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Estimating the proportion of rare diseases with a prenatal phenotype: a computational approach

Céline Chantry-Darmon, Carolina Fabrizzi, Rémi Besson, Caterina Lucano, Guillaume Corda, Nicolas Fries, Asma Khalil, Richard Kwong Wai Choy, Julien Stirnemann, Ana Rath, Yves Ville.

Introduction

Rare diseases affect more than 300 million people worldwide. Early detection is crucial to implementing appropriate interventions and improving outcomes for patients. This collaborative European project, named ERDERA aims to enhance the Human Phenotype Ontology (HPO) by incorporating a more comprehensive dataset of echographic clinical signs and to enrich the Orphanet database by annotating prenatal diseases with these terms.

Results

From the first step, out of the 6,434 syndromes listed in Orphanet, we obtained 860 syndromes with a prevalence greater than 1/1 million, 471 of which were identified as accessible to fetal ultrasound by fetal medicine experts. In the second step, a total of 185 “purely congenital” malformations were identified enabling us to obtain 1,620 syndromes with prenatal phenotypes, including 1,110 additional syndromes to study (9% with a prevalence > 1/1 million). Of the 1,620 rare diseases with a prenatal phenotype, 1,179 are not listed as ‘prenatal’ in the Orphanet database, 551 have no biological or molecular diagnosis, and 392 are not heritable or have an unknown mode of transmission.

Methods

As a first step, we selected syndromes, from Orphanet database, whose age of onset was “antenatal”, “neonatal” or “childhood” and the key text words “fetal” or “ultrasound”. In a second step, we worked with experts in the field to draw up a list of “purely congenital malformations”, i.e. malformations whose symptoms cannot have appeared after foetal life. We then filtered the Orphanet data to retain syndromes with at least one purely congenital malformation.

Conclusion

In this study, we show that many prenatal rare diseases are still poorly characterised and cannot be diagnosed molecularly. Combined diagnostic approaches involving genotyping and phenotyping therefore remain essential. By refining the prenatal phenotype of rare diseases and providing experts with a set of standardized clinical signs detectable via fetal ultrasound, this work aims to facilitate earlier and more accurate diagnoses, enabling better therapeutic decisions and pre/ postnatal care strategies.

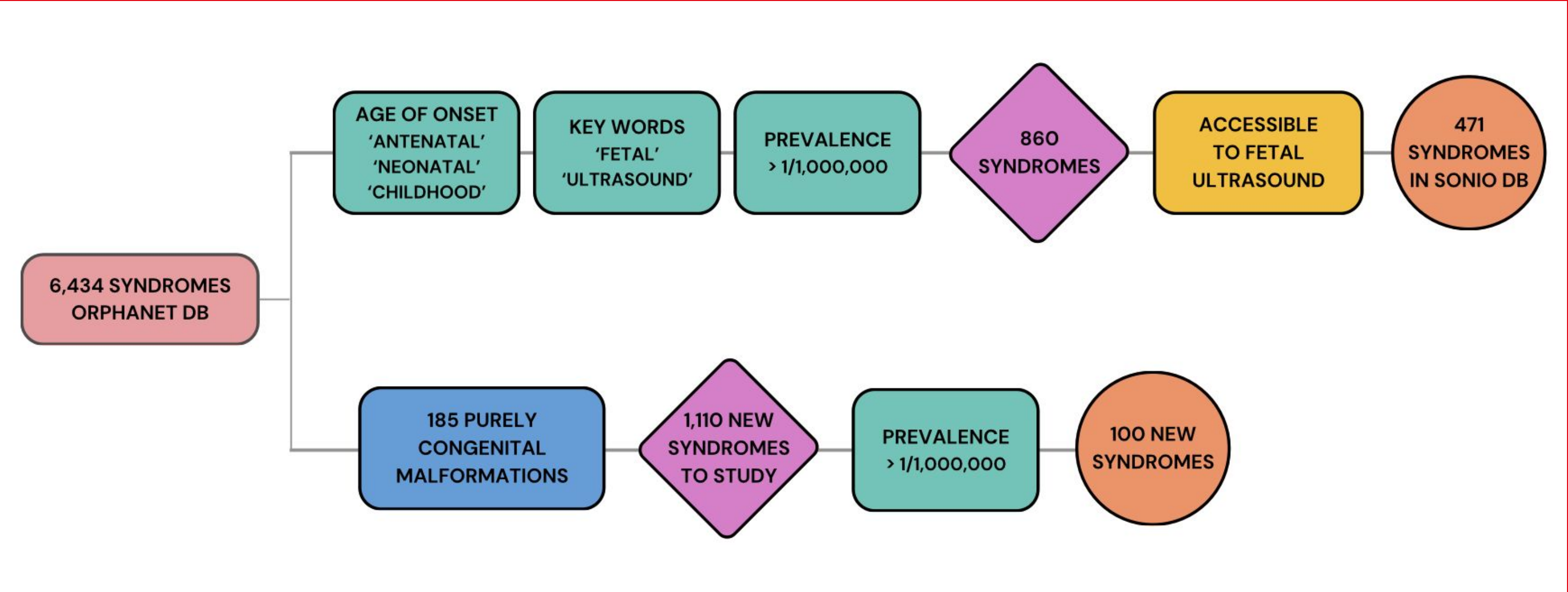


Figure 1. Flowchart of the syndromes selection process

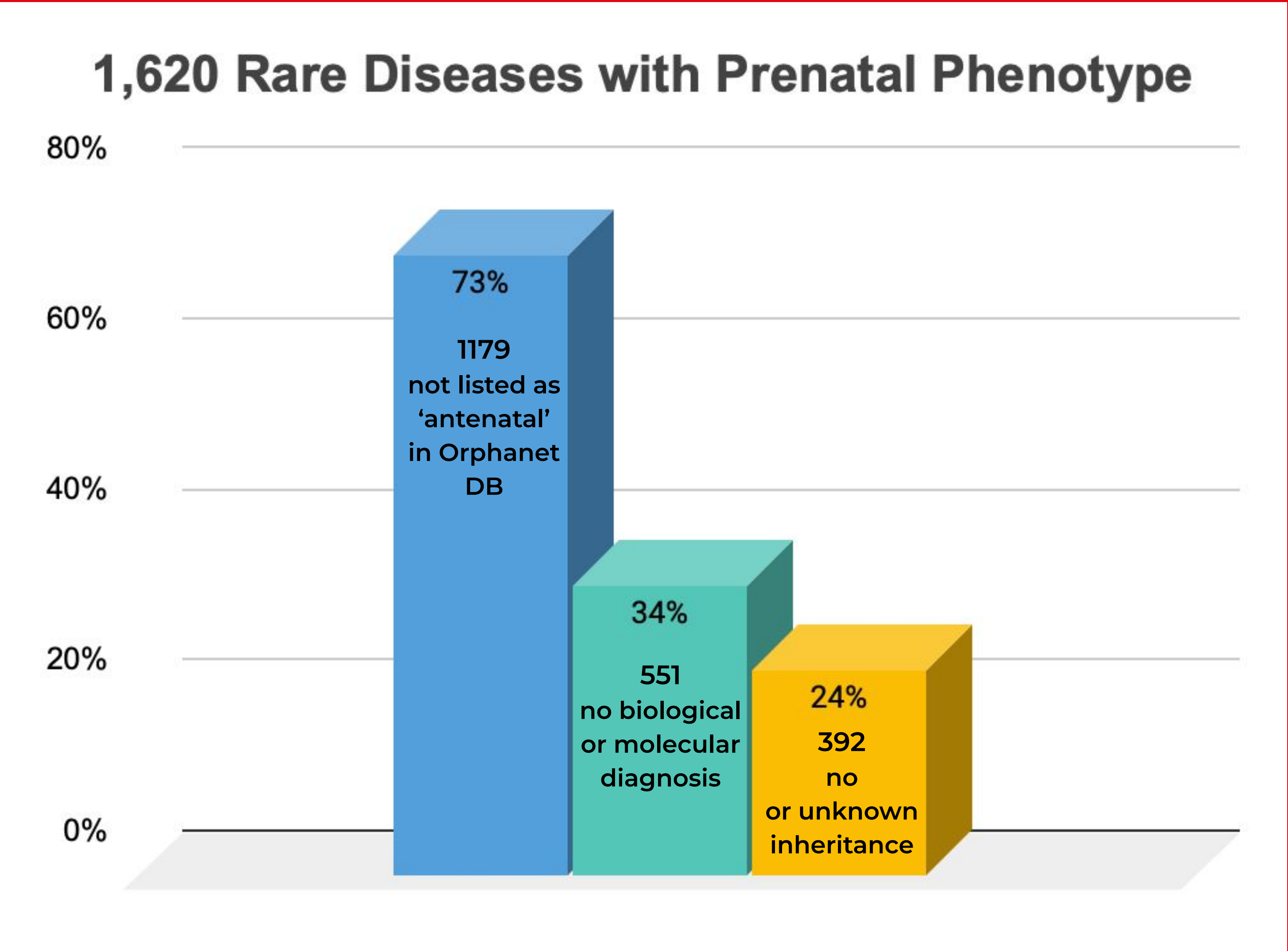


Figure 2. Analysis of rare diseases with purely congenital clinical signs