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Inheritance of ectopic ureters in Entlebucher Mountain Dogs

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Keywords
Ureteral ectopia, population genetics, canine, breeding selection, ureteral orifice
Summary

To test the hypothesis of a heritable base of ectopic ureters (EU) in Entlebucher Mountain Dogs (EMD) and to elucidate associated risk factors and mode of inheritance of the disease, 565 EMD were clinically investigated and population genetic analyses performed. Based on the location of the most caudal termination of the ureteral openings, 552 EMD were classified into three phenotype groups trigone, intravesically and extravesically ectopic based on results of abdominal sonography, urethra-cystoscopy and/or contrast-enhanced computed tomography. One third (32.9%) of the phenotyped animals had normal terminations of both ureters in the bladder trigone, 47.3% had at least one intravesicular ectopic termination and 19.8% had at least one extravesicular ectopic termination. Mixed multivariable logistic regression revealed gender as a risk factor associated with EU as males were more often affected than females. Complex segregation analysis indicated a hereditary basis for EU in EMD and the involvement of a major gene in the occurrence of the extravesicular EU phenotype.

Introduction

Ureteral ectopia is a congenital abnormality in which one or both ureters terminate in a position other than the trigone of the urinary bladder (Osborne et al. 1995). Ectopic ureters (EU) are classified according to the location of their termination as intravesicular (IVEU) or extravesicular (EVEU) (North et al. 2010), and according to their course until their terminal orifice as intramural or extramural (Ho et al. 2011).

In the dog, the condition is generally rare with reported incidences below 0.05% for clinically apparent cases (Hayes 1974; Smith et al. 1981; Dean et al. 1988). Entlebucher Mountain Dogs (EMD), Briards, Bulldogs, Golden Retrievers, Labrador Retrievers, Griffons, Border Terriers, Fox Terriers, Skye Terriers, West Highland White Terriers, Siberian Huskies, Newfoundland dogs, Miniature and Toy Poodles have been found to be at an increased risk for EU (Hayes 1974; Hayes 1984; Holt et al. 2000; Eckrich Specker 2006; North et al. 2010;
The most common clinical sign is the occurrence of urinary incontinence at a young age. However, some animals, and especially males, do not show clinical symptoms until they reach an advanced age (Holt 1990, Holt & Moore 1995). In a case series of 50 dogs undergoing EU surgery (Reichler et al., 2012) urinary incontinence was observed for the first time within the first year of life in 90% of the females but only in 50% of the males. 16% of the males were older than 5 years when the owner observed urinary incontinence for the first time (unpublished data). Besides incontinence, recurrent urinary tract infections (e.g. cystitis, pyelonephritis), hydrourerter and hydronephrosis are of clinical importance (Stone & Mason 1990; Cannizzo et al. 2003). In severely affected dogs, the course of the disease may be fatal.

The hypothesis of a genetic background of EU is supported by reports of familial aggregations (Johnston et al. 1977; Holt et al. 1982). Familial increased incidence of EU has also been reported in humans (Deweerd & Feeney 1967; Musselman & Barry 1973). Reports in related EMD and an overrepresentation of the breed in surgical EU cases (Eckrich Specker 2006; North et al. 2010; Bitterli 2011; Reichler et al. 2012) led to the implementation of a screening program for EU with the participation of the Swiss, German, Dutch and Austrian EMD kennel clubs (SKES, SSV-ES, ESC and VSSÖ). Starting in mid-2008, the German kennel club required breeding dogs to be examined for presence of EU, whereas the Swiss, Dutch and Austrian kennel club strongly recommended testing. A restrictive program which excluded severely affected dogs was established in Germany in 2009. However, the high incidence of EU in the examined EMD (n= 308, 45% IVEU and 19% EVEU) (Bitterli 2011) together with an overall small population size, the effective population size in Switzerland being 32 in 2009 (Staub 2011), make the establishment of a reasonable breeding strategy rather difficult. The knowledge of the mode of inheritance improves the chance to identify causative genes (Snow & Wijsman 1998).

The objective of this study was to evaluate risk factors associated with the occurrence of EU in EMD and to assess its mode of inheritance and its heritability.
Materials and Methods

Data: This multi-center, cross-sectional study of kennel club registered EMD was approved by the Swiss Federal Veterinary Office. Six institutes with board certified radiologists or internists in Switzerland, Germany, Austria and the Netherlands participated in the study. Pedigree information was provided by the kennels and every dog was identified by its microchip. An intravenous catheter was placed in the cephalic vein and a blood sample was collected into EDTA tubes and stored at –20°C for future molecular studies. Abdominal sonography with or without sedation was the standard screening procedure. Visible jets of urine through the ureteral openings were documented separately in longitudinal and transverse planes in B-Mode (Lamb & Gregory 1998), Color Doppler or Color B-flow mode. Intravenous (IV) crystalloid infusion (lactated Ringer’s solution) at a rate of 10ml/kg body weight (BW) and furosemide at 1mg/kg BW IV were added to reinforce the jet phenomenon. The proximal boundary of the urethra was defined as the point distal to the bladder, from where the diameter of the urinary tract remained constant (Rozear & Tidwell 2003). A normal distance between the ureteral openings and the vesicourethral junction was expected to be at least 1.5 to 2.0 cm dependent on the size of the dog. Smaller distances were considered to be ureteral orifice terminations in the “bladder neck”. If the ureteral openings could not be convincingly localized and/or separately recorded, sonography was followed by contrast-enhanced computed tomography (CT excretory urography) or urethro-cystoscopy given the owner’s consent for general anesthesia and examination. All exam-reports from the participating institutes were reviewed by the project group in Zurich and classified according to the following system: Normal, if the ureteral orifice terminated at the “bladder trigone”, ectopic intravesicular, if it terminated at the bladder neck and ectopic extravesicular, if it terminated at the urethra which also included openings just at the vesicourethral junction. According to the more caudal location of the right or left ureteral orifice, each dog was
assigned one of four phenotypes: phenotype trigone, phenotype IVEU, phenotype EVEU or unknown phenotype.

Statistical analysis: Descriptive statistics were calculated for the variables age at diagnosis, gender, reproduction status, year of birth, season of birth, litter size, sex ratio and early-death. Information on the last three variables was only available for Swiss and German EMD.

Season 1 was defined as birth between 1st December and the last day of February, Season 2 between 1st March and 31st May, Season 3 between 1st June and 31st August and Season 4 between 1st September and 30th November. Litter size was defined as the total number of puppies born in a litter including stillborn pups. Sex ratio was calculated as the number of male puppies divided by the total number of puppies per litter. The variable early-death includes stillborn littermates or puppies that died during their first 8 weeks of life.

Associations of EU with categorical variables were analyzed using contingency tables. Continuous variables were first checked for normality using QQ plots. If a variable was not normally distributed an appropriate non-parametric test was performed. Gender distribution of early-death puppies within the litters was evaluated against a ratio of 1:1. Additionally, an expanded dataset of the last 12 years (2000-2011) for gender of all born and all early-death puppies was examined. In order to evaluate the consequences of breeding restriction, EMD born before the start of the screening program (2006 - 2007) were compared to those born after breeding restrictions were established (2009 - 2010).

An univariate analysis with the categorical variables gender, early death, season, birth after 2008 and reproduction status; and the continuous variables litter size, sex ratio, year of birth and age at diagnosis was performed on the dataset of Swiss and German EMD. A mixed logistic regression model was examined to take correlated outcomes of littermates into account. Three versions with binary encoding of the phenotypes were run: (i) trigone as unaffected, IVEU together with EVEU as affected; (ii) trigone together with IVEU as unaffected, EVEU as affected; and (iii) trigone as unaffected and EVEU as affected while
specifying IVEU as no information. A multivariate mixed logistic regression was performed to determine risk factors associated with the three phenotypes. Potential interactions were also evaluated. Each variable was added separately to the model and its effect evaluated on the basis of AIC (Akaike 1974). Each of the fixed effect variables in the multivariate model was then evaluated based on its computed $P$–value. Only variables with significant effects were kept in the final model. Log odds were used to measure the association between each categorical variable and phenotypes. Descriptive statistics were performed with standard software (IBM SPSS Statistics®, version 19.0 for Mac, SPSS Inc, Chicago, IL, USA), whereas for the logistic regression models another software package was used (R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria). Values of $P < 0.05$ were considered significant.

Segregation analysis: Complex segregation analysis of the EU trait was carried out using PAP (Pedigree Analysis Package 5.ed., Hasstedt 2002). EU was encoded as a dichotomous trait with different combinations of the three phenotypes in three datasets (Table 3). The prevalence of phenotypes was based on our screening results and calculated for the different phenotype groupings within the datasets. Maximum likelihood procedures were used to estimate the following parameters: allele frequency, transmission probabilities, dominance, displacement and heritability. Five different models (general, environmental, mixed, major gene and polygenic inheritance) were compared according to their hierarchy based on the difference between their likelihoods (-2 ln L), the distribution of which follows a $\chi^2$ distribution with degrees of freedom equal to the difference in the number of the parameters estimated. A difference between two models was considered significant if $P \leq 0.05$.

Heritability: To estimate heritability of the EVEU trait the program MTDREML (Boldman et al. 1995) was used on an expanded dataset with all EMD that had a trigone or EVEU phenotype in 2012, their ancestors of five generations and individuals to connect families.

Results
Out of 565 EMD (288 females, 277 males) one third (32%) had normal terminations of both ureters in the bladder trigone area, 46% had at least one IVEU and 19% had at least one EVEU termination, whereas 13 individuals could not be classified (Table 1). There was a significant difference in gender distribution with more males having EVEU than females ($P < 0.001$). No difference in gender distribution was found within the early-death puppies ($n = 63$, $P = 0.450$) and the same was true when considering all born or all early death puppies within the last 12 years ($n = 3820$, $P = 0.116$ vs. $n = 274$, $P = 0.589$). There was a significant change in the distribution of phenotypes when comparing dogs born in the two years (2006 – 2007) before the screening started in middle of 2008 with dogs born in the first two years after breeding restrictions had been established (2009 – 2010; $P < 0.001$; Figure 1). The percentage of affected dogs changed from 49% and 25% to 50% and 10% for IVEU and EVEU, respectively.

In all three versions (i, ii, iii) of the mixed multivariate logistic regression models with the phenotyped Swiss and German EMD ($n = 430$) gender was a supporting covariate according to the best-fit models and the female gender was found to decrease the log odds ratio. Additionally in version (ii) the covariates year of birth, season and age at diagnosis, and in version (iii) birth after 2008 and season 3 were significantly associated with the outcome (Table 2). No improvement was achieved when adding interactions or litters as a random factor.

For the segregation analysis of the three datasets 282 phenotyped (141 males, 141 females, 18 litters and 43 litters where at least 50% were phenotyped) and 290 EMD with unknown phenotype were included to form seven families. In dataset 3, pedigrees had to be adjusted and litters in which all puppies were of the IVEU phenotype excluded (Table 3). The analysis of dataset 1 and 2 resulted in the rejection of the environmental model. The mixed inheritance model was superior to the general genetic model, but no difference between mixed
inheritance, major and polygene model was detected. In dataset 3, the polygene model was rejected while the major gene model was superior to the mixed inheritance model.

Heritability of the EVEU trait was estimated to be 0.65 (SE ± 0.11) in a dataset of 1611 EMD including trigone (n = 196) and EVEU phenotypes (n = 115).

Discussion

This is the first report to demonstrate a hereditary basis for EU in the dog that had been suspected for decades. A genetic involvement has been suggested with breeds of different predispositions (Hayes 1974; Holt et al. 2000; North et al. 2010) and an increased incidence of EU in the EMD has been reported previously in a clinical case study (Reichler 2012), as well as in epidemiological studies (North et al. 2010; Bitterli 2011). In the present study a decline in the number of EVEU affected dogs born after 2008 was observed, which coincided with the establishment of breeding restrictions based on the results of the screening program in the form of reducing or excluding EVEU affected dogs from breeding. This supports the premise of treating IVEU and EVEU as separate phenotypes and also questions the involvement of the IVEU phenotype in the development of the EVEU phenotype. Using complex segregation analysis we could show the presence of a hereditary basis of the disease. The environmental model was rejected in all three datasets and when IVEU phenotypes were excluded from the dataset the major gene model fitted best. Therefore we suggest the presence of a major gene involved with the occurrence of the EVEU phenotype in the EMD. This is further reflected in the result of a high heritability coefficient of 0.65 (SE ± 0.11) for EVEU. The power of testing may have been compromised by the fact of a nonrandom population. Most likely future breeding dogs and dogs with relatives affected by EU were overrepresented. Furthermore often only some but not all dogs of a litter were phenotyped. Even bearing the nonrandomly phenotyped population in mind it is still concerning that only one third of the animals in our study had normal ureteral terminations in the bladder trigone area and that 46% had IVEU and 19% had EVEU. In Germany and some other countries it is
illegal to breed animals which have a high probability of inherited disorders and welfare problems. Therefore screening examinations were introduced as mandatory for intended breeding animals and dogs with EVEU were excluded from breeding. Loosing 19% of potential breeding animals to EU does not seem like a lot, however it has to be kept in mind that in most breeds and also in the EMD only a low percentage of males are used for breeding. Together with breeding constraints already in use due to other disease conditions (hip dysplasia, progressive retina atrophy), the degree of inbreeding and thus danger to the health status of the population might increase. Discussions about outcrossing, which would be a very effective breeding strategy in such a small population having such a high incidence of EU, are ongoing. Such a breeding strategy, if performed correctly, could increase the genetic base tremendously without obviously changing outward appearance and breed characteristics. However these methods are not accepted by the FCI or the involved kennel clubs. Another option to decrease EU prevalence in this breed is the establishment of a breeding strategy using estimated breeding values. This strategy was therefore recommended to kennel clubs for future breeding.

The distinction between normal openings in the trigone and IVEU openings with sonography is difficult, as no normal values for the distance between ureterovesical junction and internal urethral orifice have been published. Based on measurements in freshly euthanized dogs (F. Degrandi, pers. comm.) and data from dogs evaluated by CT, where distances of 1.8 to 3.9 cm were reported (Rozear & Tidwell 2003), we considered distances greater than 1.5 to 2 cm to be normal according to the size of the dog. We accounted for the debatable identification of the IVEU phenotype in the complex segregation analysis by grouping it as either affected, unaffected or no information in the different datasets. According to the results of the mixed multivariate logistic regression models the female EMD, surprisingly had a lower chance of being affected than males. Possible explanations like early loss due to resorption of embryos or neonatal death of affected females could be
ruled out by analyzing the ratio of female and male EMD born in the German and Swiss populations in the last 12 years and the gender distribution of early-death puppies. Both were similar. Bias could have arisen during diagnostic work-up if males were more strictly classified than females. Historically, more females are reported to have the disease (Holt & Moore 1995) although the true prevalence in males must have been underestimated (Berent et al. 2008; Reichler et al. 2012). Using the prostate as a landmark in males facilitates the classification of EVEU. In older intact male dogs benign prostatic hyperplasia has to be taken into account, because a cranially enlarged prostate can compress the bladder neck, which may then be mistaken for the urethra and could have biased our results. To avoid misinterpretation during the screening process we focused therefore on the junction of the prostate and the urethra, which concurs anatomically with the openings of the deferent ducts. Furthermore the preliminary results of Degrandi in dog breeds not affected by EU make such a bias less likely.

Comparing intraindividually the ultrasonographic measurements of the distances between ureterovesical junction and internal urethral orifices with the measurements post dissection, she found neither diverging results regarding the measurement methods nor gender related differences (F. Degrandi, pers. comm.). An X-linked mode of inheritance, which is a further explanation for the gender distribution, could unfortunately not be ruled out due to the limited size of our dataset and PAP requiring to estimate a larger number of parameters in this mode.

Year of birth and birth after 2008 were found to be significant covariates in the versions (ii) and (iii) which exclusively assign EVEU phenotypes as affected. This reflects our observation of a decrease of EVEU affected dogs over time, which is most likely due to the applied breeding restrictions. The covariate age at diagnosis was found to decrease the log odds ratio in version (ii), indicating that older dogs were less likely to have an affected phenotype in this version. Since 2008 the screening evaluation became mandatory for all breeding dogs in Germany and was highly encouraged in Switzerland. Supposedly a higher proportion of young dogs but also older breeding dogs that had not shown any signs of disease were
presented for examination. The covariate season of birth between June and August increased the risk of having an affected phenotype in version (ii) and (iii), indicating a possible non-genetic influence on the affected outcome EVEU. In the current study we were able to demonstrate a hereditary basis of EU in dogs by example of the EMD. The complex inheritance pattern of the disease likely involves several genes as well as a major gene in association with the clinically more relevant EVEU phenotype. This breed seems to be highly affected both clinically and phenotypically (Bitterli 2011). This may allow us to identify molecular markers that will help to understand the genetic base and pathogenesis of the disease in other dog breeds and in humans as well. Fortunately, the incidence of EVEU was observed to have decreased in the EMD shortly after breeding restrictions were implemented.

Acknowledgments

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**Figures**

**Figure 1** Decline of affected EMD after establishment of breeding restrictions.

Phenotype distribution as bilateral terminations in the vesical trigone, IVEU (at least one ureteral opening is intravesically ectopic) or EVEU (at least one ureteral opening is extravesically ectopic) in EMD born two years before and after breeding restrictions were applied in 2008. The absolute number of phenotyped dogs is given within bars.

**Tables**

Table 1 Year of birth and gender distribution of 565 Entlebucher Mountain Dogs examined for ectopic ureters and phenotyped as bilateral terminations in the vesical trigone, IVEU (at least one ureteral opening is intravesically ectopic), EVEU (at least one ureteral opening is extravesically ectopic) or unknown.

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Total Male/Female</th>
<th>Phenotype trigone Male/Female</th>
<th>Phenotype IVEU Male/Female</th>
<th>Phenotype EVEU Male/Female</th>
<th>Phenotype unknown Male/Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 2002</td>
<td>40/27/13</td>
<td>12/7/5</td>
<td>8/2/6</td>
<td>17/16/1</td>
<td>3/2/1</td>
</tr>
<tr>
<td>2002</td>
<td>24/14/10</td>
<td>4/1/3</td>
<td>11/6/5</td>
<td>8/6/2</td>
<td>1/1/0</td>
</tr>
</tbody>
</table>

Kommentar [RF7]: Nimmt noch raus, keine Sorge!
Table 2 Results of the mixed multivariate logistic regression models for EU phenotypes in

EMD: Implementation of the phenotypes trigone (bilateral terminations in the vesical trigone), IVEU (at least one ureteral opening is intravesically ectopic) and EVEU (at least one ureteral opening is extravesically ectopic) with binary encoding in three versions: (i) trigone as unaffected, IVEU together with EVEU as affected; (ii) trigone together with IVEU as unaffected, EVEU as affected; and (iii) trigone as unaffected and EVEU as affected while specifying IVEU as no information.

<table>
<thead>
<tr>
<th>Year</th>
<th>Covariates</th>
<th>Version (i)</th>
<th>Version (ii)</th>
<th>Version (iii)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Log odds ratio</td>
<td>P-value</td>
<td>Log odds ratio</td>
</tr>
<tr>
<td>2003</td>
<td>Gender (female)</td>
<td>-1.673</td>
<td>&lt;0.001</td>
<td>-1.776</td>
</tr>
<tr>
<td>2004</td>
<td>Sex ratio</td>
<td>-0.678</td>
<td>0.213</td>
<td>-0.813</td>
</tr>
<tr>
<td>2005</td>
<td>Birth after 2008</td>
<td>-0.363</td>
<td>0.188</td>
<td>-0.232</td>
</tr>
<tr>
<td>2006</td>
<td>Year of birth</td>
<td>-0.45</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Season 2</td>
<td>0.585</td>
<td>0.219</td>
<td>0.709</td>
</tr>
<tr>
<td>2008</td>
<td>Season 3</td>
<td>1.141</td>
<td>0.015</td>
<td>1.759</td>
</tr>
<tr>
<td>2009</td>
<td>Season 4</td>
<td>0.481</td>
<td>0.345</td>
<td>0.776</td>
</tr>
<tr>
<td>2010</td>
<td>Age at diagnosis</td>
<td>-0.384</td>
<td>0.014</td>
<td>-0.002</td>
</tr>
</tbody>
</table>
Table 3 Segregation analysis of trichotomous (T) and dichotomous (D) datasets from different phenotype groupings for ectopic ureters in Entlebucher Mountain Dogs. Prevalences are given according to the number of phenotyped animals for trigone, IVEU (Intravesical ectopic ureter) and EVEU (Extravesical ectopic ureter) phenotypes. Chi square values (χ²) are equal to the difference of the environmental and mixed inheritance model tested with the general genetic model or of the major gene and polygene model tested with the mixed inheritance model, respectively. Degrees of freedom (df) are equal to the difference in estimated parameters between compared models.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Phenotype</th>
<th>Prevalence</th>
<th>Animals</th>
<th>Model comparison</th>
<th>χ²</th>
<th>df</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trigone</td>
<td>0.33</td>
<td>Total 572 Phenotyped 282</td>
<td>General genetic - Environmental</td>
<td>11.947</td>
<td>4</td>
<td>0.018</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>2.283</td>
<td>3</td>
<td>0.516</td>
</tr>
<tr>
<td></td>
<td>IVEU and EVEU</td>
<td>0.67</td>
<td></td>
<td></td>
<td>- Major gene</td>
<td>0.199</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Polygene</td>
<td>1.897</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Trigone and IVEU</td>
<td>0.80</td>
<td></td>
<td>Total 572 Phenotyped 282</td>
<td>General genetic - Environmental</td>
<td>21.390</td>
<td>4</td>
</tr>
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<td></td>
<td>1.755</td>
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<td>0.625</td>
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<tr>
<td></td>
<td>EVEU</td>
<td>0.20</td>
<td></td>
<td></td>
<td>- Major gene</td>
<td>2.911</td>
<td>1</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>- Polygene</td>
<td>5.534</td>
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</tr>
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<td>3</td>
<td>Trigone</td>
<td>0.80</td>
<td>Total 451 Phenotyped 137</td>
<td>General genetic - Environmental</td>
<td>26.012</td>
<td>4</td>
<td>&lt; 0.001</td>
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<td>4.530</td>
<td>3</td>
<td>0.210</td>
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<tr>
<td></td>
<td>EVEU</td>
<td>0.20</td>
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<td></td>
<td>- Major gene</td>
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<td>1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Polygene</td>
<td>20.517</td>
<td>3</td>
</tr>
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