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The smallest of the small

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ABSTRACT

Microcephalic Osteodysplastic Primordial Dwarfism (MOPD) II has recently been defined as a PCNT gene defect. Historically, it has been a disorder of interest because of the severe intrauterine growth restriction and postnatal short stature. The very shortest/smallest mature human being undoubtedly had this disorder. Maria Zarate lived between 1864 and 1890 and traveled in sideshows to England and all over North America. Her exceeding short stature was well documented in photographs and by a group of physicians in England. She was Mexican and also had an affected brother. A museum, Museo Casa Grande, about her still exists in Cempoala, Mexico.

1. Introduction

Throughout history, human beings have been fascinated with extremes—the stuff of myths and legends. In the 19th and early 20th century, the unusual physical features of humans and animals became the basis of side shows and circuses. More recently, Guinness World Records have documented extremes and record breaking events. So, of course, as molecular genetics identifies responsible genes and pathways, there is excitement about determining the basis of unusual human disorders. One such condition is the smallest of the small—Lucia Zarate is the person who is said to be the shortest and smallest human being ever documented to reach maturity.

2. Historical information

Lucia was born in San Carlos Mexico in 1864. Reportedly, Lucia weighed only 8 oz and was 7 in. long at birth. At maturity, she was 20 in. (51 cm) tall and no more than 5 lb (smaller than the average newborn)—reportedly 4.7 lb (2.1 kg) at the time she was entered into the Guinness World Record at the age of 17 years when she was a sexually mature woman.

At the age of 12 years, Lucia moved from the Veracruz area of Mexico to the United States to be part of the circus/sideshow/exhibition appearances of the time. Apparently, according to a fact book published by Oxford University, in 1876 (when she would have been 12 years old), she was visited by several medical professionals who could not certify that she was 12 years old (theoretically, because she didn't have her 12 year old molars yet), but they could ascertain that she was at least 6 years old (again, theoretically because she did have her 6 year old molars) (Fig. 1). Paranthatically, bone and dental age are delayed in the condition that Lucia is thought to have had and the teeth are often disproportionately small or missing. At that time, she was found to be healthy, animated, and intelligent, and was declared to be normal in form. She spoke her native Spanish and had also learned some English. She had an outgoing personality (Drimmer, 1973).

Lucia toured with the Barnum Circus around North America and throughout Europe. Apparently, she appeared before Queen Victoria and the Royal Family in 1881. Since she was so small, she was an enormous attraction and drew large crowds wherever she appeared. She worked for 14 years and was paid well for those times, earning as much as $20/h. She was accompanied by her father, an interpreter, and an attendant.

Lucia's career came to an end in 1890 at age 26 years when traveling over the Sierra Nevada on the way to an engagement in San Francisco. The circus train on which she was traveling became stalled in heavy snow near Truchee, California and could not be mobilized for a whole week. She died of hypothermia. Her small body was taken back to Mexico and buried in a cemetery on the family ranch in Cempoala (http://en.wikipedia.org/wiki/Lucia_Zarate). Today there is a museum

Abbreviations: ASPM asp, (abnormal spindle) homolog, microcephaly associated (*Drosophila*); ATR, ataxia telangiectasia and Rad3 related; CENP, centromere protein; CDK5RAP2, CDK5 regulatory subunit associated protein 2; cm, centimeter(s); CNS, central nervous system; Fig, Figure; IUGR, intrauterine growth restriction; LPA, Little People of America; MCPH2, microcephaly 2, primary autosomal recessive with or without cortical malformations; MOPD, microcephalic osteodysplastic primordial dwarfism; PCNT, pericentrin.

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Fig. 1. The poster advertising Lucia Zarate's exhibition during a tour in 1889 at 15 years of age.

there recording her history and her life (http://casagrande-museo.blogspot.ca/).

There appears to be a family history of another affected child. Some reports indicate that Lucia's parents had several children and one of them was a very small brother named Manuel who died in Monterrey a few years before Lucia. This would be consistent with the autosomal recessive nature of MOPD II.

Photographs from many sources show a characteristic prominent nose, a relatively proportionate body, and a slightly small head (Fig. 2). It seems very likely that she had a disorder which has become known as MOPD II. She was described as cheerful and loquacious and beloved by the circus troupe with whom she traveled.

In 1982, Frank Majewski attempted to distinguish various types of severe short stature. He called them Microcephalic Osteodysplastic Primordial Dwarfism (MOPD), implying they were affected individuals who had small head circumference, abnormal bone growth, and prenatal onset of short stature. He distinguished three types (Majewski and Goecke, 1982; Majewski et al., 1982a,b) and subsequently it was suggested that the first and third were the same disorder which evolved with aging, and also had more severe microcephaly and mental retardation, and ended up with taller height, so could be distinguished from MOPD II. Several reports of MOPD II subsequently appeared in the medical literature. It even appears that one of the Seckel's bird headed dwarfs in his original publication had MOPD II (Hall et al., 2004).

3. Delineation of the features of MOPD II

In the mid-1990s, the Little People of America (LPA—a support group for individuals less than 4′10″ in height) attracted a number of families with children who had severe proportionate short stature of prenatal onset. These families gravitated together at the annual conferences as did their affected children and they requested information from the medical advisory group of LPA about the natural history of their children's condition. For that reason, review of the medical literature was undertaken as well as a review of affected individuals known to the medical advisory board. The summary was published in 2004 and provided growth curves, physical features, and natural history (Hall et al., 2004).

The features identified were: severe intrauterine growth retardation (IUGR), severe postnatal growth retardation; relatively proportionate head size at birth which progresses to true and disproportionate microcephaly; progressive disproportion of the short stature secondary to shortening of the distal and middle segments of the limbs; a progressive

Fig. 2. A photograph taken at an older age when her facial features, prominent nose, and small head become more obvious.

bony dysplasia with metaphyseal changes in the limbs; epiphyseal delay; progressive loose-jointedness with occasional dislocation or subluxation of the knees, radial heads, and hips; unusual facial features including a prominent nose, eyes which appear prominent in infancy and early childhood, ears which are proportionate, mildly dysplastic and usually missing the lobule; a high squeaky voice; abnormally, small, and often dysplastic or missing dentition; a pleasant, outgoing, sociable personality with near normal intellect; and autosomal recessive inheritance. Far-sightedness, scoliosis, unusual pigmentation, and truncal obesity often develop with time. A number of affected individuals have developed dilation of the CNS arteries variously described as aneurysms and Moya Moya disease. These vascular changes can be life threatening, even in early years because of rupture, CNS hemorrhage, and strokes. There was recognized to be variability between affected individuals even within the same family (Hall et al., 2004).

In this summary, no adult was taller than 100 cm and most were much shorter, but above 60 cm. Thus, Lucia would be one of the very smallest of the known affected individuals (Hall et al., 2004). However, it is likely coming from the country side of Mexico. Her mother's nutrition would have been poor by today's standards and possibly compounded her short stature.

4. Molecular studies

In 2008, Rauch et al., and subsequently, Griffith et al. (2008) identified mutations in the centrosomal pericentrin (PCNT) gene on chromosome 21q.22.2 as responsible for MOPD II. Other related genes were known to cause microcephaly (MCPH2, CDK5RAP2, ASPM, CENP), but not to cause the severe short stature and relatively spared intelligence seen in MOPD II.

Subsequent studies by Willems et al. (2010) conclude that PCNT mutations cause the specific MOPD II phenotype and not the true Seckel syndrome phenotype. Pericentrin is a highly conserved centrosome protein involved in microtubule organization. It is localized to the pericentriolar material and is necessary for ATR-dependent check point signaling.

In 2012, Bober et al. produced growth curves for 26 PCNT mutation positive cases of MOPD II and provided a nice confirmation of the 2004 paper which had been based on 58 with a clinical diagnosis of MOPD II. Indeed, one of the PCNT mutation positive individuals was only about 60 cm tall at 15 years—a similar height to Lucia.

It is interesting to reflect that it took over 100 years, modern medical genetics and modern molecular biology to identify the underlying biology leading to Lucia's short stature.

Conflict of interest

The authors declare no conflict of interest.

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