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Existing data sources for clinical epidemiology: Danish registries for studies of medical genetic diseases

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Abstract: Denmark has an extensive collection of national and regional medical registries. There are many advantages to registry-based research when investigating genetic diseases which, due to their rarity, can be difficult to identify. In this study, we aimed to provide an updated overview of Danish registries for medical genetic conditions and describe how data linkage across registries can be used to collect data on genetic diseases at the individual level and at the family level. We present a list of medical genetic registries in Denmark at the national level, data sources from the departments of clinical genetics and other specialized centers, and project-specific data sources. We also summarize key general registries, such as the Danish National Registry of Patients, the Danish Medical Birth Registry, and the Civil Registration System, which are renowned for their comprehensive and high quality data, and are useful supplemental data sources for genetic epidemiology research. We describe the potential for data linkage across multiple registries, which allows for access to medical histories with follow-up time spanning birth to death. Finally, we provide a brief introduction to the Danish epidemiological research setting and legalities related to data access. The Danish collection of medical registries is a valuable resource for genetic epidemiology research.

Keywords: epidemiology, registry-based research, genetic disorders

Introduction

In many countries, identifying persons with a genetic condition in the background population can be difficult due to the rarity of genetic diseases, diagnostic challenges, and lack of systematic registration. The task can be akin to finding a "needle in a haystack," often requiring multidisciplinary and cross-national efforts. Denmark, however, has an extensive collection of medical and administrative registries and databases that provide a unique opportunity to collect patient data at the individual level routinely, in some cases at the family level, and to carry out reliable kinship tracking.[1,2] A registry-based research approach has many advantages, particularly when investigating inheritable conditions. Cohorts can be assembled relatively quickly and relevant medical histories can be obtained by linking data from multiple data sources.

In 1982, Broeng-Nielsen et al compiled a bibliography entitled "*Danish Family Studies of Medical Genetic Disorders 1927–1980*".[3] In this work, 672 bibliographic references covering 344 genetic disorders were identified, along with seven medical registries (which were listed, without providing details). To our knowledge, no updated compilation of Danish genetic data sources has been made since then. Therefore, we set out to provide an updated overview of Danish registries for medical

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genetic conditions; describe how data linkage across registries can be used to collect data on genetic diseases at the individual level and at the family level; and provide a brief introduction to the Danish epidemiological research setting and legalities related to data access.

Materials and methods

Danish health care infrastructure

The Danish health care system provides equal access to medical care for all residents. Approximately 85% of Danish health care is tax-funded, with the remaining 15% paid out-of-pocket.[4] General practitioners are gatekeepers, providing referrals to specialists when appropriate, and the majority of specialist care is hospital-based. Contacts to the primary (ie, general practitioners) and secondary (ie, hospitals) health care sectors are registered, as are prescriptions redeemed at outpatient pharmacies.[4] The treating physician/department is responsible for reporting data to the relevant registry, and reporting primarily occurs electronically and automatically. Funding by the national government for services rendered is based on the registration and coding of services provided at each health care site. Therefore, the Danish health care system is conducive to completeness of registration. Each person in Denmark is issued a unique personal (CPR) identification number upon birth or immigration. The CPR number encodes, amongst other things, date of birth and gender, and is the means by which information on a given individual can be merged unambiguously from multiple data sources.[5] Thus, the Danish health care system has a long tradition of high quality longitudinal registry data, in a setting of universal health care access.

Identification of medical registries for genetic diseases

We sent inquiries for medical data sources on genetic diseases with the potential to be used in registry-based research to relevant registry administrators, hospital departments (eg, departments of clinical genetics, pediatrics, and dermatology), specialized medical centers (eg, Center for Rare Diseases [Center for Sjældne Sygdomme], Clinic for Rare Handicaps [Klinik for Sjældne Handicaps], and Centre for Oral Health in Rare Diseases [Odontologisk Videncenter]), governmental agencies (eg, the Danish Health and Medicines Authority [Sundhedsstyrelsen], and the Danish Data Protection Agency [Datatilsynet]), and performed Internet-based searches. Once identified, we contacted key registry administrators for updated information and verification of the status of a given registry. Information on biobanks was considered beyond the scope of this work, and is therefore not included (with the exception of the Danish Newborn Screening Biobank and Registry,[6] which can be considered as both a registry and a biobank).

Data sources for genetic epidemiology research

We identified 29 potential medical data sources for genetic research and a further 12 hospital departments and specialized centers. The data sources are summarized in Tables 1–4 and categorized into four main groups: national registries (Table 1); data from hospital departments and centers (Table 2); project-specific data sources established in relation to various research projects, eg, PhD dissertations (Table 3); and supplemental registries for data linkage and collection of medical histories (Table 4).

In the following section, we list examples of well established genetic and supplemental data sources. Despite our best efforts to achieve completeness, we recognize that this may not be an exhaustive list detailing all existing genetic registries in Denmark.

National registries (Table 1)

Danish cytogenetic central register

The Danish Cytogenetic Central Register is a nationwide registry of all karyotypes done prenatally and postnatally since the advent of cytogenetic analysis in the early 1960s. The register holds over 300,000 total registrations with approximately 10,000 new registrations each year.[7,8] The register also contains information on specific genetic diseases, such as Fragile-X, Prader-Willi, and Angelman syndromes. The primary purpose of this register is to gather prenatal and postnatal data for the study of trends in prenatal diagnostics and chromosomal aberrations, including type and prevalence. The Danish Cytogenetic Central Register has been an important data source for the study of monosomy X and trisomy 13, 18, and 21, in addition to other research projects.[9,10]

Genetic cancer registries

The Hereditary Nonpolyposis Colorectal Cancer Register and Hereditary Breast and Ovarian Cancer Registry are two examples of national registries for inheritable cancer risk. Data registration occurs systematically and nationwide. The Hereditary Nonpolyposis Colorectal Cancer Register[11,12] was established in 1991, with nationwide data collection since 1995. The Hereditary Breast and Ovarian Cancer Registry was established in 1999. Both registers collect

data on index cancer cases and relatives at risk (eg, referred on to specialist evaluation because of an accumulation of relatives with specific cancers or very young individuals with cancer). The Hereditary Breast and Ovarian Cancer Registry operates under the auspices of the Danish Breast Cancer Cooperative Group and is part of an umbrella clinical database that was established by the Danish Breast Cancer Cooperative Group in the late 1970s.[13] Numerous publications have arisen from data stemming from both registries.[13,14]

The Danish Cancer Registry (DCR) has recorded solid tumor cancers in Denmark since 1943, with mandatory reporting since 1987.[15–17] Sites of malignancy are recorded using International Classification of Diseases diagnosis codes, 10th revision (ICD-10).[18] The DCR is an important data source for identifying heritable cancer risk. Former disease-specific registries, such as the Retinoblastoma Registry, can presently be found as data merged within the DCR.[19]

Registries for specific genetic diseases

The Danish Huntington's Register is an example of a nationwide, disease-specific registry that has been tracking Danish patients with Huntington's chorea since 1940 via pedigrees and genetic testing.[20] This register was converted to electronic records in 1980 and has over 12,000 registrations of subjects either known to have Huntington's disease or at risk of developing the disease. Both living and deceased individuals are registered.[21] This registry has been used to study crime among patients with Huntington's disease as well as other research topics.[21,22] The Danish Huntington's Register also contributes data to the European Huntington's Disease Network Registry.[23]

The Danish Cystic Fibrosis Patient Registry is another example of a well established, disease-specific registry.[24] It was established in 2001 and had 451 cystic fibrosis cases registered as of December 31, 2009 (ie, all patients with cystic fibrosis in Denmark, both living and deceased). This registry contributes data to the European Cystic Fibrosis Society Patient Registry[25] and serves as an important data source for ongoing research.[26]

The Danish Family Archive for Genetic Eye Diseases (Dansk Familiearkiv for Arvelige Øjensygdomme) started around 1985 as a nonelectronic register at the National Eye Clinic (Statens Øjenklinik). It is a nationwide umbrella registry of heritable eye diseases, with over 100 different conditions represented, including retinitis pigmentosa, which has its own subregistry (see Table 1). To date, there are over 100 published studies based on data from this registry, including studies on X-linked ocular albinism and retinitis pigmentosa.[27,28]

Neonatal registries

The National Registry of Congenital Malformations registers all congenital malformations detected during the first year of life, with data registration from 1983 to 1995.[29] During this period, all diagnosing physicians were required to register and illustrate (by free drawing) all structural congenital abnormalities (eg, congenital heart valve defects, cleft lip, and/or cleft palate), making these registrations very detailed and specific. Despite this, the registry is unfortunately known to have incomplete data.[30] From 1996 and onwards, congenital malformations have been electronically reported to the Danish National Registry of Patients (DNRP)[7] and can be identified using the corresponding ICD-10 codes.[18] Recent epidemiological studies have accessed data on congenital malformations directly from the DNRP.[31] Since not all birth defects are due to chromosomal abnormalities, this particular neonatal registry is unique in that it provides data on structural congenital abnormalities. Other relevant registries with perinatal/neonatal data include the Danish Medical Birth Registry[32] (see section on data linkage), the National Fetal Medicine Database,[33] and the Danish Newborn Screening Biobank and Registry[6] (see Table 4).

Data from the Danish departments of clinical genetics (Table 2)

In Denmark, the vast majority of genetic investigations and genetic counseling are undertaken at hospital departments of clinical genetics, located in the cities of Aalborg, Aarhus, Odense, Vejle, and Copenhagen. These departments store data on patients and families seen in the genetic outpatient clinics and/or investigated at clinical genetics laboratories. For instance, as of 2012, there were over 20,000 patients registered at the Department of Clinical Genetics, Aarhus University Hospital alone.

The departments of clinical genetics in Aarhus, Odense, and Aalborg currently use the Langtved database[34] to register and store patient data, primarily for genetic counseling. The Langtved database uses ICD-10 codes to encode broad categories of familial diseases, internal conventions determined by senior geneticists, and the internationally used McKusick codes.[35] Data are also registered in pedigrees (eg, the Cyrilic database, used from 1993 to 2013, and the PASS Clinical® genetic database[36] used from 2013). Table 2 shows further relevant departments and centers in Denmark.

Table 1 Overview of national medical genetic registries in Denmark

Genetic registry (Danish name)	Description	Registration start/ end	Data administrator/contact	Other details
Danish Cytogenetic Central Register[7,8] (Dansk Cytogenetisk Centralregister)	Prenatal and postnatal diagnostic chromosomal analyses	1960 to present, nationwide	Aarhus University Hospital, Skejby http://www.auh.dk/om+auh/afdelinger/klinisk+genetisk+afdeling/links/dccr	Over 300,000 registrations as of January 2010 and approximately 10,000 new registrations each year
Hereditary Nonpolyposis Colorectal Cancer Register[11,12] (HNPCC-registret)	Hereditary NonPolyposis Colorectal Cancer (HNPCC) and other inheritable/familial colorectal cancers not registered in the Danish Polyposis Register	1991 to present, nationwide since 1995	Hvidovre Hospital http://www.hvidovrehospital.dk/menu/Afdelinger/Gastroenheden/HNPCC/	Over 5103 families/76,300 individuals registered (among these, 2582 families/20,900 individuals have undergone genetic testing)
Hereditary Breast and Ovarian Cancer Registry[13] (HBOC-registret)	Hereditary Breast (and Ovarian) Cancer	1999 to present, nationwide	Danish Breast Cancer Cooperative Group. Contact: DBCG Secretariat, Rigshospitalet 2501, Blegdamsvej 9, DK-2100 Copenhagen Email dbcg@dbcg.dk www.dbcg.dk For a 2008 report of the registry, see http://www.dbcg.dk/Foredrag/4%20DBCGs%20database%20SM.pdf	8900 registered families, each with data on female family members referred for surveillance due to an increased risk of breast and/or ovarian cancer; questionnaires on lifestyle and earlier use of mammography for some of these
Danish Polyposis Register (Polypose-registeret)	Nationwide registry of polyposis patients and their relatives	1976 to present, nationwide	Hvidovre Hospital Email polreg@hvh.regionh.dk http://www.cancer.dk/NR/exeres/7B1BB82C-5205-4B0 A-A916-366ED072C7A2,frameless.htm	Persons with >100 colonic polyps and their families As of August 2011, 200 registered families; 622 patients (291 alive); and 768 first-degree relatives
Danish Huntington Register (Det Danske Huntington Register)	Huntington's disease	1940, electronic records from1980 to present, nationwide	Institute for Cellular and Molecular Genetics, Panum Institute, University of Copenhagen Contact person, Sven Asger Sørensen Email svas@sund.ku.dk http://huntingtons.dk/omlhs/LHCNyt/sidstenr.asp	12,000 registrations of patients and 600 families with HD or at risk of HD
Danish Cystic Fibrosis Patient Registry[24,26] (Cystisk Fibrose Register Denmark)	Patients with CF (including data on survival, lung function, BMI, and infections)	2001 to present, nationwide	Contact person, Hanne Vebert Olesen, Aarhus University Hospital (Skejby), Department of Pediatrics Email hannoles@rm.dk http://ecfs.eu/files/webfm/webfiles/File/ecfs_registry/ECFSPR_Report0809_v32012.pdf	451 registered (among these 442 living) CF patients as of December 31, 2009
Nordic Database for Rare Diseases[49] (Databasen for Sjældne Handicap RAREDIS)	Nordic Rare Diseases database (Denmark, Sweden, Norway, Finland, and Iceland)	2006 to present, compulsory registration since 2007, nationwide	Danish contact, Hanne Hove Department of Clinical Genetics, Rigshospitalet Email hanne.buciek.hove@regionh.dk https://raredis.eu/	1500 registered patients. Ongoing research projects to date: • scaphocephaly (variables include head circumference of parents and offspring, and surgical information)

				• neurofibromatosis • osteogenesis imperfecta • Angelman syndrome
Danish Family Archive for Genetic Eye Diseases (Dansk Familiearkiv for Arvelige Øjensygdomme)	Nationwide umbrella register of heritable eye diseases (over 100 different conditions represented, eg, retinitis pigmentosa described below)	1985 to present, nationwide	The National Eye Clinic for the Visually Impaired, Kennedy Center, Rigshospitalet (previously known as Statens Øjenklinik) Contact person, Thomas Rosenberg Email tro@eyenet.dk	45,000 registrations including about 3000 families, as of 2012. Detailed records of pedigrees including all known mutations Approximately 400 new registrations each year. Variables include CPR number, name, date of birth, position in the family tree, signature of the affected, unaffected, or carrier patients, mode of inheritance, mutation(s), and the laboratory that identified the mutation
Danish Retinitis Pigmentosa Register[50] (Dansk Retinitis Pigmentosa [RP] register)	Retinitis pigmentosa	1990 to present, nationwide	The National Eye Clinic for the Visually Impaired, Kennedy Center, Rigshospitalet (previously known as Statens Øjenklinik)	2870 registrations (as of July 2011) and approximately 50 new registrations each year Variables include age at debut, differential diagnoses (retinitis pigmentosa under groups), complexity, and others
vHL registry (vHL-registret)	von Hippel-Lindau disease	Nationwide, 1930–2010	Cellular and Molecular Medicine, Panum Institute, Blegdamsvej 3, DK-2200 København N Contact person, Søs Marie Luise Bisgaard, Email mlbi@sund.ku.dk	56 families with vHL. Registrations on organ manifestations, mutations, disease status
Fabry registry (Mb Fabry registeret)	Fabry disease	Nationwide	Institute for Cellular and Molecular Genetics Contact person, Lis Hasholt Email hasholt@sund.ku.dk	Approximately 40 registered cases
Danish Hereditary Angioedema Registry	Hereditary angioedema	Registration to Odense Patient data Explorative Network (OPEN) since 2011, Nationwide	Department of Dermatology, Odense University Hospital Contact person, Anette Bygum Email Anette.Bygum@ouh.regionsyddanmark.dk	95 HAE patients registered; 8 acquired angioedema patients registered; includes clinical data as well as a biobank Previously contributed data to the European HAE registry
Danish Porphyria Registry (Porfyriregister)	Hereditary porphyria	Started approximately 1969	Odense University Hospital Contact person, Jens Michael Hertz Email jens.michael.hertz@ouh.regionsyddanmark.dk	Reference: With TK 1969[51]

Abbreviations: BMI, body mass index; CF, cystic fibrosis; HAE, hereditary angioedema; HD, Huntington's disease; vHL, von Hippel-Lindau disease.

Table 2 Danish departments of clinical genetics and other specialized departments and centers

Department/center (Danish name)	Data/administrative system	Address and internet homepage	Contact	Other details
Departments of clinical genetics				
Clinical Genetics, Aarhus	Langtved database 1991- to present	Aarhus University Hospital Brendstrupgårdsvej 21 C, 8200 Aarhus N http://www.en.auh.dk/departments/cancer+and+inflammation+centre/department+of+clinical+genetics? and http://www.en.auh.dk/departments/cancer+and+inflammation+centre/department+of+clinical+genetics	Chief of Staff, Ida Vogel, MD, PhD Email idavogel@rm.dk	>20,000 patients registered; variables registered in Langtved include CPR number, family relationships, chromosomal/molecular analyses undertaken, and diagnosis of genetic disease
Clinical Genetics, Aalborg	Langtved database	Aalborg University Hospital Ladegårdsgade 5, Building E, 5th floor, 9000 Aalborg Email klin.gen@rn.dk http://www.aalborgsygehus.rn.dk/Afdelinger/KraeftOgDiagnostikcenter/Afdelinger/Klinisk+Genetisk+Afdeling/	Professor and Chief of Staff, Michael B. Petersen Email michael.petersen@rn.dk	Approximately 2500 patients registered since 2009
Clinical Genetics, Odense	Langtved database	Odense University Hospital Søndre Boulevard 29, DK-5000 Odense C http://www.ouh.dk/wm290661	Chief of Staff, Lotte Krogh Email lotte.krogh@ouh.regionsyddanmark.dk	National site for diagnostics and treatment of porphyria and hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu Disease
Clinical Genetics, Vejle Hospital	Genetik DB administration system	Vejle Hospital, Kabbeltoft 25, 7100 Vejle http://www.sygehuslillebaelt.dk/wm242521	Chief of Staff, Anders Bojesen Email onkogenetisk.klinik@slb.regionsyddanmark.dk	Approximately 8500 registered patient cases and 21,600 test results (eg, chromosomal and DNA analyses)
Clinical Genetics, Copenhagen	OPUS, GR, and KLIQ systems for data registration and administration	Rigshospitalet, Afsnit 4062 Blegdamsvej 9, 2100 Copenhagen www.kliniskgenetik.rh.dk	Chief of Staff, Professor Anne-Marie Gerdes Email anne-marie.gerdes@regionh.dk	
Other specialized departments/centers				
Center for Rare Diseases (Center for Sjældne Sygdomme), Aarhus	Patient Administrative System	Aarhus University Hospital Brendstrupgårdsvej 21 C, 8200 Aarhus N http://www.css.auh.dk	Centre for Rare Diseases (Center for Sjældne Sygdomme), Aarhus Email css@rm.dk	Center in the Department of Pediatrics; about 2000 patients registered with the center. Diagnosis, follow-up, treatment, and counseling of children with a rare condition/disease and adults with Marfan, von Recklinghausen, Prader-Willi, Spielmeyer-Vogt, and vascular Ehlers-Danlos syndromes
Clinic for Rare Handicaps (Klinik for Sjældne Handicaps), Copenhagen	OPUS, GR, and KLIQ systems for data registration and administration	Rigshospitalet, Afsnit 4062 Blegdamsvej 9, 2100 Copenhagen www.kliniskgenetik.rh.dk	Professor and Chief of Staff Anne-Marie Gerdes Email anne-marie.gerdes @regionh.dk	Center within the Department of Clinical Genetics, Copenhagen

Kennedy Center, Copenhagen	Cosmic (patient administration program); PASS clinical genetic database (pedigrees); and progeny (program for family archives)	Juliane Marie Center, Rigshospitalet, Gl Landevej 7, 2600 Glostrup http://www.kennedy.dk/	Director, Professor Karen Brøndum-Nielsen Email karen.broendum-nielsen@regionh.dk	National research center for genetics, visual impairment, and mental retardation. Centers: Fragile X Center PKU Center, Rett syndrome center, The National Eye Clinic
Department of Dermatology, Aarhus	Patient Administrative System	Aarhus University Hospital, PP Ørums Gade 11, 8000 Aarhus C http://www.auh.dk/om+auh/afdelinger/dermato-venerologisk+afdeling+s	Mette Sommerlund, Dermatologist, specialist in genodermatoses	Dermatological focus on genodermatoses: ichthyosis, keratoderma palmoplantaris, epidermolysis bullosa, ectodermal dysplasia, dyskeratosis follicularis, pseudoxanthoma elasticum, neurofibromatosis, tuberous sclerosis, syndromes associated with immune defects, Rothmund Thomson syndrome, Birt-Hogg-Dubé syndrome, Cowden syndrome, and other rare syndromes with cutaneous involvement
Department of Dermatology, Odense	Patient Administrative System	Odense University Hospital Søndre Boulevard 29, 5000 Odense http://www.sdu.dk/om_sdu/institutter_centre/klinisk_institut/forskning/forskningsenheder/open/projekter/op_19+hereditaert+angiooedem+hae See also http://www.haei.org/?q=node/1005/28	Anette Bygum, Dermatologist specialist in genodermatoses Email anette.bygum@hae.dk	National site for diagnosis and treatment of HAE and acquired C1 inhibitor deficiency
Centre for Oral Health in Rare Diseases, Department of Maxillofacial Surgery, (Odontologisk Landsdels og Videncenter, Kaebekirurgisk afdeling), Aarhus	Patient Administrative System	Aarhus University Hospital, Nørrebrogade 44, Building 9D, 2nd floor, 8000 Aarhus C www.odontviden.auh.dk	Center Chief, Hans Gjørup Email hangjo@rm.dk	Center focusing on development and function of the stomatognathic system in children and adults with rare conditions/diseases, eg, ectodermal dysplasia, osteogenesis imperfecta, Ehlers-Danlos syndrome, congenital neuromuscular diseases, hereditary rickets, cleidocranial dysplasia, amelogenesis imperfecta, and dentinogenesis imperfecta
Centre for Rare Oral Diseases (Odontologisk Videncenter), Copenhagen		Odontologisk Videncenter, Rigshospitalet, 5811 Blegdamsvej 9, 2100 København Ø http://www.rigshospitalet.dk/menu/AFDELINGER/Hovedortocentret/Odontologisk+Videncenter/	Center Chief, Jette Daugaard-Jensen Email jette.daugaard-jensen@rh.regionh.dk	Expertise in treatment of ectodermal dysplasia, tooth mineralization disturbances, and tooth eruption anomalies

Table 3 Examples of project-specific data sources established in relation to past research projects, eg, PhD dissertations

Genetic registry (Danish name)	Description	Registration start/end	Data administrator/contact	Other details
Danish Mole Register	Hydatidiform moles, >400 cases	Western Denmark, 1986 to present	Department of Clinical Genetics, Aarhus University Hospital/Lone Sunde Email lonsun@rm.dk	
Katballe cohort (Katballe kohorten)	Cohort of all colorectal cancer (CRC) patients diagnosed in former counties Aarhus, Viborg, Ringkøbing, and Ribe, and relatives to these patients	1995–1998	Departments of Clinical Genetics and Clinical Epidemiology, Aarhus University Hospital Contact person, Charlotte Kvist Lautrup Email cl@dce.au.dk	1657 CRC patients of whom 1200 have filled in a questionnaire regarding number of relatives; more than 10,000 of the relatives have been identified; the database contains information regarding self-reported and verified CRC
FHH and PHPT cohort (FHH/PHPT kohorten)	Familial hypocalciuric hyperecalcaemia (FHH) and primary hyperparathyrodism (PHPT)		Aarhus University Hospital, Signe Engkjær Christensen	66 FHH patients; 147 PHPT patients References: Christensen et al[52] Christensen et al[53]
Borberg NF1 cohort (Borberg kohorten)	212 Danish patients with Neurofibromatosis 1 (NF1)	1924–1944; updated in 1986	Institute for Cellular and Molecular Genetics, Panum Institute, University of Copenhagen Contact person, Sven Asger Sørensen Email svas@sund.ku.dk	76 NF1 probands References: Borberg[38] Sørensen et al[39]
XLHED cohort (XLHED kohorten)	X-linked hypohidrotic ectodermal dysplasia	2007; updated 2012	Department of Clinical Genetics, Aarhus University Hospital, Contact person, Mary Nguyen Nielsen Email mary.n.nielsen@dce.au.dk	91 molecularly confirmed XLHED cases; 146 registered HED cases References: Lexner et al[54] Nguyen-Nielsen et al[42]

Abbreviations: XLHED, X-linked hypohidrotic ectodermal dysplasia; FHH, familial hypocalcuric hypercalcemia; NF1, neurofibromatosis 1; PHPT, primary hyperparathyroidism; CRC, colorectal cancer.

Project-specific data sources (Table 3)

Data from completed PhD dissertations or clinical studies are other important data sources. It is here that many hours of "field work" finding and meeting patients with rare genetic diseases have taken place, and from which future studies can expand upon (see Table 3). The annotated bibliography published by Broeng-Nielsen et al is a historical list of over 600 genetic studies conducted up until 1980. The Danish National Research Database (www.forskningsdatabasen.dk) contains a public list of Danish research projects from which past PhD dissertations can be queried, as well as conference publications and scientific articles.[37] The established projects can be a springboard for future studies, with the advantage of having pre-established patient cohorts.

In 1980, Broeng-Nielsen et al warned about the potential loss of valuable pedigree data upon retirement or death of the principal investigators listed in the bibliography.[3] Data from more than half of the studies listed in this annotated bibliography were stored by individual investigators, many of them close to retirement age. Therefore, the establishment and maintenance of numerous genetic registries over recent decades has had an important role in the conservation of medical genetic data. Owing to this, several Danish genetic registries contain pedigrees and cohorts that span several generations. In the following section, we illustrate project-specific data sources with two examples, ie, the neurofibromatosis 1 cohort and the X-linked hypohidrotic ectodermal dysplasia cohort.

Neurofibromatosis 1 cohort

Neurofibromatosis 1, also known as von Recklinghausen disease, is an autosomal dominant condition with varying clinical manifestations, including characteristic café-au-lait spots in the skin and neurofibromas. The Borberg cohort of patients with neurofibromatosis 1 was established in 1940[38] and reinvestigated in a follow-up study 46 years later. Sørensen et al[39] revisited this established cohort and linked to data from the DCR to follow patients for the development of malignant neoplasms after diagnosis of neurofibromatosis 1. The registry-based approach was also used in the same study to investigate risk factors and survival.

X-linked hypohidrotic ectodermal dysplasia cohort

XLHED is a monogenetic condition affecting the skin, hair, and teeth. Using CPR numbers, data were collected from the relevant clinical departments, the Statens Centrale Odontologiske Register (SCOR) database,[40] the DNRP, and the Civil Registration System.[41] A cohort of 1224 persons was assembled, and population-based prevalence estimates and frequency of clinical features were calculated.[42] Patients with X-linked hypohidrotic ectodermal dysplasia (XLHED) (ie, gene tested and/or clinically diagnosed) were identified by inquiry at the relevant departments. The DNRP and SCOR database were then searched to identify additional cases by finding patients with a clinical diagnosis of XLHED and cardinal features associated with the condition (eg, skin, hair, and teeth disorders). The cohort can be expanded by linking to the Danish Medical Birth Registry to identify additional obligate carriers. This cohort can be used for future studies of disease incidence, mortality, and other outcomes.

Supplemental registries for data linkage and the collection of medical histories (Table 4)

The DNRP,[43] the Civil Registration System,[41] the DCR,[15] the Danish Medical Birth Registry,[32] and the National Pathology Registry[44] are examples of major nationwide medical and administrative registries that can be used as supplemental data sources in epidemiologic studies of genetic diseases (Table 4).

The DNRP is a nationwide patient registry of diagnoses, procedures, and treatments from all hospitals in Denmark. Established in 1977, the DNRP uses the International Classification of Diseases diagnosis codes. Prior to 1994, the ICD-8 was used; from 1994 and onwards, the ICD-10 version has been used. Patients can be identified by the specific ICD diagnosis code, by alternative identification methods (eg, predefined clinical algorithms based on a constellation of diagnoses and/or procedures), or in combination with data on medication use from the Danish Prescription Registry.[45] Further, when linked to the DNRP for inhospital treatment data and/or to the Danish Prescription Registry for redeemed prescriptions, a genetic cohort can potentially be used in comparative effectiveness research to provide evidence on the effectiveness, benefits, and harms of different treatments. One limitation of the DNRP with regard to identifying patients with genetic conditions is that some genetic disorders are not registered with a specific ICD-10 code, but rather with a general ICD-10 code, eg, DZ80.0 (family history of gastrointestinal cancer) or the unspecific ICD-10 Z848 (family history of other specified conditions). This registration practice is used by geneticists to protect patient privacy. Further, family history is likely to be under-reported in the DNRP. Therefore, it is crucial that clinical geneticists or other

Table 4 Supplemental registries for data linkage and collection of medical histories

Genetic registry (Danish name)	Description	Registration start/end	Data administrator/contact	Other details
Danish National Registry of Patients[43] (Landspatient registeret)	Nationwide registration of all hospital admissions, diagnoses, and outpatient contacts	1977 to present, since 1995 includes contacts to emergency rooms and outpatient clinics	State Serum Institute http://www.sst.dk/Indberetning%20og%20statistik/Landspatientregisteret.aspx	Diagnoses registered with ICD-8 from 1977 to 1993 and the ICD-10 from 1994 to present
Civil Registration System[5,41] (Det Centrale Personregister)	Administrative registry of all persons with legal residence in Denmark	April 2, 1968 to present	The Central Office of Civil Registration, Copenhagen http://www.cpr.dk/cpr/site.aspx?p=194&ArticleID=4327	Variables include the personal identification number of parents and their children, date of birth, gender, vital status, marital status, profession, place of birth, and others
Danish Cancer Registry[15,17] (Cancerregisteret)	Registration of all incident solid tumor cancers	1943 to present; mandatory reporting since 1987	State Serum Institute http://www.ssi.dk/Sundhedsdataogit/Registre/Cancerregisteret.aspx	From 1943 to 2003 tumors were classified with ICD-7; since 1994, classification with ICD-10
Danish Medical Birth Registry[32] (Fødselsregisteret)	Peripartum data on all children born in Denmark	1973 to present (electronic reporting directly to DNRP since 1995)	State Serum Institute http://www.ssi.dk/Sundhedsdataogit/Registre/Fodselsregister.aspx	Variables include gender, birth weight, gestational age, birth length, Apgar score, and maternal variables such as parity, smoking status during pregnancy, and others
National Registry of Congenital Abnormalities[29,30] (Misdannelsesregistret)	Congenital malformations detected during first year of life, stillborn with congenital malformations and late miscarriages (>12 gestational weeks)	1983 to present (electronic reporting directly to DNRP since 1995)	State Serum Institute http://www.ssi.dk/Sundhedsdataogit/Registre/Misdannelsesregister.aspx	Diagnoses of congenital malformations, which were specified by the Danish Health and Medicines Authority. More specific and detailed than the ICD-diagnosis codes
National Fetal Medicine Database[33] (National Føtalmedicinsk Database; FØTOdatabasen)	Prenatal ultrasound examinations	January 1, 2006 to present, nationwide since 2008	Center for Fetal Medicine and Pregnancy, Department of Obstetrics, Rigshospitalet, Copenhagen Contact person, Ann Tabor Email Ann.Tabor@regionh.dk http://www.dfms.dk/foetodata.shtml	Over 260,000 prenatal registrations, eg, first trimester ultrasound scans and biomarker diagnostics; second trimester malformation scans with ICD-10 registration of congenital malformations; linked to the DCCR (for data on perinatal chromosomal analyses), DNRP, and DMBR
Danish Twin Registry[55] (Det Danske Tvillingregister)	Multiple pregnancies	1870 to 2008, nationwide	National Institute of Public Health, University of Southern Denmark, Odense Email tvilling@health.sdu.dk http://www.sdu.dk/en/Om_SDU/Institutter_centre/Ist_sundhedstjenesteforsk/Centre/DTR	>80,000 twin pairs registered. Variables include pedigree data from church books and Civil Registration System registry; data on lifestyle, cause of death, patient questionnaires, clinical examinations, and interviews

Danish Cerebral Palsy Registry[56] (Cerebral Parese Registret)	Cerebral palsy	1965 to present, nationwide since 1995	National Institute of Public Health, University of Southern Denmark, Odense http://www.si-folkesundhed.dk/Forskning/Generelt%20om%20forskning/Registre%20og%20follow-up%20studier/Cerebral%20Parese%20Registret.aspx	Variables include type and severity, type of functional handicaps, treatment, data on mother and case pertaining to pregnancy, birth, and postnatal period
SCOR Database[40] (Sundhedsstyrelsens Centrale Odontologiske Register)	Children's dental health status	1972 to present, nationwide	Danish Health and Medicines Authority http://www.sst.dk/publ/publ1999/indb_tandpleje/indhold.html	Variables include teeth eruptions, missing teeth, and caries status
Danish National Pathology Registry[44] (Patobank)	Reports of all pathological examinations conducted in Denmark	1997 to present	Danish Health and Medicines Authority http://www.sst.dk/publ/Publ2011/DOKU/FaellesindhBasregPatoAnatUs.pdf and http://www.patobank.dk/	Includes some incomplete data prior to 1997
Danish Newborn Screening Biobank and Registry[6] (Den Neonatale Screenings Biobank/ Phenylketonuria biobank)	Phenylketonuria	1982 to present, nationwide	State Serum Institute Contact person; David Haugaard www.ssi.dk See also the Danish National Biobank http://www.biobankdenmark.dk/The%20Biobank%20Register/More%20about%20Biobank%20Register.aspx	Approximately 1.9 million neonatal blood samples to date

experts are consulted about the coding/registration practices for a particular genetic condition. For a number of genetic disorders, querying the DNRP should be supplemented with accessing data from the departments of clinical genetics or other specialized centers (see Table 2).

The National Pathology Registry[44] (www.patobank.dk) is a registry of histological examinations reported by pathologists. Data have been collected since 1997. Variables include (but are not limited to) histological specimens, procedures, and diagnoses (primarily topography and morphology, but other features may also be registered). Diagnoses are coded using the International Systemized Nomenclature of Medicine. The National Pathology Registry is a potential source of data for conditions diagnosed by histopathological examination, such as cancers and genodermatoses.

The Civil Registration System is an administrative registry that provides up-to-date information on age, gender, region of residence, vital status, parent/child relationships, and other variables, including the CPR number.[5,41] The Civil Registration System has data on every person who has legally resided in Denmark since April 1968. The CPR number enables linkage of data from multiple registries, and thereby the collection of data at the individual and familial levels, unambiguously and without double-counting. Data in the Civil Registration System is virtually complete, eg, vital status is updated electronically on a daily basis.

In addition to the previously mentioned data sources (ie, the Civil Registration System and the Danish Medical Birth Registry), church book archives are also potential sources for identifying relatives and pedigrees. Finally, Statistics Denmark (www.dst.dk), which includes StatBank Denmark (www.statbank.dk), contains descriptive statistical information on the Danish society, including data on household/families and children.

Danish research setting

Access to Danish registry data and data linkage requires authorization by the Danish Data Protection Agency (Datatilsynet) and in some cases, additional authorization from the Danish Health and Medicines Authority, typically when medical charts are to be accessed,[46] and/or authorization from the National Committee on Health Research Ethics (Den Nationale Videnskabsetiske Komité) if biological specimens are to be used or if living persons are to participate in clinical studies. The Danish privacy laws on the use of personal data are stipulated in The Act on the Processing of Personal Data (Act Number 429; May 31, 2000).[47,48]

As a general rule, the results of statistical analyses may be published or publicly released in an aggregated form such that individuals remain nonidentifiable. Otherwise, public release of any individual data (ie, data that can lead to identification of an individual) requires explicit consent from that person. For further information on Danish privacy laws and online application for authorization to access registry data, visit the Danish Data Protection Agency homepage (http://www.datatilsynet.dk).

Once authorization for data access has been granted by the Danish Data Protection Agency, data can be obtained after approval and release by the individual registry administrators. For the national registries housed at the Danish State Serum Institute (Statens Serums Institut), an application for data release must be filed at the research service unit of this institute (Forskerservice, at http://www.ssi.dk/Sundhedsdataogit/Forskerservice.aspx).

Scientists in other European Union countries are subject to the same guidelines and procedures for data access as scientists in Denmark (described above). Release of registry data to non-European Union countries may require further evaluation by the Danish Data Protection Agency in order to ensure sufficient data security and handling in accordance with Danish law. Detailed information on the application procedure for data access for researchers outside Denmark can be found at the Danish Data Protection Agency homepage (http://www.datatilsynet.dk/erhverv/tredjelande/overfoersel-til-tredjelande/).

Conclusion

There is a wealth of existing medical data sources on genetic diseases in Denmark. The ability to link and collect data at both the individual and familial levels allows for rapid identification of relevant study subjects/families and the collection of comprehensive medical histories spanning from time of birth to death. The Danish collection of medical registries is a valuable resource for genetic epidemiology and comparative effectiveness research, both in and outside of Denmark.

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Disclosure

The authors declare no conflicts of interest in this work.

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