Familial aggregation of congenital hydrocephalus in a nationwide cohort

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The objective of the study was to investigate familial aggregation of primary congenital hydrocephalus in an unselected, nationwide population. Based on the Danish Central Person Register, we identified all children born in Denmark between 1978 and 2008 and their family members (up to third-degree relatives). Information on primary congenital hydrocephalus was obtained from the National Patient Discharge Register. Using binomial log-linear regression, we estimated recurrence risk ratios of congenital hydrocephalus. An alternative log-linear regression model was applied to quantify the genetic effect and the maternal effect. Of 1,928,683 live-born children, 2,194 had a diagnosis of idiopathic congenital hydrocephalus (1.1/1000). Of those, 75 (3.4%) had at least one other family member with primary congenital hydrocephalus. Significantly increased recurrence risk ratios of primary congenital hydrocephalus were observed for same-sex twins, first- and second-degree relatives as follows: 34.8 (95% confidence interval: 16.4–74.0), 6.2 (95% confidence interval 4.3–8.9) and 2.2 (95% confidence interval 1.6–3.1), respectively. Recurrence risk ratio for third-degree relatives was 1.5 (95% confidence interval 0.8–2.7). A maternal component was supported by the facts that recurrence risk ratios for opposite-sex twins (37.3, 95% confidence interval 11.9–116.7) were significantly higher than other first-degree relatives and that recurrence risk ratios for maternal half-siblings (8.4, 95% confidence interval 3.7–18.7) were significantly higher than for paternal half-siblings (3.0, 95% confidence interval 0.8–12.2). This population-based study found strong evidence of familial aggregation of primary congenital hydrocephalus, which supports the existence of a genetic component to the aetiology. In addition, the pattern of association suggests that a strong maternal component contributes to the familial aggregation.

Keywords: congenital; hydrocephalus; brain development; genetic risk; complex disease

Introduction

Congenital hydrocephalus is characterized by a pathological accumulation of CSF in the ventricular system causing pressure on the surrounding developing brain. If left untreated, the condition leads to various degrees of cognitive impairment, cerebral palsy and visual deficits. In severe cases the condition is fatal. In developed countries, most patients undergo surgical treatment, but the
long-term prognosis is highly variable (Christensen et al., 2003; Persson et al., 2006; Lindquist et al., 2010).

Very few environmental factors have consistently been associated with congenital hydrocephalus. Genetic factors may be involved in congenital hydrocephalus, although studies on this topic are also limited as reviewed elsewhere (Zhang et al., 2006). One human hydrocephalus gene has been identified so far and is located on the X-chromosome (Kanemura et al., 2006; Zhang et al., 2006). The affected gene (L1CAM) encodes L1 protein, which is a neuronal cell adhesion molecule essential for nervous system development and function. The phenotype characteristics include congenital hydrocephalus due to aqueductal stenosis, adducted thumbs, agenesis or hypoplasia of corpus callosum and corticospinal tracts, mental retardation and spastic paraplegia.

According to Zhang et al. (2006), it is estimated that X-linked hydrocephalus may account for 5–15% of congenital hydrocephalus cases. This estimate is based on case reports and few observational studies among small populations comprising only congenital hydrocephalus cases with aqueductal stenosis and case reports (Jansen, 1975; Halliday et al., 1986; Kuzniecky et al., 1986; Haverkamp et al., 1999). Hence, the proportion of X-linked hydrocephalus among all types of primary congenital hydrocephalus cases is rather uncertain. The same review estimated an empirical recurrence risk rate for congenital hydrocephalus excluding cases of X-linked aetiology ranging from below 1 to 4%. This estimate is based on three publications from 1979 (Bay et al., 1979; Burton, 1979a, b) and one prospective study from 1988 of 261 pregnancies in couples who had had one previous child with hydrocephalus. In the latter study a sibling recurrence risk of 4% was found (Varadi et al., 1988).

Based on information obtained by interview, 12.1% of 596 cases with congenital hydrocephalus treated at the Mississippi Medical Centre between 1998 and 2007 reported having an affected family member (Van Landingham et al., 2009). The fact that the diagnoses of affected family members rely on proxy interviews challenges the reliability of the diagnoses and more importantly may be influenced by differential misclassification (e.g. interviewed cases remember better the cases in their family than non-cases). The study does not report the specific underlying aetiologies of hydrocephalus among the affected family members. Since acquired hydrocephalus generally is far more common than idiopathic congenital hydrocephalus, the diagnoses of most of the relatives may in fact be incomparable to the diagnoses of the index patients.

Based on the existing literature, a genetic component to the aetiology is assumed in addition to the known gene defect causing X-linked congenital hydrocephalus. To further explore this subject, we determined to carry out the first nationwide, population-based familial aggregation study on congenital hydrocephalus including twins, first-, second- and third-degree relatives. This was done by means of a cohort encompassing the entire Danish population and access to the unique nationwide Danish registers. Furthermore, model-based estimates of the genetic and environmental components of the risk for congenital hydrocephalus were made.

**Materials and methods**

**Study cohort**

Familial aggregation of congenital hydrocephalus in Denmark was analysed in a cohort consisting of all individuals born in Denmark from 1 January 1978 to 31 December 2008. Since 1968 all residents living in Denmark have been assigned a personal identification number in the Civil Registration System (Pedersen et al., 2006). Information on gender, parents, date and place of birth and continuously updated information on date of death and emigration are registered. The individuals included in the cohort were identified by the personal identification number, which further allowed linkage to the various Danish population-based health registers. This enabled us to identify cases and their relatives.

**Identification of relatives**

Relatives were identified from the Danish Family Relations Database established at Statens Serum Institut, Copenhagen (Oyen et al., 2009a). The database is based on the parent–child links registered by their personal identification numbers in the Civil Registration System. The Danish Family Relations Database can identify parents, siblings and half-siblings residing in Denmark for nearly all persons born in Denmark since 1950. Using the parental links of parents, it is also possible to identify grandparents and thereby cousins and half-cousins. Ninety-four per cent of the children born after 1990 have a known grandparent, whereas 64% of the children born between 1977 and 1989 have a known grandparent (Oyen et al., 2009a; b; Schnack et al., 2010). Twins were identified as individuals having the same mother and being born on the same day (±1 day on either side of midnight).

First-degree relatives of a proband (an older affected relative) were defined as younger opposite-sex twins, offspring and younger siblings; second-degree relatives were defined as younger half-siblings, grand-children, younger nieces/nephews and aunts/uncles; and third-degree relatives were defined as younger first cousins. For twin pairs, one was randomly chosen as the (younger) relative.

**Identification of cases with congenital hydrocephalus**

Information on congenital hydrocephalus was obtained by linkage to the Danish National Patient Register, a mandatorily reportable nationwide register of all hospital discharge diagnoses of inpatients since 1977 (Andersen et al., 1999). From 1995 all outpatients were registered as well.

The aim was to obtain cases diagnosed within the first year of life without a known causative aetiology. Thus, we included all individuals with one of the following codes according to the International Classification of Disease, eighth revision (ICD-8) up to 1993 and 10th revision (ICD-10) from 1994 to 2009: ICD-8 74200, 74201, 74208, 74209, 34793-5 and ICD-10 Q03x, G910-G912, G918-G919. Cases with Arnold–Chiari or Dandy–Walker syndrome were included in this definition. Congenital hydrocephalus associated with spina bifida was not included because spina bifida is perceived as a disease secondary to folic acid depletion. The inclusion diagnoses are specified in Supplementary Table 1.

In order to identify primary cases, individuals with known causative aetiology were excluded. Hence, cases having one or more of the...
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following diagnoses prior to or at the time of the first given diagnosis of hydrocephalus were excluded: ICD-8 0130x, 02701, 03609, 045x, 05x, 09490, 320x, 322x, 324x (CNS infection); 191x, 19219, 194x, 225x, 226x, 227x, 23839 (intracranial tumour); 430x, 431x (intracranial haemorrhage, non-traumatic); 803x, 851x, 852x, 853x, 854x (intracranial traumatic lesion) and 77201, 77208-9 (birth-related traumatic intracranial lesions). ICD-10 codes were G0x (CNS infection); C7x (intracranial tumour); I60x, I61x, I62x (intracranial haemorrhage, non-traumatic); S06x (intracranial traumatic lesion); P10x, P11x (birth-related traumatic intracranial lesions) and P918A (cerebral atrophy). The same definitions were used for affected relatives but without the criteria of diagnosis within the first year of life, thus allowing the inclusion of relatives diagnosed before 1978.

As part of the study, we performed stratified analysis of isolated versus syndromic congenital hydrocephalus cases. In case of more than one inclusion diagnosis, the priority of diagnoses was as follows: (i) Arnold–Chiari syndrome; (ii) Dandy–Walker syndrome; (iii) congenital hydrocephalus with malformations inside and/or outside the CNS; and (iv) isolated congenital hydrocephalus (e.g. communicating and obstructive).

Cases of syndromic congenital hydrocephalus were defined as one or more of (i), (ii) and (iii) above. The following diagnostic codes for congenital malformations inside and outside the CNS were used: ICD-8 740, 741x, 743x-75x, ICD-10 Q00-02, Q04-07 and Q10-Q99.

Statistical analyses

Familial aggregation of congenital hydrocephalus was expressed as the recurrence risk ratio, which is the ratio between the risk of congenital hydrocephalus for individuals with a proband (an older affected relative) and the risk for individuals with known relatives of the same type, where none of them are probands. Thus, for instance, the recurrence risk ratio for siblings was calculated as the risk for the group of individuals having older affected siblings compared with the risk for the group of individuals with older known and only unaffected siblings. Since a proband could only be an older affected relative, a given pair could only contribute once. The recurrence risk ratio for each type of relative was estimated in a log-linear binomial regression analysis using the SAS procedure GENMOD (SAS version 9.2).

An alternative log-linear binomial regression model for the recurrence risk was fitted to estimate the effect of having a mother in common with an affected relative and the effect of having an affected monozygotic twin (using the SAS procedure NLMIXED, SAS version 9.2). The joint model for the log-recurrence risk included variables representing: the effect of having an affected first-degree relative, second-degree relative and third-degree relative; the effect of having a mother in common with an affected relative (i.e. having an affected sibling, maternal half-sibling or twin) and the effect of having an affected twin. The variables were categorized as ‘yes’, ‘no’ or ‘no such relative’.

A parameter representing the risk for congenital hydrocephalus in monozygotic twins due to genetics was estimated from the assumption that half of the same-sex twin pairs were monozygotic, which is a reasonable approximation (Skytthe et al., 2002). Following this approximation, the risk of congenital hydrocephalus in children having an affected same-sex twin was estimated as 0.5 times the total risk when having an affected dizygotic twin (i.e. having an affected first-degree relative and sharing a mother with an affected relative) plus 0.5 times the risk when having an affected monozygotic twin (i.e. having an affected monozygotic twin and sharing a mother with an affected relative). This parameterization made it possible to identify the effect of having an affected monozygotic twin. A parameter representing ‘not having a monozygotic twin’ was included using the same reasoning.

The overall recurrence risk for each type of relative was thought to consist of a genetic and a maternal effect. The effect of sharing a mother with an affected relative was termed ‘maternal effect’ and was assumed to cover the potential risks related to the mother and therefore present in all her pregnancies. Such risk factors could be maternal health status, repeated behavioural patterns related to environmental exposures (smoking, alcohol, etc.) and anatomical characteristics influencing potential birth-related risk factors. In the statistical model, the maternal effect was allowed to be different for twins than for siblings to cover risk factors unique for a specific pregnancy, such as medicine exposures, pre-eclampsia and X-ray radiation, etc. The remaining differences are most likely to represent genetic effects although shared environmental exposures in the various types of relatives in families during pregnancy cannot be excluded to account for a part of this effect. The genetic effect was allowed to vary according to the degree of relatedness (i.e. monozygotic twin, first-, second- or third-degree relative). We used simple extensions of the same model to evaluate whether the genetic effects of first- and second-degree members varied by type of relative (test with 5 degrees of freedom) and to evaluate whether the genetic effects differed for maternal and paternal relatives (test with 3 degrees of freedom).

In analyses with several subtypes of congenital hydrocephalus as the outcome, the recurrence risk ratios were estimated by polychotomous regression using the SAS procedure NLMIXED (SAS version 9.2). All confidence intervals (CIs) were Wald test based. All tests of homogeneity were likelihood ratio based. All analyses were adjusted for birth year (1978–82, 1983–87, 1988–92, 1993–97, 1998–2002 and 2003–08).

Ethical approval

Permission to use data from the national registries was obtained from the Danish Data Protection Agency. According to the Danish law, purely register-based studies are exempted from ethical approval.

Results

Of the 1928666 cohort members of live-born children in Denmark from 1978 to 2008, 2194 cases fulfilled the criteria for congenital hydrocephalus (1.1/1000). Of those, 65% were males. Among the cases with congenital hydrocephalus, 75 (3.4%) had at least one family member with a diagnosis of idiopathic hydrocephalus. The distribution of affected pairs was as follows: seven same-sex twin pairs, three opposite-sex twin pairs, 15 sibling pairs, 13 parent–child pairs, eight pairs of half-siblings, 13 pairs of grandparent–grandchildren, 13 aunt/uncle–niece/nephew pairs and 11 first cousin pairs.

Table 1 shows recurrence risk ratios for congenital hydrocephalus according to the type of affected relative. We observed significantly increased recurrence risk ratio for congenital hydrocephalus in same-sex twins (34.8, 95% CI: 16.4–74.0), first-degree relatives (6.2, 95% CI: 4.3–8.9) and second-degree relatives (2.2, 95% CI: 1.6–3.1) but not for third-degree relatives (1.5, 95% CI: 0.8–2.7). For same-sex twins, the observed recurrence risk ratio was not significantly different from the recurrence risk ratio for opposite-sex twins: 34.8 (95% CI: 13.5–131.6) versus
Table 1. Recurrence risk ratios for congenital hydrocephalus, according to the type of (older) affected relative in Denmark 1978–2008

<table>
<thead>
<tr>
<th>Type of affected relative</th>
<th>Total no. of affected relatives</th>
<th>No. of affected pairs</th>
<th>Recurrence risk ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same-sex twin</td>
<td>75</td>
<td>7</td>
<td>34.8</td>
<td>16.4–74.0</td>
</tr>
<tr>
<td>First-degree relative</td>
<td>4157</td>
<td>29</td>
<td>6.2</td>
<td>4.3–8.9</td>
</tr>
<tr>
<td>Opposite-sex twin</td>
<td>32</td>
<td>3</td>
<td>37.3</td>
<td>11.9–116.7</td>
</tr>
<tr>
<td>Sibling</td>
<td>2013</td>
<td>15</td>
<td>7.5</td>
<td>4.5–12.6</td>
</tr>
<tr>
<td>Parent</td>
<td>2112</td>
<td>13</td>
<td>5.4</td>
<td>3.1–9.3</td>
</tr>
<tr>
<td>Second-degree relative</td>
<td>14,176</td>
<td>34</td>
<td>2.2</td>
<td>1.6–3.1</td>
</tr>
<tr>
<td>Half siblings, all</td>
<td>1089</td>
<td>8</td>
<td>5.7</td>
<td>2.9–11.5</td>
</tr>
<tr>
<td>Maternal half-brother</td>
<td>532</td>
<td>6</td>
<td>8.4</td>
<td>3.7–18.7</td>
</tr>
<tr>
<td>Paternal half-brother</td>
<td>552</td>
<td>2</td>
<td>3.0</td>
<td>0.8–12.2</td>
</tr>
<tr>
<td>Grandparent</td>
<td>7514</td>
<td>13</td>
<td>1.6</td>
<td>0.9–2.7</td>
</tr>
<tr>
<td>Uncle/aunt</td>
<td>5573</td>
<td>13</td>
<td>2.2</td>
<td>1.3–3.8</td>
</tr>
<tr>
<td>Third-degree</td>
<td>7183</td>
<td>11</td>
<td>1.5</td>
<td>0.8–2.7</td>
</tr>
</tbody>
</table>

Note: Recurrence risk ratios were adjusted for birth year. The reference group in the specific analyses was individuals with no such type of older affected relative who had at least one registered family member of the type.

37.3 (95% CI: 11.9–116.7), respectively. However, the recurrence risk ratio for opposite-sex twins was based on three pairs only.

Regarding second-degree relatives, the overall recurrence risk ratio for individuals with older affected half-brothers was 5.7 (95% CI: 2.9–11.5). When dividing half-brothers into maternal and paternal half-brothers, the recurrence risk ratios were 8.4 (95% CI: 3.7–18.7) and 3.0 (95% CI: 0.8–12.2), respectively. For individuals with affected grandparents and uncles/aunts, the recurrence risk ratios were 1.6 (95% CI: 0.9–2.7) and 2.2 (95% CI: 1.3–3.8), respectively.

A maternal component was supported by the facts that recurrence risk ratio for opposite-sex twins was significantly higher than other first-degree relatives, recurrence risk ratio for maternal half-brothers was significantly higher than for paternal half-brothers and that recurrence risk ratio for siblings was higher than for offspring. Based on the observed recurrence risk ratios presented in Table 1, we estimated model-based relative risks for both the genetic and maternal effects thought to contribute to the familial aggregation of congenital hydrocephalus, which are shown in Table 2. Being born to the same mother as an affected relative increased the genetic effect on the risk 2.4-fold (95% CI: 1.2–4.8). Having an affected twin, the effect was 11.3-fold (95% CI: 3.2–40). Taking the maternal effect into account, the estimated genetic effects were only modest, i.e. having an affected first-degree relative increased the genetic risk 3.3-fold (95% CI: 1.8–6.0). The model-based recurrence risk ratios were equal to the product of the estimates for genetic and maternal effects. Thus, as shown in Table 2, the model allowed us to estimate the recurrence risk ratio in a person having an affected monozygotic twin with congenital hydrocephalus (recurrence risk ratio 28.6, 95% CI: 4.3–190). However, the estimates for the effects in twins carry high uncertainty.

Taking the maternal effect into account, the observed differences in the recurrence risk ratios among affected, same degree relatives (for instance paternal half-brothers versus grandparents) were not significant (P = 0.13). Furthermore, there was no overall difference in the recurrence risk ratios for having a maternal or a paternal same degree relative (for instance cousins on the maternal side versus cousins on the paternal side) (P = 0.21).

In order to investigate the influence of X-linked hydrocephalus, the analyses were divided according to gender. As shown in Table 3, the recurrence risk ratios were not higher for male than female relatives.

It was further investigated whether familial aggregation of congenital hydrocephalus was higher in the subgroup of syndromic congenital hydrocephalus, which contains the X-linked hydrocephalus. The results shown in Table 4 demonstrated equally high and significantly increased recurrence risk ratios in same-sex twins, first- and second-degree relatives for both isolated and syndromic congenital hydrocephalus. In total, 1194 (54%) cases were isolated congenital hydrocephalus and 1000 were syndromic cases.

Finally, the cohort was stratified according to calendar time of diagnosis (before and after 1995) in order to investigate whether the change from the ICD-8 to the ICD-10 coding system in 1994 and the overall increasing access to CT scans from the mid-1990s influenced the results. The stratification did not influence the recurrence risk ratios (data not shown).

The previously described model was applied to describe the contribution of genetic and maternal effects on the recurrence risk ratios for male versus female relatives, as well as for isolated versus syndromic cases. Overall, the results showed the same pattern of the two effects for the subgroups, however, with very wide CIs due to the more limited number of affected pairs in each type of relatives (data not shown).

Discussion

We conducted a nationwide cohort study investigating familial aggregation of congenital hydrocephalus in up to third-degree relatives. The observed recurrence risk ratios were significantly increased for same-sex twins, first- and second-degree relatives,
whereas the recurrence risk ratio for third-degree relatives was not significant. The increasing aggregation with closer genetic relationship supports the involvement of a genetic component in the aetiology of congenital hydrocephalus. In addition, a maternal component was supported by the fact that recurrence risk ratio for opposite-sex twins was significantly higher than other first-degree relatives, recurrence risk ratio for maternal half-siblings was significantly higher than for paternal half-siblings and that recurrence risk ratio for siblings was higher than for offspring. The results were summarized in an alternative model that included significant genetic and maternal effects, where the maternal effects reflected an increased recurrence risk when having the same mother as an affected relative, an effect that was even higher when the relative was a twin.

Previous investigations on familial aggregation of congenital hydrocephalus are very few. Burton (1979b) reported a recurrence risk of congenital hydrocephalus of 1.4% among younger siblings of 205 cases. More recently, Varadi et al. (1988) found a sibling recurrence risk of 4% in the younger siblings of 261 affected cases. A recurrence risk for siblings as the only type of relative is rather inconclusive regarding whether the observed increased recurrence risk may have been due to genetic factors or shared

### Table 2

<table>
<thead>
<tr>
<th>Type of affected relative</th>
<th>Model components</th>
<th>Model-based RRRs&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genetic effect&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Maternal effect&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>RR CI</td>
<td>RR CI</td>
</tr>
<tr>
<td>Monozygotic twin</td>
<td>2.5 (0.2–39.7)</td>
<td>11.3 (3.2–40)</td>
</tr>
<tr>
<td>First-degree relative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizygotic twin</td>
<td>3.3 (1.8–6.0)</td>
<td>11.3 (3.2–40)</td>
</tr>
<tr>
<td>Sibling</td>
<td>3.3</td>
<td>2.4 (1.2–4.8)</td>
</tr>
<tr>
<td>Parent</td>
<td>3.3</td>
<td>–</td>
</tr>
<tr>
<td>Second-degree relative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal half-sibling</td>
<td>2.0 (1.5–2.9)</td>
<td>2.4 (1.2–4.8)</td>
</tr>
<tr>
<td>Paternal half-sibling</td>
<td>2.0</td>
<td>–</td>
</tr>
<tr>
<td>Grandparent</td>
<td>2.0</td>
<td>–</td>
</tr>
<tr>
<td>Uncle/ aunt</td>
<td>2.0</td>
<td>–</td>
</tr>
<tr>
<td>Third-degree relative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cousin</td>
<td>1.4</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> Recurrence risk ratios were adjusted for birth year. The reference group in the specific analyses was individuals with no such type of older affected relative who had at least one registered family member of the type.

<sup>b</sup> The remaining effect after the model-based estimation of the maternal effect, which is assumed to equalize the genetic effect.

<sup>c</sup> The 95% CI.

<sup>d</sup> The maternal effect is further increased by 4.7-fold (95% CI: 1.4–15.6) for twins (e.g. the product of the shared risk factors related to the mother and the risk factors related to the intrauterine environment unique for a specific pregnancy).

<sup>e</sup> The combined effect is estimated as the product of the genetic and the maternal effect (e.g. for twins: $2.5 \times 11.3 = 28.3$).

### Table 3

<table>
<thead>
<tr>
<th>Type of affected relative</th>
<th>Female No. of affected pairs</th>
<th>Recurrence risk ratios&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
<th>Male No. of affected pairs</th>
<th>Recurrence risk ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same-sex twin</td>
<td>3</td>
<td>43.7 (14.0–136.3)</td>
<td>4</td>
<td>28.8 (10.5–78.6)</td>
</tr>
<tr>
<td>First-degree relative</td>
<td>12</td>
<td>7.2 (4.1–12.7)</td>
<td>17</td>
<td>5.7 (3.5–9.1)</td>
</tr>
<tr>
<td>Opposite-sex twin</td>
<td>1</td>
<td>38.6 (5.0–298.4)</td>
<td>2</td>
<td>43.0 (11.2–165)</td>
</tr>
<tr>
<td>Sibling</td>
<td>5</td>
<td>7.0 (2.9–16.8)</td>
<td>10</td>
<td>7.9 (4.2–14.7)</td>
</tr>
<tr>
<td>Parent</td>
<td>6</td>
<td>6.8 (3.1–15.2)</td>
<td>7</td>
<td>4.6 (2.2–9.7)</td>
</tr>
<tr>
<td>Second-degree relative</td>
<td>11</td>
<td>2.1 (1.1–3.8)</td>
<td>23</td>
<td>2.3 (1.5–3.4)</td>
</tr>
<tr>
<td>Half sibling</td>
<td>1</td>
<td>2.2 (0.3–15.5)</td>
<td>7</td>
<td>7.3 (3.5–15.3)</td>
</tr>
<tr>
<td>Grandparent</td>
<td>3</td>
<td>1.1 (0.3–3.3)</td>
<td>10</td>
<td>1.8 (1.0–3.4)</td>
</tr>
<tr>
<td>Aunt/uncle</td>
<td>7</td>
<td>3.4 (1.6–7.1)</td>
<td>6</td>
<td>1.5 (0.7–3.4)</td>
</tr>
<tr>
<td>Third-degree relative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cousin</td>
<td>5</td>
<td>1.9 (0.8–4.6)</td>
<td>6</td>
<td>1.2 (0.6–2.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Recurrence risk ratios were adjusted for birth period. The reference group in the specific analyses was individuals with no such type of older affected relative who had at least one registered family member of the type.
maternally related risk factors. Our findings were based on 2194 cases and we were able to compare the risk of congenital hydrocephalus for individuals with an affected relative to the risk for individuals with known, unaffected relatives of the same type. This method provides highly reliable estimates for several degrees of relatedness, which further provide valuable information on the pattern of heritability for congenital hydrocephalus.

The observed maternal effect most likely reflects the effect of shared pregnancy- and perinatal-related risk factors supposedly related to pre-existing morbidities of the mother, repeated lifestyle patterns during pregnancies and anatomical variants influencing potential perinatal risk factors. The even higher effect when having an affected twin most likely reflects additional exposure to risk factors related to the individual pregnancy, for instance the use of medicine with teratogen effects, intra-uterine infections, pre-eclampsia and X-ray exposure. Little is known regarding intra-uterine exposures and/or perinatal risk factors that might increase the risk for congenital hydrocephalus. Toxoplasmosis infection is associated with congenital hydrocephalus (Melamed et al., 2001; Joo et al., 2008) as are other infectious causes. However, some of these associations are only suggestive and a causal link remains to be established (Schinazi and Yao, 1995; Tsunoda et al., 1997; Zajicek et al., 2010). Another potential explanation could be complicated deliveries leading to undiagnosed intracranial haemorrhage and subsequent congenital hydrocephalus (Looney et al., 2007). To better understand the observed maternal effect on the risk of congenital hydrocephalus, there is a need for large-scale epidemiological studies of sufficient size to access potential pregnancy- and perinatal-related risk factors for the development of congenital hydrocephalus.

Our findings demonstrated a notable over-representation of males among affected cases (65%), which corresponds to findings in other studies (Christensen et al., 2003; Garne et al., 2010). Hypothetically, the observed increased risk in individuals sharing the same mother and the overweighting of male cases with congenital hydrocephalus could be more or less attributable to the known X-linked hydrocephalus. As any Xlinked recessive trait, it is characterized by transmission of the affected gene from an unaffected mother resulting mainly in affection of the male offspring. Thus, higher recurrence risk ratios for males than females of affected relatives would be expected but were not found (Table 3).

The distribution of 54% of isolated congenital hydrocephalus cases and 46% syndromic cases is in line with the literature (Stoll et al., 1992; Glinianaia and Rankin, 1999; Christensen et al., 2003; Garne et al., 2010). We noted with interest that familial aggregation was observed at a similar level among cases with isolated and syndromic congenital hydrocephalus (Table 4). These findings strongly suggest that other lines of inheritance contribute to the aetiology of congenital hydrocephalus than the known monogenetic diseases causing syndromic congenital hydrocephalus. The described X-linked hydrocephalus would be among the cases with syndromic congenital hydrocephalus. Examples of other inherited syndromes that might contribute to the familial aggregation observed in syndromic congenital hydrocephalus include Marden–Walker syndrome (autosomal recessive) and Walker–Warburg syndrome (autosomal recessive) (Verhagen et al., 2011).

Our study has several strengths. The Danish Civil Registration System allowed for nearly complete follow-up of our cohort, which minimized selection bias. Since discharge diagnoses in the health care system are mandatorily reportable in Denmark, and health care is free and easily accessible, the registration of congenital hydrocephalus is considered virtually complete in the National Patient Register (Andersen et al., 1999). This is particularly true for a serious condition observed in a child and often leading to surgery. The Danish Family Relations Database made it possible to identify pedigrees without having to contact cohort members and their families, which ensured the absence of differential misclassification of disease due to self-reported family histories (Oyen et al., 2009a). Recurrence risk ratios only compared cohort members with identifiable relatives of the same type to reduce bias from incomplete identification of relatives. Finally, our cohort size yielded the largest and most comprehensive study of familial congenital hydrocephalus, which we explored in detail.

A potential limitation of this study was incomplete registration of the specific subtypes of hydrocephalus. We were aware of this potential limitation and dealt with the problem by carefully defining rather conservative diagnostic criteria of relevance to this study. Furthermore, some of the included cases with congenital hydrocephalus may have been caused by non-clinically detected intra-uterine infections, perinatal intracranial haemorrhage due to preterm delivery or the asymptomatic traumatic intracranial haemorrhages known

### Table 4 Recurrence risk ratios for isolated and syndromic congenital hydrocephalus according to the type of (older) affected relative

<table>
<thead>
<tr>
<th>Type of affected relative</th>
<th>Isolated congenital hydrocephalus (n = 1194)</th>
<th>Syndromic congenital hydrocephalus (n = 1000)</th>
<th>P&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of affected pairs</td>
<td>Recurrence risk ratio (95% CI)</td>
<td>No. of affected pairs</td>
</tr>
<tr>
<td>Same-sex twins</td>
<td>3</td>
<td>27.4 (8.2–91.6)</td>
<td>4</td>
</tr>
<tr>
<td>First-degree relative</td>
<td>15</td>
<td>5.9 (3.6–9.9)</td>
<td>14</td>
</tr>
<tr>
<td>Second-degree relative</td>
<td>19</td>
<td>2.3 (1.4–3.6)</td>
<td>15</td>
</tr>
<tr>
<td>Third-degree relative</td>
<td>5</td>
<td>1.2 (0.5–3.0)</td>
<td>6</td>
</tr>
</tbody>
</table>

- **a** Congenital hydrocephalus cases where hydrocephalus is the only malformation.
- **b** Congenital hydrocephalus cases with other malformations inside and/or outside the CNS. Of the 1000 syndromic cases, 19 cases were diagnosed with Arnold–Chiari malformation and 20 cases with Dandy–Walker syndrome. None of these had older affected relatives.
- **c** P-value for homogeneity of the recurrence risk ratios for each type of relative.
- **d** Recurrence risk ratios were adjusted for birth period. The comparison group in the specific analyses was individuals with no such type of older affected relative who had at least one registered family member of the type.
to occur even after uncomplicated vaginal deliveries (Looney et al., 2007). However, in case we had been able to better avoid such potential misclassification it would only tend to increase the observed recurrence risk ratios and thus strengthen our results. As noted above, some of the relative risks have wide CIs, especially concerning the effects related to twins.

In conclusion, this large population-based cohort study found strong evidence for familial aggregation of congenital hydrocephalus. The pattern and strengths of association support the existence of a genetic component other than the already described X-linked condition in syndromic congenital hydrocephalus. Independent of the familial aggregation most likely attributable to a genetic influence, we found support for a significant maternal factor. Both the genetic and the maternal effects seem to play important roles in congenital hydrocephalus pathogenesis.

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**Supplementary material**

Supplementary material is available at Brain online.

**References**


