Original Contribution

Familial Aggregation of Cryptorchidism—A Nationwide Cohort Study

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Although cryptorchidism is the most common birth defect in boys affecting 4–9 percent of newborns and 1–2 percent of boys 1 year of age, the etiology remains largely unknown. The authors investigated the contribution of genetic and environmental factors to familial aggregation of cryptorchidism. Using Danish health registers, they identified 25,395 boys diagnosed with cryptorchidism in a cohort of 1,022,713 boys born in 1977–2005. Using binomial log-linear regression, they estimated recurrence risk ratios (RRRs) of cryptorchidism for male twin pairs and first-, second-, and third-degree relatives of a cryptorchidism case. The RRR in same-sex twins was 10.1 (95% confidence interval (CI): 7.78, 13.1). The RRR among first-degree relatives was significantly higher among brothers (RRR = 3.52, 95% CI: 3.26, 3.79) than for offspring of a cryptorchidism case (RRR = 2.31, 95% CI: 2.09, 2.54). The RRR was also found to be significantly higher in maternal (RRR = 2.12, 95% CI: 1.74, 2.60) than paternal (RRR = 1.28, 95% CI: 1.01, 1.61) half brothers. In conclusion, inherited factors were found to have a moderate influence on the risk of cryptorchidism. The data are compatible with the hypothesis that maternal factors operating in utero are important for the risk of cryptorchidism.

aggregation; cohort studies; cryptorchidism; Denmark; familial data; heredity; twins

Abbreviations: CI, confidence interval; RRR, recurrence risk ratio.

“Cryptorchidism” is defined as the failure of one or both testes to descend to a normal position in the scrotum (undescended testes). The condition is the most common congenital malformation in boys with a prevalence of 4–9 percent among newborns and 1–2 percent of boys 1 year of age (1). It is associated with a two- to eightfold increase in testicular cancer risk and left untreated may lead to low sperm counts and infertility (2–6). Despite years of study, answers to questions relating to causes of undescended testes remain elusive, and few consistent risk factors have been found (7–11).

Observations from families with a clustering of cryptorchidism and the feature of cryptorchidism in genetic syndromes favor a genetic background. However, recent reports on increases in the prevalence of cryptorchidism point toward environmental factors in the etiology of cryptorchidism (12). A hormonal imbalance caused by lifestyle or environmental estrogenic and/or antiandrogenic substances has been suggested as causative agent. The few previous studies of familial aggregation have been based on interview data or self-reported questionnaires, which are prone to bias, and while the familial nature of these anomalies is well recognized (11, 13, 14), familial aggregation has been defined primarily from studies of first-degree relatives.

The primary aim of this study, based on the entire population of Denmark, was to describe the familial aggregation of cryptorchidism within same-sex twins and among first-, second-, and third-degree relatives. Furthermore, we wanted to evaluate the mode of inheritance according to the paternal and maternal contribution to the development of cryptorchidism.
MATERIALS AND METHODS

Study population

Familial aggregation of cryptorchidism in Denmark was analyzed in a cohort consisting of all boys born from 1977 to 2005. The boys included in the cohort were identified by a unique personal identification number in the Civil Registration System (15). Information from various sources, including Danish population-based registers, can be linked via the personal identification number. Since April 2, 1968, the Civil Registration System has assigned a personal identification number to all residents who live in Denmark. Furthermore, date and place of birth, sex, and continuously updated information on date of death and emigration are registered in the Civil Registration System.

Identification of relatives

Relatives were identified from the Danish Family Relations Database. This database is based on the parental links as registered in the Civil Registration System. Using this system, one can identify parents by shared address for individuals living at home when the Civil Registration System was created in 1968. Individuals not living at the parent’s home in 1968 generally have no parental link. All individuals born in Denmark in 1968 or later have parental links reflecting the legal parents. Consequently, the identities of the father and thereby of half/full brothers and same-sex twins were known for all Danish-born boys in our cohort. For boys in our cohort who were born abroad, the identity of both parents was known for 55 percent. Using the parents’ parental link, one can identify grandparents and thereby cousins and uncles/nephews. However, because of the above-described construction of parental links, only boys born in 1990 or later in Denmark had an almost complete registration of grandparents, whereas, for boys born between 1977 and 1989, 60 percent had a known grandfather. For boys born abroad, the statistics were 12 percent for boys born in 1977–1989 and 51 percent for boys born in 1990 or later. It should be emphasized that, although the cohort was restricted to boys born from 1977 to 2005, there was no restriction on the birth cohorts of the relatives besides the one imposed by the way in which the parental links were constructed in the Civil Registration System.

Identification of cryptorchidism cases

Information on cryptorchidism status, other congenital malformations, chromosomal abnormalities, and surgeries in the cohort and among relatives was obtained from the Danish Hospital Discharge Register, which contains a nationwide registration of all hospital discharge diagnoses and performed operations from 1977 to 2005, as well as outpatient diagnoses since 1995 (16). Of 42,015 identified cases of cryptorchidism, 1,913 (4.6 percent) cases had other congenital malformations registered, and 20,398 (48.5 percent) had surgical confirmation. A total of 25,395 males born between 1977 and 2005 were identified with a diagnosis of cryptorchidism. Of these, 9,124 (36 percent) had surgical confirmation. Information on the 16,620 cases born prior to 1977 was used only to identify affected relatives. Data on cryptorchidism were not recorded before 1977; thus, only relatives with a registration from 1977 or later were treated as affected. However, for a large proportion of cryptorchidism cases, treatment and thus registration of cryptorchidism were performed in adolescence or later. As cryptorchidism is a congenital malformation, the date of diagnosis was set to the date of birth.

Statistical analysis

Familial aggregation of cryptorchidism in twins and first-, second-, and third-degree relatives was evaluated by recurrence risk ratios (RRRs) as the ratio between the recurrence risk of cryptorchidism for individuals with a proband (an older affected relative) and the risk for individuals with known (i.e., registered in the Danish Family Relations Database) relatives of the same type where none of them is a proband. Thus, for instance, the RRR in brothers was estimated as the risk for brothers with an affected older brother compared with the risk for brothers with known and only unaffected older brothers. Comparing only individuals with the same type of relatives reduces bias due to incomplete registration of family members in older birth cohorts in the Danish Family Relations Database and furthermore adjusts the RRRs for the effect of having a specific relative. For example, the RRR for twins is adjusted for an effect per se of being a twin on the risk of cryptorchidism. Defining only the older relatives as a proband ensures that an affected pair, where both pair members are included in the cohort, contributes only once. In male twin pairs, one of them was chosen (at random) to be the “older.” First-degree relatives of a proband were defined as offspring (sons) or younger brothers; second-degree relatives as grandchildren, younger half brothers, or nephews/uncles; and third-degree relatives as younger brothers; second-degree relatives as grandchildren, younger half brothers, or nephews/uncles; and third-degree relatives as younger first cousins. To study the maternal and paternal contributions to the inheritance of cryptorchidism separately, all probands were further subdivided into maternal and paternal grandfathers, uncles/nephews, half brothers, and first cousins.

The RRRs were estimated by binomial log-linear regression with adjustment for birth period (5-year categories). We evaluated whether a variable length of follow-up could have biased our results by 1) stratifying our cohort by birth period and looking for differences in the RRR for first-, second-, and third-degree relatives’ estimates over time and 2) using Poisson regression to account for attained age at the end of follow-up in addition to potential confounders.

The expected RRR based on genetic contributions alone in male-male twin pairs was approximated by a weighted average of contribution from dizygotic twins and monozygotic twins. The RRR due to genetic contributions alone for dizygotic twins was assumed to be equal to RRR_{father}. The RRR due to genetic contributions alone for monozygotic twins was assumed to be equal to RRR_{father} \times RRR_{father} following the strategy of Risch (17) and assuming many small genetic effects. As a crude approximation, the two weights were both set to 0.5 because of almost equal amounts of dizygotic and monozygotic twins among same-sex twins (18). In other words, the expected RRR based on
genetic contributions alone in male-male twin pairs was approximated by \( 0.5 \times \text{RRR}_{\text{father}} + 0.5 \times \text{RRR}_{\text{father}} \times \text{RRR}_{\text{father}} \).

**RESULTS**

Of the 1,022,713 males in the study cohort, 25,395 (2.48 percent) had a diagnosis of cryptorchidism. Among these males, we identified 2,716 relatives with a diagnosis of cryptorchidism distributed as follows: 58 same-sex twin pairs, 393 father-son pairs, 693 male sibling pairs, 50 grandfather-grandchild pairs, 167 half-brother pairs, 653 uncle(s)/nephew pairs, and 752 first-cousin pairs.

First-, second-, and third-degree relatives of a cryptorchidism case all had a significantly increased RRR of cryptorchidism. All RRRs presented in Table 1 were adjusted for birth period. We found a 52 percent (95 percent confidence interval (CI): 37, 76) higher RRR in brothers (RRR = 3.52, 95 percent CI: 3.26, 3.79) compared with offspring (RRR = 2.31, 95 percent CI: 2.09, 2.54). In second-degree relatives, the RRR was 1.65 (95 percent CI: 1.42, 1.92) in half brothers, 1.38 (95 percent CI: 1.28, 1.50) in uncle(s)/nephews, and 1.40 (95 percent CI: 1.06, 1.83) in grandchildren. Among third-degree relatives (first cousins), the RRR was 1.25 (95 percent CI: 1.16, 1.34). When comparing the recurrence risk ratio in maternal and paternal second-degree relatives, we observed a 66 percent (95 percent CI: 22, 125) higher RRR in maternal half brothers (RRR = 2.12, 95 percent CI: 1.74, 2.60) compared with paternal half brothers (RRR = 1.28, 95 percent CI: 1.01, 1.61) (Table 2). In maternal and paternal third-degree relatives, the RRRs were 1.23 (95 percent CI: 1.11, 1.37) and 1.26 (95 percent CI: 1.14, 1.40), respectively (Table 2).

The overall RRR of cryptorchidism among twin brothers was 10.1 (95 percent CI: 7.78, 13.1). Further division into monozygotic and dizygotic twins was not possible. However, on the basis of a simple model, we estimated the RRR in male-male twin pairs to be 2.6 times higher than what would be expected from genetic contributions alone.

We used different restrictions in four different subanalyses. 1) First, we restricted the cohort to children of parents born in Denmark and of grandparents not born abroad (approximately 75 percent of the cohort). 2) The cohort was restricted to cases of cryptorchidism with no other congenital malformations or chromosomal abnormalities. 3) Probands were restricted to those probands who had undergone surgery for cryptorchidism (according to the registers) in addition to the cryptorchidism diagnosis. 4) Cases were divided into cases who had surgery or a diagnosis of cryptorchidism at 6 months of age or later (40,494 cases) and cases who had a diagnosis of cryptorchidism only before 6 months of age (1,521 cases). The results of the subanalyses were similar to the estimates in Table 1, but an overall strengthening of the results in Table 1 was observed when the analysis was restricted to probands who had surgery for cryptorchidism and cases who had either surgery for cryptorchidism or a diagnosis at 6 months of age or later. The estimates for brothers, offspring, maternal half brothers, and paternal half brothers diagnosed at 6 months or later were 3.65 (95 percent CI: 3.37, 3.94), 2.32 (95 percent CI: 2.10, 2.57), 2.20 (95 percent CI: 1.78, 2.71), and 1.30 (95 percent CI: 1.02, 1.65), respectively, compared with 2.63 (95 percent CI: 1.82, 3.79), 2.15 (95 percent CI: 1.47, 3.15), 1.81 (95 percent CI: 0.80, 4.12), and 1.15 (95 percent CI: 0.42, 3.11) among the men who had a diagnosis before 6 months of age only. Furthermore, stratified analyses based on the parts of the cohort who were born before and after 1985, respectively, as well as results obtained by use of Poisson regression as opposed to log-linear binomial regression models, and adjustment of the family history variables in Table 1 for each other all gave RRRs similar to the presented RRRs (data not shown), suggesting that birth period, length of follow-up, and other family history did not affect our results.

**DISCUSSION**

In this nationwide cohort study, we investigated the familial aggregation of cryptorchidism within male twin pairs and first-, second-, and third-degree relatives. Our findings underline the impact of familial aggregation on the development of cryptorchidism. The inheritance appears to be transmitted through the maternal side to a higher extent than through the paternal side, and the RRR is higher for brothers than for offspring of a cryptorchidism case, which points toward a contribution of in utero exposures to familial aggregation.

So far, few reports have been published regarding the familial aggregation of cryptorchidism (11, 13, 14). In a small case-control study, Elert et al. (13) found that 23 percent of cryptorchidism cases had a family history of cryptorchidism. In our population-based approach, 10.2 percent

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**TABLE 1. Recurrence risk ratios* † for cryptorchidism in relatives of a proband with cryptorchidism, according to type of proband, Denmark, 1977–2005**

<table>
<thead>
<tr>
<th>Type of proband</th>
<th>No. of probands</th>
<th>No. of affected pairs</th>
<th>RRR ‡</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same-sex twin</td>
<td>241</td>
<td>58</td>
<td>10.1</td>
<td>7.78, 13.1</td>
</tr>
<tr>
<td>First degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother</td>
<td>8,666</td>
<td>693</td>
<td>3.52</td>
<td>3.26, 3.79</td>
</tr>
<tr>
<td>Father</td>
<td>8,296</td>
<td>393</td>
<td>2.31</td>
<td>2.09, 2.54</td>
</tr>
<tr>
<td>Second degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half brother</td>
<td>4,076</td>
<td>167</td>
<td>1.65</td>
<td>1.42, 1.92</td>
</tr>
<tr>
<td>Uncle</td>
<td>21,389</td>
<td>653</td>
<td>1.38</td>
<td>1.28, 1.50</td>
</tr>
<tr>
<td>Grandfather</td>
<td>1,593</td>
<td>50</td>
<td>1.40</td>
<td>1.06, 1.83</td>
</tr>
<tr>
<td>Third degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cousin</td>
<td>26,872</td>
<td>752</td>
<td>1.25</td>
<td>1.16, 1.34</td>
</tr>
</tbody>
</table>

* The comparison group in the specific analyses was individuals without this type of older proband but with at least one registered family member of the type.
† Adjusted for birth period.
‡ RRR, recurrence risk ratio.
TABLE 2. Recurrence risk ratios*;† for cryptorchidism in relatives of a maternal or a paternal proband, according to type of proband, Denmark, 1977–2005

<table>
<thead>
<tr>
<th>Type of proband</th>
<th>Maternal relatives</th>
<th>Paternal relatives</th>
<th>RRRmaternal/RRRpaternal</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of probands</td>
<td>No of affected pairs</td>
<td>RRRmaternal †</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Second degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half brother</td>
<td>1,885</td>
<td>96</td>
<td>2.12</td>
<td>1.74, 2.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.20</td>
<td>1.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncle/nephew</td>
<td>11,782</td>
<td>372</td>
<td>1.41</td>
<td>1.27, 1.56</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>1.32</td>
<td>1.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grandfather</td>
<td>849</td>
<td>30</td>
<td>1.59</td>
<td>1.12, 2.26</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>1.39</td>
<td>1.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third degree</td>
<td>First cousin</td>
<td>12,943</td>
<td>360</td>
<td>1.23</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.27</td>
<td>1.14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The comparison group in the specific analyses was individuals without this type of older proband but with at least one registered family member of the type.
† Adjusted for birth period.
‡ RRR, recurrence risk ratio.

of cryptorchidism cases had at least one older family member with cryptorchidism. The recurrence risk in brothers and fathers of a cryptorchidism case was estimated in two smaller case-control studies. Czeizel et al. (14) found that fathers and brothers of a cryptorchidism case had a 9.3- and an 8.3-fold increased risk of developing cryptorchidism, respectively. The former study, the one by Elert et al. (13), also estimated odds ratios for more distant relatives: 6.9 (95 percent CI: 2.7, 17.9), 4.6 (95 percent CI: 2.0, 10.6), 5.2 (95 percent CI: 1.8, 15.4), 3.0 (95 percent CI: 0.6, 15.1), and 2.4 (95 percent CI: 0.9, 6.8) for brothers, fathers, uncles, grandfathers, and cousins of a case, respectively, which are all higher than the estimates found in our study. In general, these studies report higher estimates of the recurrence risk than we have found in our material. This may in part be due to small numbers and the fact that these studies were performed as case-control studies based on questionnaires and interview data. Such a study design is especially prone to recall bias and differential misclassification. In addition, these studies also suffer from a varying degree of non-participation, which may lead to selection bias toward more severe cases or cases with a family history of cryptorchidism. However, we note with interest that the ratio between the risk in fathers and the risk in brothers in the studies mentioned above corresponds to our finding of a 52 percent increased risk in brothers compared with offspring.

It has been emphasized by some groups that cryptorchidism is part of a syndrome called the “testicular dysgenesis syndrome,” which may be increasingly common as the result of adverse environmental influences, for example, estrogenic or antiandrogenic chemicals (19). The unique size of our study enabled us to divide second- and third-degree relatives into paternal and maternal family members. This is especially of interest in half brothers, because only maternal half brothers have the same mother and therefore share common gestational factors related to the intrauterine milieu. Indeed, it has previously been found that intrauterine factors, for example, the gestational hormone level, are strongly correlated in successive pregnancies of the same women (20). As maternal and paternal half brothers share the same proportion of genes, it is possible to evaluate the impact of the intrauterine milieu by looking at the difference in risk between maternal and paternal half brothers. The 1.66 times higher RRR for maternal half brothers compared with paternal half brothers, as well as a similar difference in RRR observed between first-degree relatives, that is, a higher RRR for brothers (who have the same mother) than for offspring of a cryptorchidism case, can be interpreted as the part of the inheritance deriving from internal and/or external environmental factors during life in utero. This is in accordance with the hypothesis that cryptorchidism in part is caused by in utero exposures to internal or external environmental substances as stated under the testicular dysgenesis syndrome (19, 21). This is further underlined by our finding of a 2.6 times higher overall RRR in male-male twin pairs compared with the RRR expected if the inheritance of cryptorchidism was solely a result of genetic inheritance. We would indeed expect this factor to be higher for twin brothers who share the intrauterine milieu under the same pregnancy than for brothers/half brothers. Part of the observed difference between maternal and paternal half brothers could also be explained by selection due to impaired paternal fertility and thereby reduced recurrence risk in the paternal half brothers. Indeed, cryptorchidism has been associated with impaired fertility, but, in unilateral cases of cryptorchidism, the paternity rate is not decreased (22), and, although fertility is severely impaired in bilateral cases of cryptorchidism, the paternity rate in males who have attempted paternity is as high as 65 percent compared with 93 percent in the background population (23). As bilateral cases make up only 15–20 percent of all cryptorchidism cases, we consider selection of minor importance for the findings in our study.

Another explanation for the observed difference between maternal and paternal relatives, as well as the difference in the offspring and brother estimates, could be ascertainment bias. If mothers of cryptorchid boys are more aware of cryptorchidism than fathers and/or other mothers at subsequent
births, then this could result in differential misclassification. However, all citizens in Denmark have equal access to free health care, and testing for cryptorchidism is part of the perinatal examination, as well as the routine 5-week examination by the general practitioner; therefore, we consider this issue of minor importance to our results.

The introduction of the personal identification number in 1968 and the establishment of the Danish Hospital Discharge Register in 1977 combined have provided the opportunity to perform studies with good power (large cohorts), a minimum of bias (e.g., recall and selection bias), and good validity (24). The main strength of the present study is the fact that Denmark provides a unique setting for epidemiologic and genetic studies of various diseases, such as congenital malformation and others. However, a potential limitation is the collection of probands diagnosed prior to 1977, as cryptorchidism was not recorded until 1977. This is due to the fact that cryptorchidism is a congenital disease, and most cases are registered in infancy or adulthood. Therefore, registration at older ages may be related to having an affected relative, which could result in misclassification. This may in particular influence the grandchildren estimate. Furthermore, incomplete links to grandparents and thus uncles and cousins prior to 1985 may have influenced our estimates. However, we found no significant differences in subanalyses including the children born before and after 1985, respectively.

In conclusion, cryptorchidism aggregates within male-twin pairs and first-, second-, and third-degree relatives. Inherited factors appear to have a moderate influence on the risk of cryptorchidism. However, as the maternal line contributes to a higher extent to the inheritance of cryptorchidism than the paternal line and as the RRR in brothers is 1.52 times higher than the RRR in offspring of a cryptorchidism case, our data suggest that a maternal factor related to the children born before and after 1985.

In conclusion, cryptorchidism aggregates within male-twin pairs and first-, second-, and third-degree relatives. Inherited factors appear to have a moderate influence on the risk of cryptorchidism. However, as the maternal line contributes to a higher extent to the inheritance of cryptorchidism than the paternal line and as the RRR in brothers is 1.52 times higher than the RRR in offspring of a cryptorchidism case, our data suggest that a maternal factor related to the intrauterine environment is important for the risk of developing cryptorchidism.

ACKNOWLEDGMENTS

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