Research Article Open Access

suggest that the decrease of MOR protein level caused by the N40D polymorphism involves posttranslational mechanisms such changes in protein folding and/or tra cking. In this regard, the asparagine at the 40^{h} position has been proposed as a potential N-glycosylation site [18]. GPCR N-glycosylation is necessary for correct activity of chaperone proteins that control the folding and tra cking of GPCRs. A recent report showed di erences in N-glycosylation levels between the human MOR-D and the human MOR-N variants [19] and a reduction in the half-life of the receptor protein by pull chase studies [19]. us, changes in N-glycosylation could explain the di erence observed in expression levels, including the discrepancy between mRNA and protein level changes observed. On the other hand, other authors failed to see di erences in the protein levels in transiently transfected COS cells [5].

Several reports also show that the N40D polymorphism modi es the intracellular pathways involved downstream MOR activation. MOR couples to Gi/o proteins and its acute activation reduces protein kinase A (PKA) activity and increases the Extracellular Receptor Kinases 1 and 2 (ERK1/2) phosphorylation [20-22]. Befort et al. [5] have quanti ed the [^{35}S] GTP S binding evoked by increasing concentrations of DAMGO in COS cells transiently transfected with human MOR-N and MOR-D. e apparent EC50 was similar for both receptor variants but the maximal response (e cacy) was higher for MOR-D than for MOR-N indicating that the amino acid replacement ReceptorTD (MOR-D thDecrgher)0i-1.267

Correlation between pain sensation and analgesic requirements and the MOR N40D polymorphism

Studies performed in vitro have been very important to understand the molecular basis of the changes on MOR functionality due to N40D substitution. Additionally, genetically modi ed mouse models have been essential to investigate the physiological implications of the A118G SNP in a highly controlled experimental setting. en, pain studies with human populations have well stressed the impact of A118G SNP on pain sensation and analgesic requirements. In this section we discuss the available mouse models and the more relevant clinical and population paper describing the impact of N40D in human pain treatment.

Mouse genome has an A118G equivalent polymorphism at position 112 (A112G). is substitution exchanges an asparagine residue to an aspartic acid residue at position 38 (N38D), homologous to position 40 of human MOR [30]. Mague et al. [30] taking advantage of genetic engineering techniques has produced knock-in mouse lines that are homozygous A/A or G/G at position 112 of opmr1. e authors found that MOR mRNA and protein levels were lower for G/G mice than for A/A mice in brain regions related to pain without changes in binding a nity for several agonists [30]. Moreover, the molecular mass of brain MOR was smaller in A/A mice as compared to G/G mice, presumably due to a decreased N-linked glycosylation in MOR-D variant. Using the hot plate test as a nociception assay, the authors tested the impact of A112G substitution in pain sensation and morphine requirements to relieve pain and found no di erences in pain threshold between A/A and G/G mice. Interestingly, morphine potency was lower for G/G mice than A/A mice when anti-nociception was tested. Increasing the noxious thermal stimulus unmasks a greater baseline jumping behavior and lower EC50 for morphine-mediated anti-nociception in G/G mice compared with A/A mice [30]. As we previously mentioned, two humanized mouse lines also have been generated, where exon 1 of mouse oprm1gene was replaced by exon 1 of human OPRM1 gene, containing A allele or G allele exclusively [31]. Here the behavioral observations were also opposite to what was expected since: authors found a higher morphine requirement for G/G humanized mice and no di erences when fentanyl was used as a MOR agonist. One explanation for these discrepancies is that human-mouse chimera receptor could have molecular consequences that carry arti cial di erences or similarities for polymorphism e ect on MOR function. M in hum7era reaT.5(.103 Tw 0 11the noxious ed)0.6(to)0 (for these dntroll11 Td

we could not exclude that other MOR SNPs in linkage disequilibrium with A118G could be counting for the genetic structure detected.

In conclusion, we were able to detect a worldwide population genetic structure by analyzing A118G SNP genetic variance. Moreover A118G frequency distributions within populations correlate with ethnic genetic background. is nding may be related to the shared genetic history by populations on the same continent and the large inter-group di erences among the human population groups analyzed.

Conclusion

A118G is a relevant human polymorphism that changes MOR physiology and impact on pain sensation and opioids requirements. Here, we analyzed the distribution of alleles A and G in di erent human populations including a novel Argentinean population supporting the notion that A118G could be useful to determine the ethnic background in a human population. Futures studies about this and others opioids system polymorphisms could contribute to develop individual and population targeted therapies to manage pain conditions.

Acknowledgement

:H ZRXOG OLNH WR WKDQN WR 'U 0DULR 3HUHOOR IRU FULWLFDOO\ UHDGLQJ WKLV PDQXVFULSW 7KLV ZRUN ZDV VXSSRUWHG E\ WKH $UJHQWLQHDQ 1DWLRQDO &RXQFLO RI 6FLHQFH (-/6 && DQG -5 WKH &RXQFLO RI VFLHQWL¿F ,QYHVWLJDWLRQ RI %XHQRV $LUHV)$ DQG E\ JUDQWV 3,&7 DQG 3,&7 RI WKH 1DWLRQDO $JHQF\ RI 6FLHQWL¿F and technological promotion (JR).

References

1. +DPLOWRQ *5 %DVNHWW 7) ,Q WKH DUPV RI 0RUSKHXV WKH GHYHORSPHQW RI PRUSKLQH IRU SRVWRSHUDWLYH SDLQ UHOLHI &DQ - $QDHVWK

2.

single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is
D V V R F L D W H G Z L W K S U H V V X U H S D L Q V H Q V L W L Y L W \ L Q K X P D Q V - 3 D L Q

2 H U W H O 6 F K P L G W 5 6 F K Q H L G H U $ * H L V V O L Q J H U * / R W V F K - 7 K H P X
R S L R L G U H F H S W R U J H Q H S R O \ P R U S K L V P $! * G H S O H W H V D O I H Q W D Q L O L Q G X F H G