease manifestation according to genotype**

![Graph showing disease manifestation by genotype](image1)

**Supplemental Figure 2**

**Title: Workforce attachment according to genotype**

![Graph showing attachment to the workforce](image2)
Supplemental Figure 3

Title: Genotype distribution according to workforce attachment

[Diagram showing genotype distribution stratified by workforce attachment one year after established diagnosis.]

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**Supplemental Figure 4**

**Title:** Odds ratio of detachment from the workforce among patients with cLQTS, six months after diagnosis

Legend: Forest plot showing odds ratio of detachment from the workforce for different risk factors within the group of cLQTS patients six months after diagnosis with cLQTS.

| Risk factors                        | Odds Ratio [95% CI]        |
|-------------------------------------|--------------------------|
| Age at diagnosis                    | Reference                |
| Age 18-30                           | 1.70 (0.32 - 9.00)       |
| Age 30-45                           | 1.16 (0.19 - 7.07)       |
| Sex                                 | Reference                |
| Female                              | 1.69 (0.55 - 5.16)       |
| Disease manifestation               | Reference                |
| Asymptomatic                        | Reference                |
| Unspecified                         | 0.74 (0.15 - 3.61)       |
| VT or syncope                       | 5.01 (1.16 - 21.66)      |
| Aborted cardiac arrest              | 23.79 (4.74 - 119.45)    |
| Comorbidities at diagnosis          | Reference                |
| Hypertension                        | 0.68 (0.14 - 3.22)       |
| Diabetes                            | 6.61 (1.05 - 41.48)      |
| Any psychiatric diagnosis           | 1.02 (0.19 - 5.55)       |
| Employment status at diagnosis      | Reference                |
| Employed                            | Reference                |
| Study/maternity leave, vacation, etc.| 0.28 (0.03 - 2.55)  |
| Unemployed                          | 2.31 (0.44 - 12.16)      |
| Education level at diagnosis        | Reference                |
| Basic school                        | 0.75 (0.20 - 2.89)       |
| High school or Vocational education | 1.38 (0.29 - 6.55)       |
| Indexregulated income               | Reference                |
| 1. quartile                         | 0.55 (0.17 - 1.75)       |
| 2. quartile                         | 1.38 (0.26 - 7.42)       |
| 3. quartile                         | 0.90 (0.13 - 6.12)       |
| 4. quartile                         | 0.67 (0.09 - 5.11)       |
| Living alone                         | Reference                |
**Supplemental Figure 5**

**Title:** Workforce attachment after cLQTS diagnosis according to disease manifestation and age-, sex-, and employment status-matched controls

Legend: Bar chart showing proportion of patients with cLQTS (stratified by disease manifestation) and matched control population attached to the workforce (A) three years and (B) five years after time of diagnosis (index date for control population); ACA, aborted cardiac arrest; VT, ventricular tachycardia
**Supplemental Appendix**

**Codes for treatment and diagnosis definition**

| Diagnoses/comorbidities                          | ICD codes         |
|-------------------------------------------------|-------------------|
| Aborted cardiac arrest                          | I469, I460, I490, I490B |
| Anoxic brain damage                             | G931              |
| Any psychiatric disease                         | F                 |
| Atrial fibrillation                             | I48               |
| Epilepsy                                        | G40, G41          |
| Ischemic heart disease or prior myocardial infarction | I20-25           |
| Syncope                                         | R559              |
| Ventricular tachycardia                         | I470, I472, I472A, I472B, I472D |

| Therapy                                         | ATC codes         |
|-------------------------------------------------|-------------------|
| ACE-inhibitors                                  | C09A              |
| Antiarrhythmic drugs                            | C01B              |
| Antidepressants                                 | N06A              |
| Anxiolytics                                     | N05B, N05C        |
| β blockers                                      | C07               |
| Calcium channel blockers                        | C08               |
| Lipid lowering drugs                            | C10               |
| Loop diuretics                                  | C03C              |
| Thiazides                                       | C03A              |

**Comorbidities based (partly) on ATC codes**

| ATC or ICD codes                               |
|------------------------------------------------|
| Diabetes¹                                      |
| Diagnosis code within 5 years of diagnosis of ICD10: E10-E14 and/or |
| A dispensed prescription within 180 days of diagnosis of the following: |
| ATC: A10                                      |

| Hypertension²                                  |
| 2 or more dispensed prescriptions of the following within 180 days of diagnosis (ATC): |
| α adrenergic blockers: C02A, C02B, C02C |
| Non-loop diuretics: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C09BA, C09DA, C09XA52 |
| Vasodilators: C02DB, C02DD, C02DG |
| β blockers: C07 |
| Calcium channel blockers: C07F, C08, C09BB, C09DB |
| Renin–angiotensin system inhibitors: C09 |
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