

COMMENTARY

Growth Hormone Receptor Deficiency in South America: Colonial History, Molecular Biology, and Growth and Metabolic InsightsArlan L. Rosenbloom^{1,2} and Jaime Guevara-Aguirre^{1,2}¹*Division of Endocrinology, Department of Pediatrics,
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On March 31 1492, King Ferdinand and Queen Isabella of Spain issued the edict of expulsion to the Jews, following a century of unbearable persecution, beginning with massacres in 1391 and proceeding to the establishment of ghettos in which Jews were locked in and guarded at night, were excluded from a variety of professions and trades, and were required to wear distinctive yellow garments. To escape from this oppression, many became conversos, i.e. baptized as Catholics, such that conversos eventually outnumbered Jews in Spain and they returned to the professions and trades, rising to important positions. By the start of the Inquisition in 1481, conversos accounted for half of the key positions in the court of Aragon.

While the edict of expulsion did not require conversos to leave, a decade of experience with an Inquisition directed against conversos denounced for being secret Jews, an accusation which could be a brutal shortcut to resolving a debt, a rivalry in court, or an argument, told conversos that conversion could not be depended on to protect them. Along with the Jews, many chose exile in North Africa, other Mediterranean areas, or The Netherlands, or they crossed the border to Portugal where Jews were forcibly converted to Christianity 5 years after the edict and the Inquisition soon followed.

Continued oppression motivated immigration to the New World, where it is estimated that one-third

of early Spanish immigrants were conversos. The historical record indicates immigration of conversos to southern Ecuador in the early 1500s, where they sought the protection of isolation in remote Andean loci and had a high degree of consanguinity, reflected in their limited repertoire of typical converso names.

It was in this area that Guevara-Aguirre discovered, and with his colleagues, beginning in 1989, studied the world's largest population of individuals with growth hormone receptor deficiency (GHRD)¹. This condition was originally described in 1966 by Laron, Pertzalan, and Mannheimer in Oriental Jewish immigrants in Israel². The Ecuadorian population was not only unique in its size, eventually comprising approximately one-third of all individuals with GHRD (~75), but the only large population with a single GHR mutation. The other large geographically concentrated population, in Israel, is genetically heterogeneous. Among the 250 or so affected individuals identified worldwide, approximately two-thirds are Semitic and half of the rest of Mediterranean or South Asian origin. Among approximately half of those outside Ecuador whose GHR defect has been identified, over 40 mutations have been found. These are family specific with the few exceptions representing mutational hotspots, occurring in geographically disparate populations and on different genetic backgrounds.

When Berg *et al.*³ originally described the E180 splice mutation in the Ecuadorian cohort, it was thought that this represented a new mutation and founder effect in a highly inbred population permitting recombination. Subsequently, an Israeli patient of Moroccan origin was identified by Berg

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and Francke⁴ with the 'Ecuadorian mutation', indicating that the mutant GHR gene was brought to Ecuador from Iberia by the founder. Given the history of Spanish Jewish/converso migration, either directly to South America or initially to Portugal, it is not surprising that the E180 splice mutation would appear with a common genetic background in Israel, Ecuador, Chile⁵, and Brazil⁶. In this regard, it should be noted that the reference in the paper by Espinosa *et al.*⁵ to occurrence of the E180 splice mutation "in Israeli patients of Yemeni origin" is inaccurate. There has only been one such individual identified who is, as noted above, of bilateral Moroccan origin.

These fascinating genetic relationships await studies of cultural anthropology of the affected groups, including examination of the 16th century emigration records said to still exist in Spain and Portugal.

One of the advantages of having a large genetically homogeneous population with GHRD is the opportunity to appreciate the variability of effects of severe GH insensitivity without the confounding factor of heterogeneity for the specific mutation responsible. Nonetheless, we have noted among 25 adult (23+ years) Ecuadorians affected, wide variability of statural effect, from -12 to -5.3 SDS, a range of 6.7 SD, greater than in 16 other adults reported (-9 to -3.8 SDS, range 5.2 SD), and emphasizing the relative short stature of the Ecuadorian population. The mean SDS difference between the homogeneous Ecuadorian (-9.1) and heterogeneous other affected adults (-5.8) was highly significant ($p < 0.0001$)⁷. The two 18 year-olds among the six Brazilian patients with the E180 splice mutation have height SD scores of -6.4 and -7.8, well within the range among the affected Ecuadorians. The adult female in the report of Espinosa *et al.*⁵ is said to have a height SDS of -5.5, but calculation using US National Center for Health Statistics (NCHS) reference data gives a different score of -4.35, quite similar to that for her brother who attained a height at -3.93 SDS (re-calculated using NCHS reference data to be as reported), following several years of adolescence suppression and rhIGF-I treatment. While his relatively tall stature for individuals with the E180 splice mutation might be explained by treatment,

hers cannot be, and heights of unaffected family members are similar to those seen in the unaffected relatives of the Ecuadorian GHRD population.

Among the observations made in the Ecuadorian GHRD group is that despite almost uniform obesity, often severe, with typically 50% body fat, diabetes mellitus has not been seen. In their Table 1, Espinosa *et al.*⁵ record BMI SD scores and insulin concentrations that demonstrate severe obesity in both parents, both patients with GHRD, two of five unaffected siblings, and overweight in another two of the siblings. Insulin concentrations recorded in Table 2 generally reflect obesity-related insulin resistance except in the obese individuals with GHRD. The absence of hyperinsulinemia in the patients with GHRD with comparable degrees of obesity to other family members with hyperinsulinism suggests an important role of GH action in the development of insulin resistance and type 2 diabetes mellitus.

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