

Phenotypic spectrum in uniparental disomy: Low incidence or lack of study?

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CONTEXT: Alterations in the human chromosomal complement are expressed phenotypically ranging from (i) normal, via (ii) frequent fetal loss in otherwise normal person, to (iii) sub-clinical to severe mental retardation and dysmorphism in live births. A subtle and microscopically undetectable chromosomal alteration is uniparental disomy (UPD), which is known to be associated with distinct birth defects as per the chromosome involved and parental origin. UPD can be evident due to imprinted genes and/or activation of recessive mutations.

AIMS: The present study comprises of data mining of published UPD cases with a focus on associated phenotypes. The goal was to identify non-random and recurrent associations between UPD and various genetic conditions, which can possibly indicate the presence of new imprinted genes.

SETTINGS AND DESIGN: Data mining was carried out using the homepage "http://www.fish.uniklinikum-jena.de/UPD.html," an online catalog of published cases with UPD.

MATERIALS AND METHODS: The UPD cases having normal karyotype and with or without clinical findings were selected to analyze the associated phenotypes for each chromosome, maternal or paternal involved in UPD.

RESULTS: Our results revealed many genetic conditions (other than the known UPD syndromes) to be associated with UPD. Even in cases of bad obstetric history as well as normal individuals chance detection of UPD has been reported.

CONCLUSIONS: The role of UPD in human genetic disorders needs to be studied by involving larger cohorts of individuals with birth defects as well as normal population. The genetic conditions were scrutinized in terms of inheritance patterns; majority of these were autosomal recessive indicating the role of UPD as an underlying mechanism.

Key words: Autosomal recessive, birth defects, data mining, phenotypic expression, uniparental disomy

Introduction

The causative role of chromosomal anomalies in patients with inherited disorders is well-established. In addition to the known syndromes, there are other genetic conditions involving a large number of microscopic (structural and numerical karyotypic anomalies) as well as submicroscopic genetic alterations. The submicroscopic anomalies include micro deletions, point mutations, genomic imprinting and uniparental disomy (UPD). UPD can either be maternally or paternally derived. The concept of UPD was initially introduced by Eric Engel in 1980,^[1] the experimental evidence was obtained when UPD(7)mat was demonstrated in a cystic fibrosis patient.^[2] This was followed by more reports of UPD in other syndromes such as Angelman syndrome (AS), Prader Willi syndrome (PWS), Beckwith-Wiedemann syndrome (BWS) or Silver Russel-syndrome (SRS) and were non-random enough to have diagnostic implications.^[3]

Studying the role of UPD in a disease phenotype is complex due to various factors. First, it has been observed that even in well-defined syndromes [Table 1] the incidence of UPD along with a disease phenotype is 2-5% in AS, 25% in PWS, 20% in BWS, and 5% in SRS.^[4] Second, based on the chromosome involved in paternal or maternal UPD, the phenotypic manifestation varies, ranging from normal, multiple abortions, mental

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retardation and certain syndromes that are not reported to be solely due to the UPD [Table 2].

Materials and Methods

This data mining study was carried out using freely available and regularly updated online database of all published UPD cases.^[5] The main focus of this study was to know the extent of genetic conditions that are associated with UPD in addition to those, which are clinically diagnosed in terms of specific chromosomal UPD [Table 1]. The cases with a normal karyotype were selected and those with microscopic chromosomal aberrations were excluded in order to focus on the occult chromosomal aberrations [Figure 1].

Results

The reports of cases as per the inclusion criteria mentioned above, i.e., more than 170 (out of about 670) were analyzed for the phenotypic expression, chromosome involved in UPD in terms of maternal or

paternal origin and related information. In addition to the known UPD related syndromes [Table 1], many other genetic conditions were also associated with UPD [Table 2] in addition to non-specific and unclear phenotypes in about 18 reports, which suggest wide ranging role of UPD. The role of Robertsonian translocations is known in multiple abortions; however, there have also been by chance findings of UPD in cases of bad obstetric history.^[6] The presence of UPD in normal individuals detected by chance, for example while paternity testing^[7] suggests that the frequency of UPD in human population may not be as rare as perceived. The inheritance pattern of majority of the disease conditions was found to be autosomal recessive as queried using Online Mendelian inheritance in Man.

Discussion

A number of genes are found to be imprinted either for paternal or maternal chromosomal origin.^[8] UPD can result in disease mainly if it affects an imprinted gene, i.e., the expression of which is dependent on the parent of origin due to either heterodisomy (inheritance of both the chromosomes from one parent) or isodisomy (inheritance of two copies of the same chromosome from single parent).^[9] UPD can also facilitate expression of recessive mutation by loss of wild type allele due to the absence of other parental

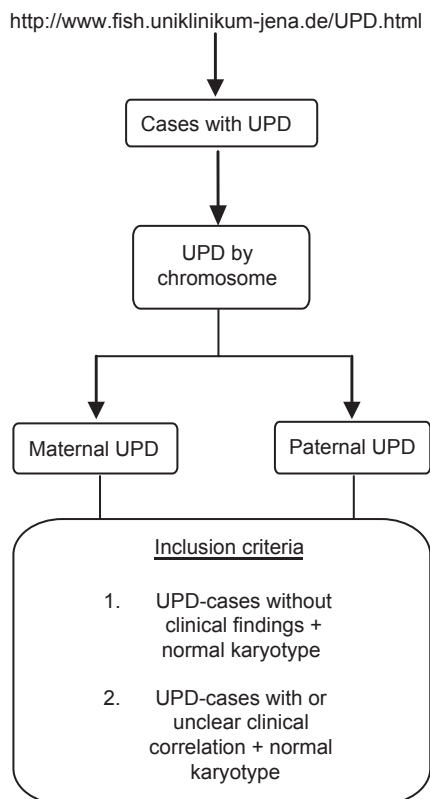


Figure 1: Data mining strategy

Table 1: Syndromes diagnosed using UPD analysis in clinical set-up

Parental origin and chromosome	Syndromic condition
mat UPD (6)	Transient neonatal diabetes (TND; OMIM #601410)
mat UPD (7)	Silver Russell syndrome (SRS; OMIM #180860)
pat UPD (11)	Beckwith-Wiedemann syndrome (BWS; OMIM #130650)
mat UPD (11)	Silver Russell syndrome (SRS; OMIM #180860)
mat UPD (14)	Temple syndrome (TS; OMIM*605636 and #176270)
pat UPD (14)	Paternal UPD (14) syndrome (pat UPD (14); OMIM #608149)
mat UPD (15)	Prader Willi syndrome (PWS; OMIM #176270),
pat UPD (15)	Angelman syndrome (AS; OMIM #105830).
mat UPD (20)	Maternal UPD (20) syndrome (n.a.; OMIM n.a.)
pat UPD (20)	Pseudohypoparathyroidism (PHP; OMIM #103580, #603233, #612462)

UPD: Uniparental disomy, OMIM: Online Mendelian Inheritance in Man

Table 2: Chromosome wise genetic conditions (number of cases in curly brackets) from the reports of UPD with normal karyotypes

Chromosome number	Genetic conditions
1	Herlitz JEB (mat UPD) {2}, Herlitz JEB (pat UPD) {2}, Maple syrup urine disease types 2 (mat UPD) {1}, pycnodysostosis (pat UPD) {1}, congenital insensitivity to pain with anhidrosis (pat UPD) {2}, Usher syndrome type II and Retinitis pigmentosa (pat UPD) {1}, Fumarase deficiency (pat UPD) {1}, Stargardt disease (pat UPD) {1}, Charcot-Marie-Tooth and Gaucher disease type 3 (pat UPD) {1}, retinal degeneration (pat UPD) {1}, Rhizomelic chondrodysplasia punctata (pat UPD) {1}, Complement factor H deficiency and endocapillary glomerulonephritis (pat UPD) {1}, Zellweger syndrome (mat UPD) {1}, Hutchinson–Gilford progeria syndrome (mat UPD) {1}, Complement membrane cofactor protein-associated hemolytic-uremic syndrome (pat UPD) {1}
2	Harlequin ichthyosis (pat UPD) {1}, Congenital hypothyroidism (mat UPD) {2}, Steroid 5 α -Reductase 2 Deficiency (pat UPD) {1}, Infantile-onset ascending spastic paralysis (mat UPD) {1}, Trifunctional Protein deficiency (mat UPD) {2}, Primary congenital glaucoma (par UPD) {1}, Lethal surfactant Protein-B deficiency (mat UPD) {1}, Familial male-limited precocious puberty (mat UPD) {1}, Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (pat UPD) {1}, Donnai-Barrow syndrome (pat UPD) {1}, Crigler-Najjar syndrome type I (pat UPD) {1}
3	Hallopeau–Siemens recessive dystrophic epidermolysis bullosa (mat UPD) {2}, congenital disorder of glycosylation type Id (mat UPD) {1}, Fanconi-Bickel syndrome (mat UPD) {1}, Pierson syndrome (pat UPD) {1}
4	congenital afibrinogenemia (mat UPD) {1}, Limb-girdle muscular dystrophy (mat UPD) {1}, Autosomal dominant polycystic kidney disease (mat UPD) {1}
5	Netherton syndrome (mat UPD) {1}, homocystinuria cblE type (pat UPD) {1}, Type III spinal muscular atrophy (pat UPD) {1}
6	Intrauterine growth retardation (mat UPD) {2}, 3M syndrome (pat UPD) {1}, 3M syndrome with intrauterine growth retardation (mat UPD) {1}, isolated complete deficiency of the fourth component of complement with systemic lupus erythematosus (pat UPD) {1}, Mendelian susceptibility to mycobacterial disease (pat UPD) {1}, Spinocerebellar ataxia type 17 (origin unclear) {1}
7	Cystic fibrosis (mat UPD) {4}, Cystic fibrosis (pat UPD) {3}, Primary ciliary dyskinesia (pat UPD) {2}, Developmental verbal dyspraxia with SRS (mat UPD) {7}, Becker congenital myotonia (mat UPD) {2}, Col alpha 1 mutation (mat UPD) {1}
8	Lipoprotein lipase deficiency (pat UPD) {1}, Late-infantile-onset forms of neuronal ceroid lipofuscinosis (mat UPD) {1}, Asperger syndrome (pat UPD) {1}
9	Cartilage-hair hypoplasia (mat UPD) {2}, Leigh syndrome (mat UPD) {2}, Syndromic Congenital Hypothyroidism due to FOXE1 mutation (mat UPD) {2}
11	Congenital hyperinsulinism (pat UPD) {4}, Sickle cell disease (pat UPD) {1}, Jacobsen syndrome (mat UPD) {1}
12	Von Willebrand disease type 3 (mat UPD) {1}
13	Prelingual hearing impairment due to mutation in connexin26 (mat UPD){4}, Autosomal recessive spastic ataxia of Charlevoix-Saguenay (pat UPD) {1}, propionic acidemia (mat 13) {1}
14	Alpha 1-antitrypsin deficiency (mat UPD) {1}
16	Fatal malonyl CoA decarboxylase deficiency (mat UPD) {1}, Hb Bart's hydrops fetalis (mat UPD) {1}, Lethal ABCA3 deficiency (pat UPD) {1}, Unusual phenotype of macular corneal dystrophy (mat UPD) {1}, Adenine phosphoribosyl transferase deficiency (mat UPD) {1}, PMM2 gene related congenital defect of glycosylation (mat UPD) {1}, Morquio A syndrome (mat UPD) {1}
17	Nephropathic cystinosis (mat UPD) {1}, Junctional epidermolysis bullosa with pyloric atresia (pat UPD) {1}
22	Recessive congenital methemoglobinemia (mat UPD) {1}, infantile neuroaxonal dystrophy (mat UPD) {1}

UPD: Uniparental disomy

chromosome. The clinical diagnosis of certain syndromes is based on the detection of UPD [Table 1]; however, there are a number of UPD reports; maternal or paternal [Table 2] in various disease conditions as well as normal individuals detected mainly by chance. A larger population study of whole chromosome or segmental UPD affecting these genes may provide important clues regarding contribution of UPD as a mechanism of pathogenesis in recessive genetic conditions mainly.

Isodisomy of a chromosomal region bearing heterozygous recessive mutation leads to homozygosity and hence disease condition. The data mining exercise indicated that the majority of the disease conditions were due to the isodisomy of autosomal recessive

mutations. Prenatal molecular diagnosis in such cases can be suggested if an isodisomy affecting the disease causing recessive mutation is detected. As highlighted by Chediak-Higashi syndrome, in case of this kind of disease causing mechanism imprinting does not play a role. It is just activation of a recessive gene and not related to any imprinting defect!

Summarizing, the range of phenotypes associated with UPD of a chromosome, i.e., maternal or paternal is wide and needs to be comprehensively studied with larger cohorts. Such studies can bring to light the extent of correlation of UPD, genomic imprinting, mechanisms favoring expression of recessive mutations and associated phenotypes. These studies involving

whole genome scanning in terms of single nucleotide polymorphism arrays in various unclassified birth defects and even normal population can be informative.

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