Epidemiology of achondroplasia

A population-based study in Europe

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Epidemiology of achondroplasia: a population-based study in Europe

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ABSTRACT

Achondroplasia is a rare genetic disorder resulting in short-limb skeletal dysplasia. We present the largest European population-based epidemiological study to date using data provided by the European Surveillance of Congenital Anomalies (EUROCAT) network. All cases of achondroplasia notified to twenty-

eight EUROCAT registries (1991-2015) were included in the study. Prevalence, birth outcomes, prenatal diagnosis, associated anomalies, and the impact of paternal and maternal age on *de novo* achondroplasia were presented. The study population consisted of 434 achondroplasia cases with a prevalence of 3.72 per 100,000 births (95%CIs: 3.14–4.39). There were 350 live births, 82 terminations of pregnancy after prenatal diagnosis, and two fetal deaths. The prenatal detection rate was significantly higher in recent years (71% in 2011-2015 vs. 36% in 1991-1995). Major associated congenital anomalies were present in 10% of cases. About 20% of cases were familial. After adjusting for maternal age, fathers >34 years had a significantly higher risk of having infants with *de novo* achondroplasia than younger fathers. Prevalence was stable over time, but regional differences were observed. All pregnancy outcomes were included in the prevalence estimate with 80.6% being live born. The study confirmed the increased risk for older fathers of having infants with *de novo* achondroplasia.

Keywords: achondroplasia, skeletal dysplasia, epidemiology, EUROCAT, prevalence, paternal age

INTRODUCTION

Achondroplasia (ORPHA: 15, OMIM: 100800) is a rare genetic disorder resulting in short-limb skeletal dysplasia. It is characterized by clinical features visible at birth, such as macrocephaly, frontal bossing, depressed nasal bridge, midline facial hypoplasia, rhizomelia, short broad hands with a trident hand configuration, hypoplastic foramen magnum, and a small skull base (Simmons et al., 2014; Pauli et al., 1998; Waller et al., 2008). Health problems commonly associated with achondroplasia include episodes of obstructive sleep apnea, recurrent ear infections, spinal stenosis, and obesity (Hecht et al., 1988; Ednick et al., 2009). Average adult height is 131±5.6 cm for males and 124±5.9 cm for females. Cognitive function is normal unless hydrocephalus or other central nervous system complications occur (Wigg et al., 2016). Infants and children with achondroplasia have an increased risk of apnea and sudden death due to compression of the foramen magnum (Hecht et al., 1987; Horton et al., 2007). This risk of sudden death led to recommendations for surgical evaluation and potential intervention with decompression of the cervical cord in infants and children (Horton et al., 2007). An improvement in survival has been shown in recent years (Hashmi et al., 2018).

Achondroplasia is caused by mutations (G1138A and G1138C) in the fibroblast growth factor receptor 3 (*FGFR3*) gene, encoding a receptor regulating the linear bone growth. Achondroplasia is an autosomal dominant disorder, but about 80% of cases are sporadic, due to a *de novo* mutation in offspring of unaffected parents (Pauli et al., 1998).

Diagnosis of achondroplasia is based on the presence of characteristic clinical features and radiological findings (prenatal ultrasound, radiographs) (Pauli et al., 1998). When achondroplasia is suspected either prenatally or postnatally, *FGFR3* analysis can be performed to confirm the diagnosis. Differential diagnosis includes hypochondroplasia (OMIM: 146000), thanatophoric dwarfism (type I, OMIM: 187600; type II, OMIM: 156830 and 187601), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) syndrome (OMIM: 616482), pseudoachondroplasia (OMIM: 177170), and metaphyseal dysplasias.

The effects of maternal and paternal age on *de novo* cases of achondroplasia have been investigated. The effect of increasing maternal age seemed to disappear when adjusted for paternal age (Orioli et al., 1995), but increasing paternal age has been observed to have an association with *de novo* achondroplasia (Waller et al., 2008; Moffit et al., 2011).

Achondroplasia has an estimated birth prevalence of about 3.8 per 100,000 live births worldwide (Simmons et al., 2014). Few population-based epidemiological studies have been published worldwide because of the need for large populations given the rarity of the condition and standardized data collection. Three small population-based studies and one wider study involving seven programs worldwide have been published between 1979 and 1993, mainly based on livebirths and stillbirths (Oberklaid et al., 1979; Andersen et al., 1989; Stoll et al., 1989; Kallen et al., 1993). Two recent studies have been carried out in USA (Waller et al., 2008; Moffit et al., 2011). No large population-based studies investigating all birth outcomes have been performed in Europe.

The aim of this study was to investigate the epidemiology of achondroplasia, including the prevalence of different birth outcomes, associated anomalies, and the impact of paternal and maternal age on *de novo* achondroplasia, from a large European network of population-based registries for congenital anomalies.

MATERIALS AND METHODS

The EUROCAT congenital anomaly registries are population-based, registering cases diagnosed mostly up to 1 year of age with major structural congenital anomalies, chromosomal abnormalities and genetic syndromes among live births, fetal deaths with gestational age (GA) ≥ 20 weeks (FD), and terminations of pregnancy for fetal anomaly (TOPFA) following prenatal diagnosis at any gestation, using standardized definitions and coding. The defined populations, the methods of case ascertainment, the definitions and coding instructions of EUROCAT have been described in previous publications (Boyd et al., 2011; Kinsner-Ovaskainen et al., 2018; Tucker et al., 2018; EUROCAT website; EUROCAT guide 1.4; EUROCAT 'Members & Registry Decriptions').

In many EUROCAT registries, clinical geneticists are involved in the examination and diagnosis of infants with congenital anomalies. In this study, a medical geneticist (IB) and a pediatrician (EG) reviewed all records. Written text descriptions were evaluated to ensure that all the relevant clinical information was included in the study. Local registries were contacted for any additional information required.

All full member EUROCAT registries were invited to participate in the study. Twenty-eight EUROCAT registries in 17 European countries, were included. All cases of achondroplasia born between 1 January 1991 and 31 December 2015, notified to the registries, coded with the International Classification of Diseases, ninth (ICD-9) or tenth revision (ICD-10) with British Pediatric Association (BPA) one-digit extensions for achondroplasia (ICD9-BPA, 75643; ICD10-BPA, Q774) were extracted from the EUROCAT central database which is operated by the JRC-EUROCAT Central Registry, European Commission Joint Research Centre Ispra, Italy.

Registries submit individual anonymized records of cases of congenital anomalies thus no ethical approval for the study was required.

For each case, the following data were evaluated: age at diagnosis, birth outcome, survival up to one week of age, sex, GA in completed weeks, GA at discovery if prenatally diagnosed, birth weight, associated anomalies, family history, and maternal and paternal age at delivery (where available) in *de novo* achondroplasia.

Statistical Analysis

Descriptive data are presented as numbers for continuous variables and percentages for categorical variables. 95% confidence intervals (95%CIs), based on Poisson distribution, were calculated for prevalence

estimates. Overall and live birth prevalence were estimated using Poisson regression with random effects models to allow the prevalence in different registries to vary.

A Poisson regression model was also used for statistical testing of time trends in prevalence. The Poisson model presented prevalence rate ratio (PRR) estimates and 95% CIs referred to the baseline period 1991-1995. The χ^2 test for homogeneity was performed to assess whether differences in prevalence estimates across registries reflected real differences or were due to random fluctuation.

Survival up to one week of age was estimated only for registries with a percentage of unknown/missing information less than 10%.

The association between maternal and paternal age and *de novo* achondroplasia was assessed using Poisson regression (paternal age baseline group: < 30 years). This analysis was performed on a subset of eight registries, for which both paternal and maternal age distribution in the population was available. Models were adjusted for maternal age and for registry.

When performing the statistical analyses, a *p*-value less than 0.05 was considered statistically significant.

Statistical analysis was conducted using STATA version 13.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Prevalence and birth outcomes

The total number of births covered by the 28 EUROCAT registries over the 25 years was 11,402,594.

Four hundred and thirty-four cases with achondroplasia were identified in the 28 EUROCAT registries during the study period giving an overall prevalence of 3.72 per 100,000 births (95%CIs: 3.14–4.39) and live birth prevalence of 3.05 per 100,000 (95%CI: 2.62-3.55). The 5-year prevalence rates are reported in Table 1. Prevalence estimates across the 5-year periods did not differ significantly (p=0.620).

Data on the number of cases and prevalence by registry are presented in Table 2. Prevalence between regions differed significantly (p < 0.05) with the highest prevalence estimates of achondroplasia observed for Malta, Paris, and Ukraine (OMNI-Net).

There were 350 live births (80.6%), two FDs (0.5%) and 82 TOPFA (18.9%) (Figure 1).

Among the cases with known information about family history (n=208), there were 42 (20.2%) confirmed familial cases and 166 (79.8%) *de novo* achondroplasia cases. A higher percentage of TOPFA was observed

in *de novo* cases when compared to familial cases (29.3% vs. 21.4%), but this difference was not statistically significant (p=0.409).

The mean maternal age (±SD) was 31.2±5.6 years and the mean paternal age 36.5±7.7 years.

Among the cases with available information on the time of diagnosis (n=415), 263 (63.4%) were diagnosed prenatally and 152 (36.6%) postnatally (Figure 1), among which 24.1% (n=100) were diagnosed at birth and 3.4% (n=14) in the first week of life.

Among the live births, with available information on the time of diagnosis (n=331), 179 (54.1%) were diagnosed prenatally. There was no statistically significant difference in the prenatal detection rate between the groups of *de novo* and familial cases. When achondroplasia was prenatally discovered, about 1 out of 3 (32%) of the parents opted to terminate the pregnancy.

No significant trend over time was observed in prenatal detection rate (p=0.264), but there was a stepped change with the prenatal detection rate, being significantly lower in the period 1991-1995 (35.9%) than in the following 5-year periods (65.8% in 1996-2000, 64.0% in 2001-2005, 63.6% in 2006-2010, and 71.0% in 2011-2015).

The mean birth weight (±SD) was 2951±848 grams for males and 2936±812 grams for females. The median GA at birth for live births was 39 (range 28–42) weeks for males and 39 (range 32–45) weeks for females. The male-to-female ratio was 1.10.

For the 82 cases resulting in TOPFA, the median gestational age at prenatal diagnosis was 24 weeks (range: 10-35), which, as expected, is significantly lower ($p<0.01$) than the median gestational age at prenatal diagnosis for the 179 live births (31 weeks, range: 12-39).

Among the live born infants with available information about survival beyond one week of age (n=280), 275 (98.2%) were alive one week after birth. Five infants died during the first week (1.8% of total live births). Among them, one case had severe associated anomalies (hydranencephaly and occipital encephalomeningocele) and one case was born very preterm. The rate of FD was 0.02 per 100,000 births and the rate of early neonatal deaths (deaths during the first week of life) was estimated at 0.04 per 100,000 births. This gives a total estimated contribution to perinatal mortality of 0.06 per 100,000 births associated with achondroplasia.

Associated anomalies

Major associated congenital anomalies were present in 44 cases (10.1% of total) and listed in Table 3. The most frequent anomalies were related to the nervous system (3.7%), congenital heart defects (2.5%), and urinary anomalies (1.8%).

De novo achondroplasia

Out of the 208 cases of achondroplasia with known information about family history, we identified a total of 166 cases of *de novo* achondroplasia. Since paternal age distribution in the reference population was not available for all the participating registries, an analysis was performed on a subset of eight registries, corresponding to 93 *de novo* cases, in order to assess the association between paternal and maternal age and *de novo* achondroplasia.

The risk of *de novo* achondroplasia among fathers in age-groups 35-39 years, and 40+ years was significantly higher compared to the risk among fathers under 30 years (baseline), with PRR=2.68 (1.44-4.99) for the age group 35-39 years vs baseline and PRR=2.91 (1.51-5.61) for age-group 40+ years vs baseline (Table 4). The risk is significantly higher also after adjustment for maternal age and for registry (PRR=4.86, 95%CIs: 2.37-9.98 and PRR=5.57, 95%CIs: 2.57-12.07 for 35-39 and 40+ age-groups, respectively). The association with paternal age was highly significant ($p<0.01$).

In contrast, maternal age was not associated with *de novo* achondroplasia, when adjusted for paternal age and for registry.

DISCUSSION

This study using data from the JRC-EUROCAT network represents the largest series of cases of achondroplasia in Europe.

In this population-based study, the prevalence of achondroplasia in 28 EUROCAT registries in the 1991-2015 period was 3.72 per 100,000 births, with a stable prevalence since 1991, but with heterogeneity in the prevalence rates among the European regions and countries. We found that a high percentage of old fathers in the population was not associated with a high prevalence of achondroplasia. This result would suggest that the heterogeneity in prevalence is not explained by differences in the percentage of older fathers across regions. Achondroplasia prevalence might be explained by different distributions of resident

families with the mutated gene across different European countries. Heterogeneity of prevalence estimates was also observed in other studies.

Four published population-based studies between 1979 and 1993 have reported prevalence estimates ranging from 1.3 to 6.4 per 100,000 (Oberklaid et al., 1979; Andersen et al., 1989; Stoll et al., 1989; Kallen et al., 1993). In a more recent population-based study carried out in seven regions of the US and covering a population of 10,800,000 births, a heterogeneous range of prevalence from 3.6 to 6.0 per 100,000 has been reported (Waller et al., 2008). In 2011, Moffit et al. have estimated the prevalence at 3.04 per 100,000 live births in the population-based registry of Texas, which corresponds to the live birth prevalence reported in our study (3.05 per 100,000).

Most of the infants reported in our study survived the neonatal period, as expected for this non-lethal skeletal dysplasia (Waller et al., 2008; Hecht et al., 1987).

The birth outcomes of our study were similar to those reported by Pauli et al. (1998). In our study, 80.6%, 0.7% and 18.9% of live births, FDs, and TOPFA were reported, respectively. Waller et al. (2008), have reported significantly more live births: 95% live births (76 out of 79), 2.5% of FD (2 out of 79) and 1.3% TOPFA (1 out of 79) for the state of Texas (2 042 554 births) in the study period 1996-2002. The higher percentage of TOPFA in our study could be related to the higher prenatal detection rate observed in more recent years when compared to that of the 1990s and 2000s, but may also relate the availability of TOPFA in Texas. In our study, the percentages of TOPFA differ between countries, which could be due to different legal situations and varying cultures across Europe. We observed that 40% of all TOPFA cases (33 out of 82) were from one registry and that 7 out of 28 registries have a proportion of TOPFA above 20% for this condition.

We found that 20.2% of familial cases and 10% of cases with achondroplasia had associated major congenital anomalies. Our findings related to associated anomalies are not readily comparable with other studies that were mainly based on case series. Hydrocephalus in the neonatal period is very rare for infants with achondroplasia, and a later hydrocephalus diagnoses is most likely based either on the presence of benign macrocephaly or equally benign ventriculomegaly (Pauli, 2019).

Other central nervous system anomalies are occasionally described in the literature (Pauli et al., 1998; Awad et al., 2014; Ceroni et al., 2018). Some authors have reported associations with congenital heart defects (ventricular and atrial septal defects), hydronephrosis, microphthalmos and, more rarely, with sex chromosomal anomalies (Ceroni et al., 2018; Nakanishi et al., 2017; Mantle et al., 2003; Weiss et al., 1989).

We found that *de novo* achondroplasia was associated with higher paternal age (age-classes 35-39 and 40+ vs. age class < 30). This is consistent both with older case series (Orioli et al., 1995; Murdoch et al., 1970) and more recent studies (Waller et al., 2008; Moffit et al., 2011). The results of Waller et al. (2008) are closely in line with the findings in our study: they have evidenced increased prevalence rates with increasing paternal age, but no association have been observed between increased maternal age and *de novo* achondroplasia. Moffit et al. (2011) have observed both an increased paternal and maternal age association with *de novo* achondroplasia in a subset of 73 non-inherited cases, but they did not use adjusted statistical models in their analysis.

The observed paternal age effect in *de novo* achondroplasia could be driven by the *FGFR3* mutation conferring a selective advantage during spermatogenesis, leading to the clonal expansion in the testis (Veltman and Brunner, 2012).

This is the only epidemiological population-based study in Europe in the last 25 years. The main strengths of this study are the large population, a standardized data collection, and the use of genetic expertise in case evaluation and coding. Moreover, in addition to prevalence estimates, this study investigates all types of pregnancy outcome such as TOPFA, FD, prenatal diagnosis, and the independent effect of paternal age on *de novo* achondroplasia.

Concerning the limitations of the study, when combining epidemiological data from many different registries, potential variation due to coding practices, completeness of data sources, and accuracy of the case description must be taken into consideration. In the same way, some data concerning the reference population of each register, such as the distribution of births by paternal age, were not always available because of the heterogeneous accessibility of such information at local level.

Conclusion

Achondroplasia is a rare skeletal dysplasia with a prevalence of 3.72 per 100,000 births in Europe. The prevalence across the period 1991-2015 appeared stable, but differences were observed between the European regions.

The prenatal detection rate has increased in recent years compared to the period 1991-1995. When prenatally discovered, about 1 out of 3 (32%) of affected pregnancies were terminated.

The perinatal mortality was low (0.06 per 100,000), as expected for a non-lethal skeletal dysplasia, which is important information for genetic counselling of affected families.

The risk of associated major congenital anomalies was 10%. About 20% of cases were confirmed familial cases.

Concerning *de novo* achondroplasia, after adjusting for maternal age, fathers of 35 years and older had a significantly higher relative risk of having infants with achondroplasia than younger fathers.

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Conflict of Interest

The authors declare no conflict of interest.

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Figure Legends

Figure 1. Birth outcomes and pre/postnatal diagnosis of the 434 cases with achondroplasia. TOPFA-termination of pregnancy for fetal anomaly; LB – Live birth; FD – fetal death.

Table 1. 5-year prevalence of achondroplasia in 28 EUROCAT registries.

Surveillance period	Total births	Total no. of cases	Prevalence per 100,000 (95%CI)	
1991-1995	1,207,678	41	3.39	(2.44-4.61)
1996-2000	1,716,517	76	4.43	(3.49-5.54)
2001-2005	2,266,209	89	3.93	(3.15-4.83)
2006-2010	3,166,905	116	3.66	(3.03-4.39)
2011-2015	3,045,285	112	3.68	(3.03-4.43)

Table 2. Number of cases and prevalence of achondroplasia in 28 EUROCAT registries.

Registry	Years included	Total births	Number of cases	Prevalence per 100,000 births (95%CIs)
Malta	1991-2015	110,174	7	6.35 (2.55-13.09)
Paris (France)	1991-2015	768,885	47	6.11 (4.49-8.13)
OMNI-Net (Ukraine)	2005-2015	333,189	20	6.00 (3.67-9.27)
Isle de Reunion (France)	2001-2015	218,796	13	5.94 (3.16-10.16)
Emilia Romagna (Italy)	1991-2015	806,485	46	5.70 (4.18-7.61)
Antwerp (Belgium)	1991-2014	400,634	22	5.49 (3.44-8.31)
Odense (Denmark)	2000-2014	76,625	4	5.22 (1.42-13.37)
Tuscany (Italy)	1991-2015	672,268	34	5.06 (3.50-7.07)
Saxony Anhalt (Germany)	1991-2015	357,516	17	4.76 (2.77-7.61)
Wielkopolska (Poland)	1999-2015	626,876	28	4.47 (2.97-6.46)
Wessex (UK)	1994-2015	615,000	25	4.07 (2.63-6.00)
Auvergne (France)	1991-2015	334,612	13	3.89 (2.07-6.64)
Zagreb (Croatia)	1991-2015	160,988	6	3.73 (1.37-8.11)
Vaud (Switzerland)	1991-2015	192,684	7	3.63 (1.46-7.49)
Wales (UK)	1998-2015	602,776	21	3.48 (2.16-5.33)
Cork & Kerry (Ireland)	1996-2015	179,563	6	3.34 (1.23-7.27)
Northern Netherlands	1991-2015	465,261	14	3.01 (1.65-5.05)
South West England (UK)	2005-2015	545,302	17	3.12 (1.82-4.99)
Northern England (UK)	1991-2015	824,745	25	3.03 (1.96-4.47)
Basque Country (Spain)	1991-2014	441,896	12	2.72 (1.40-4.74)
Valencia Region (Spain)	2007-2015	446,903	12	2.69 (1.39-4.69)
Norway	1999-2012	836,535	20	2.39 (1.46-3.69)
Thames Valley (UK)	1991-2015	411,928	8	1.94 (0.84-3.83)
Styria (Austria)	1991-2012	247,210	4	1.62 (0.44-4.14)
French West Indies (France)	2009-2015	n.r.	less than 3 cases	1.46 (0.04-8.11)
South East Ireland	2005-2014	n.r.	less than 3 cases	1.34 (0.03-7.48)
Brittany (France)	2011-2015	n.r.	less than 3 cases	1.12 (0.14-4.03)
South Portugal	1991-2015	n.r.	less than 3 cases	0.50 (0.06-1.79)
Total		11,402,594	434	3.72 (3.14-4.39)

For registries with less than 3 cases, the exact number of cases was not reported due to confidentiality problems with small numbers. For the same reason, the total number of births were not reported in table (abbreviation: n.r.), but used to calculate the prevalence estimates.

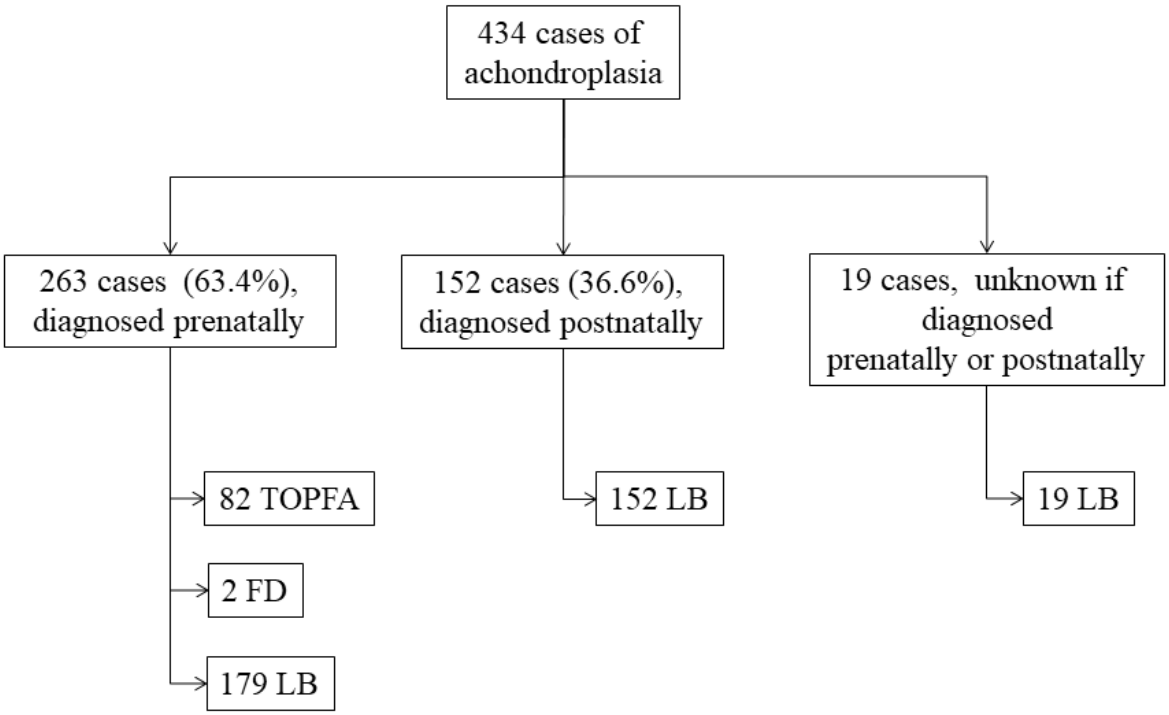
Table 3. Types and frequency of major anomalies associated with achondroplasia in a study of prevalence across 28 regions in Europe, between 1991 and 2015.

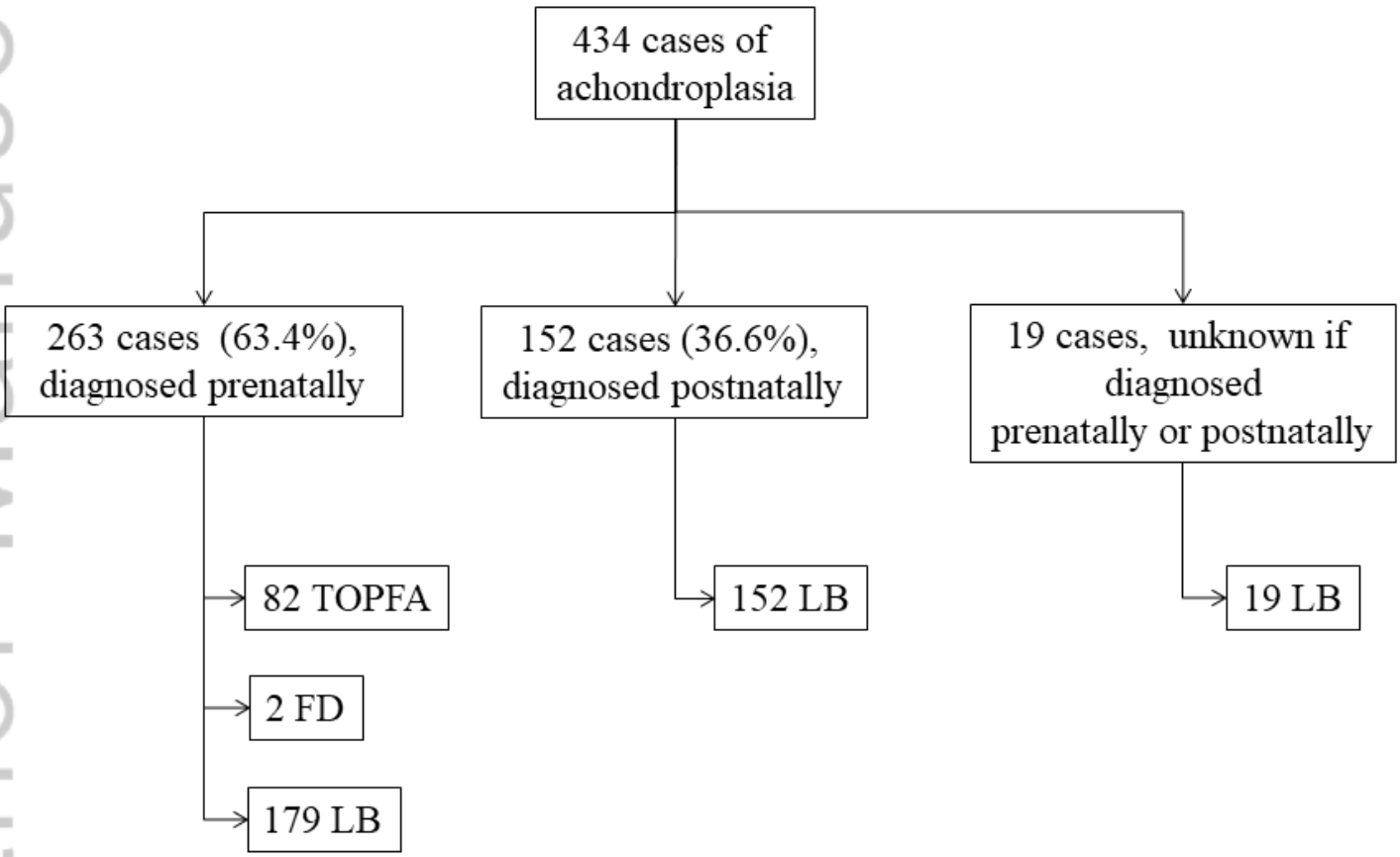
Type of anomaly	No. (% on total no. of cases)
Nervous System	
Hydrocephalus	10 (2.3)
Arnold-Chiari malformation	2 (0.5)
Other nervous system anomalies	4 (0.9)
Eye	
Microphthalmos	1 (0.2)
Other eye anomalies	3 (0.7)
Congenital heart defects	
Ventricular septal defect	7 (1.6)
Atrial septal defect	3 (0.7)
Patent ductus arteriosus (in LB ≥37 weeks)	1 (0.2)
Omphalocele	1 (0.2)
Urinary system	
Hydronephrosis	6 (1.4)
Double ureter	1 (0.2)
Other urinary	1 (0.2)
Hypospadias	1 (0.2)
Clubfoot	4 (0.9)
Chromosomal	1 (0.2)
Other	4 (0.9)

Table 4. Crude and adjusted prevalence rate ratios of *de novo* achondroplasia by paternal age groups (years)

Paternal age	PRR (95%CIs)	Adjusted* PRR (95%CIs)
< 30	baseline	baseline
30-34	1.17 (0.59-2.34)	1.71 (0.82-3.54)
35-39	2.68 (1.44-4.99)	4.86 (2.37-9.98)
≥40	2.91 (1.51-5.61)	5.57 (2.57-12.07)

*Adjusted for maternal age and for registry.
Abbreviations: PRR, Prevalence rate ratio; CIs, Confidence Intervals





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