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ORIGINAL ARTICLE

Effect of inbreeding on intellectual disability revisited by trio sequencing

Kimia Kahrizi[1] | Hao Hu[2*] | Masoumeh Hosseini[1] | Vera M. Kalscheuer[2] | Zohreh Fattahi[1] | Maryam Beheshtian[1] | Vanessa Suckow[2] | Marzieh Mohseni[1] | Bettina Lipkowitz[2] | Sepideh Mehvari[1] | Zohreh Mehrjoo[1] | Tara Akhtarkhavari[1] | Zhila Ghaderi[1] | Maryam Rahimi[1] | Sanaz Arzhangi[1] | Payman Jamali[3] | Milad Falahat Chian[1] | Pooneh Nikuei[4] | Farahnaz Sabbagh Kermani[5] | Farnaz Sadeghinia[1] | Roshanak Jazayeri[6] | S. Hassan Tonekaboni[7] | Atefeh Khoshaeen[8] | Haleh Habibi[9] | Fatemeh Pourfatemi[10] | Faezeh Mojahedi[11] | Mohammad-Reza Khodaie-Ardakani[12] | Reza Najafipour[13] | Thomas F. Wienker[2] | Hossein Najmabadi[1,14] | Hans-Hilger Ropers[2,15]

[1]Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

[2]Max Planck Institute for Molecular Genetics, Berlin, Germany

[3]Shahrood Genetic Counseling Center, Welfare Office, Semnan, Iran

[4]Molecular Medicine Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

[5]Clinical Research Unit, Afzalipour Hospital, University of Medical Sciences, Kerman, Iran

[6]Department of Biochemistry, Genetic and Nutrition, Faculty of Medicine, Alborz University of Medical Sciences, Karaj, Iran

[7]Pediatric Neurology Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[8]Genetic Consultant, Sari, Iran

[9]Hamedan University of Medical Science, Hamedan, Iran

[10]Sari Genetic Counseling Center, Welfare Office, Sari, Iran

[11]Mashhad Medical Genetic Counseling Center, Mashhad, Iran

[12]Razi Hospital, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

[13]Cellular and Molecular Research Centre, Genetic Department, Qazvin University of Medical Sciences, Qazvin, Iran

[14]Kariminejad - Najmabadi Pathology and Genetics Center, Tehran, Islamic Republic of Iran

[15]Institute for Human Genetics, University Medicine Mainz, Germany

Correspondence
Hans-Hilger Ropers, Max Planck Institute for Molecular Genetics, Ihnestr. 63-73, D-14195 Berlin, Germany.
Email: ropers@molgen.mpg.de

[*]**Present address**
Hao Hu, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, 9 Jinsui Road, Guangzhou, Guangdong, 510623, P.R.China.

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In outbred Western populations, most individuals with intellectual disability (ID) are sporadic cases, dominant *de novo* mutations (DNM) are frequent, and autosomal recessive ID (ARID) is very rare. Because of the high rate of parental consanguinity, which raises the risk for ARID and other recessive disorders, the prevalence of ID is significantly higher in near- and middle-east countries. Indeed, homozygosity mapping and sequencing in consanguineous families have already identified a plethora of ARID genes, but because of the design of these studies, DNMs could not be systematically assessed, and the proportion of cases that are potentially preventable by avoiding consanguineous marriages or through carrier testing is hitherto unknown. This prompted us to perform whole-exome sequencing in 100 sporadic ID patients from Iran and their healthy consanguineous parents. In 61 patients, we identified apparently causative changes

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in known ID genes. Of these, 44 were homozygous recessive and 17 dominant DNMs. Assuming that the DNM rate is stable, these results suggest that parental consanguinity raises the ID risk about 3.6-fold, and about 4.1 to 4.25-fold for children of first-cousin unions. These results do not rhyme with recent opinions that consanguinity-related health risks are generally small and have been "overstated" in the past.

KEYWORDS
impact of inherited and de novo mutations, intellectual disability risks, parental consanguinity, parent-patient trios, whole-exome sequencing

1 | INTRODUCTION

Parental consanguinity (PC) is known to raise the risk of having children with recessive disorders, and it is associated with increased prenatal and pre-reproductive mortality. In the offspring of first-cousin matings, the prevalence of major congenital malformations (CM) is 2% to 2.5% higher than in children of unrelated parents; in Western countries, this more than doubles the CM risk ([1–5] and refs therein). Moreover, 3- to 5-fold elevated intellectual disability (ID) risks have been reported for children whose parents are first cousins,[6–10] but these estimates are based on few and mostly small studies with different designs, rendering direct comparisons difficult.

PC and autosomal recessive forms of ID (ARID) are rare in most parts of Europe and the United States, where the vast majority of ID patients are sporadic cases and dominant *de novo* mutations (DNMs) are common.[11–13] In contrast, PC is common in many developing countries, from Morocco through the near- and middle-east to parts of India (see Ref. 14), with current consanguinity rates being highest in Pakistan and Sudan. Recessive disorders are also a major health care problem in many other countries of the so-called "consanguinity belt," including Iran and, for example, Qatar, where a 30-year health plan aims to reduce the frequency of consanguineous matings.[15]

As shown a decade ago,[16] ARID is extremely heterogeneous, and the number of causative genes is likely to run into thousands.[17] This has been confirmed by large-scale, high-throughput sequencing in consanguineous families with two or more intellectually disabled children (see Ref. 18 and refs therein): between the first and the most recent study of this kind,[18,19] the percentage of multiplex families with mutations in known ARID genes has only risen from one-third to about one half[18] while the number of known ARID genes has increased from about a dozen to about 800 today.[18,20,21]

In a recent study of the British Deciphering Developmental Defects (DDD) project,[22] whole-exome sequencing (WES) identified bi-allelic (recessive) mutations in 3.6% of the patients with developmental disorders (DD) and European ancestry, compared to 49.9% DNMS in known DD genes. To date, no comparable molecular data have been published for countries where PC is common, because most sequencing studies performed in Iran, Turkey, Saudi Arabia or Pakistan focused on recessive gene defects and were not designed to capture DNM (eg,[19–21]), did not quantify consanguinity or autozygosity, or were simply too small[23].

Therefore, and in view of persisting disputes about the size of health care risks conferred by PC and the appropriateness and efficiency of efforts to discourage consanguineous matings (eg, see Refs. 24 and 25), we present here the results of molecular investigations designed to infer the proportion of DNM and recessive inherited mutations causing ID in the offspring of healthy consanguineous parents. These data provide a backbone for estimating preventable ID risks, in countries where PC is common and world-wide.

2 | MATERIAL AND METHODS

2.1 | Patients

The study was approved by the Ethics Committee of the University of Social Welfare and Rehabilitation, Tehran, Iran. Consent for participation of their child in this study was obtained from at least one of the parents and if possible, from the patients themselves.

Families with a single intellectually disabled child and healthy consanguineous parents were recruited from different provinces of Iran, who had been pre-screened to exclude chromosomal rearrangements as well as fragile X syndrome. In total, 100 unrelated ID patients and their parents were included in this study. All underwent a comprehensive clinical examination by experienced clinical geneticists. To determine the intelligence quotient (IQ) of children and their parents, we used Wechsler Intelligence Scales for Children (WISC) and adults (WAIS). Clinical findings in affected children are provided in Table 1 and Table S1.

2.2 | Whole-exome sequencing and array-comparative genomic hybridization

We extracted genomic DNA from white blood cells of patients and parents, enriched exomic sequences with the Agilent SureSelectXT Human All Exon V5 enrichment kit, performed 100 bp paired-end sequencing on an Illumina HiSeq sequencer and employed the MERAP pipeline for sequence analysis, as previously described.[18,26]

Previous studies[16,19] had shown that in consanguineous ARID families, microdeletions or duplications are very rare, and that the analysis of WES data with our previously described MERAP pipeline[26] identifies most clinically relevant homozygous copy number variants (CNVs). Therefore, array-based comparative genomic hybridization