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REVIEW PAPER

Molecular Autism Research in Africa: Emerging Themes and Prevailing Disparities

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Abstract
African populations are consistently underrepresented in molecular research on autism spectrum disorders (ASD). Yet, Africa's genetic diversity could reveal novel mechanisms associated with ASD etiology. We review the molecular ASD research from Africa between 2016–2022, highlighting region-specific limitations, opportunities, and areas of progress. We emphasize a need to advance null-hypothesis based molecular studies in Africa, particularly in critically understudied Sub-Saharan African (SSA) populations. Using South Africa as a case study, we show that this geographical disparity is not solely attributable to sociocultural barriers nor to an absence of molecular research infrastructure. We emphasize the importance of interdisciplinary collaboration within SSA and internationally to harness existing infrastructure for the expansion of molecular ASD research in Africa.

Keywords Autism · Africa · Sub-Saharan Africa · Research Equity · Metabolic · Redox

Introduction

Autism spectrum disorder (ASD), a neurodevelopmental condition characterized by challenges related to behavior, communication, and cognition, is a leading cause of psychological distress in children and adolescents (Divan et al. 2021). The global prevalence of ASD is estimated to range from 0.6–1% but data availability varies widely between continents (Salari et al. 2022; Zeidan et al. 2022). The majority of current research is conducted in high-income countries (HICs) across the Global North while little is known about ASD in low-to-middle-income countries (LMICs) in the Global South, despite 95% of children with developmental disabilities residing in these settings (Vries 2016; Olusanya et al. 2018). Several studies have highlighted a critical shortage of ASD research from Africa during the preceding decades (Bakare and Munir 2011; Abubakar et al. 2016; Franz et al. 2017; Bakare et al. 2022; Salari et al. 2022). The three most recent reviews of ASD research in African regions found that there were no population-based prevalence studies of ASD in Sub-Saharan Africa (SSA), with only 0.5% of the world's ASD research conducted in this region (Abubakar et al. 2016; Franz et al. 2017; Bakare et al. 2022). Several studies with limited scope in SSA reported prevalence rates of 0.08 to 2.3% (Pillay and Brownlow 2017; Abubakar et al. 2016; Salari et al. 2022), however these studies largely relied on convenience-based sampling and generally do not incorporate validated ASD diagnostic tools. Moreover, studies on the molecular etiology of ASD are the most limited; there are only four such publications from two African countries identified across all three reviews. Notably, none of these reviews go beyond reporting the significant shortage of molecular autism research in Africa, without discussing factors that may contribute to, exacerbate, or mitigate this geographical disparity.

Autism research aims to be inclusive and internationally relevant, but this requires that molecular research includes underrepresented populations. This is particularly pertinent in the context of ASD, given that it is a highly heterogeneous condition that is underpinned by substantial genetic complexity (Lord et al. 2020). Molecular research aims to elucidate the underlying mechanisms that contribute to ASD, which has crucial implications for the development of diagnostic biomarkers, therapeutic interventions, and other strategies to improve quality of life. However, since

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genetic associations differ significantly among populations, mitigating the geographical disparity in genomic research is recognized as a top priority in the field (Martin et al. 2018; Oni-Orisan et al. 2021; Sirugo et al. 2019). Thus, several recent scoping reviews have summarized the existing data on ASD in understudied populations, including Arabian (Almandil et al. 2019; Hussein and Taha 2013), Indian (Patra and Kar 2021), and Middle Eastern (Rahmani et al. 2021) populations.

However, a comprehensive scoping review of molecular ASD etiology in Africa has not been conducted in the last century. This is likely a result of the documented scarcity of molecular data from African populations. Moreover, research in Africa being driven by African research groups may not be a priority for most international publishers and African countries often lack the resources to fund research on non-communicable and neuropsychiatric conditions. Nevertheless, African genomes are characterized by rich genetic diversity and reduced linkage disequilibrium, which represents a unique resource for the discovery of novel genetic loci and high-powered genetic fine-mapping (Campbell and Tishkoff 2008; Sirugo et al. 2019; Tishkoff and Verrelli 2003). Thus, expanding molecular ASD research to include African populations has the potential to make valuable contributions to both local and global research efforts to characterize ASD etiology.

In this comprehensive scoping review, we collate data from molecular ASD research in Africa published since 2016. We quantitatively examine the geographical disparity in molecular ASD research and we thematically summarize the existing molecular literature on ASD in Africa. We explore molecular trends in current research with respect to molecular methodologies and convergent mechanisms implicated in African ASD cohorts. We consider the strengths and limitations of the current body of work in order to inform future research in this context. Finally, we interrogate the trends in ASD research and molecular research capacity in South Africa (SA) more closely, as a case study to inform the progression of ASD research in SSA.

Methods

Search Strategy

This scoping review was conducted according to the Arksey and O'Malley framework (Arksey and O'Malley 2005; Levac et al. 2010) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (Moher et al. 2009). Briefly, we identified the research question, captured the studies for screening, selected the relevant studies for inclusion, charted the data, and finally, we collated, summarized, and reported our results. To identify peer-reviewed original research publications from 1 January 2016 to 31 December 2022, we conducted searches of PubMed and Scopus, and we searched AfricaWide, CINAHL, PsychArticles, and PsychInfo through EBSCOhost. For the PubMed search, both text words and Medical Subject Headings (MeSH) terms were used. The search strategy used a combination of three key concepts to identify molecular ASD research in the respective geographical regions of interest, using the search terms listed in Table 1. Concept one related to ASD and comprised a string of keywords such as "Autism Spectrum Disorder" OR "autism" OR "ASD". Concept two defined molecular study aspects using keywords such as "genetic" OR "molecular". The third concept specified the geographical region of interest with keywords such as "Brazil" OR "Brazilian". Using concepts one, two, and three, separate searches were done for the five regions of interest, i.e., Africa, Brazil, India, the United Kingdom (UK), and the United States of America (USA). Finally, we conducted a search to capture the volume and scope of all ASD publications from SA (2016–2022), using concepts one and three.

Eligibility Criteria

Articles from the molecular ASD searches in each region of interest were screened for eligibility based on the title and abstract using the following inclusion criteria:

i. ASD was the primary focus of the study,
ii. the study was carried out within the region of interest by authors from that region,
iii. the study generated primary data, and
iv. the study used molecular methods or reported molecular data.

For the search of all ASD research outputs from SA, eligibility criteria were as above, with the exception that the methods used in the study were not restricted to molecular techniques.

All searches were filtered for the date of publication (1 January 2016 – 31 December 2022). Studies that did not meet the above criteria were excluded. Dissertations and conference reports/abstracts were also excluded. Where there were numerous authors from multiple regions, studies were excluded if the main author and/or the ethics approval was not from the region of interest.

Screening and Selection

All research articles captured by the search strategy were exported to an EndNote 20 library and then uploaded to Rayyan (Ouzzani et al. 2016) which was used to remove

Table 1 Database Search Strategy

Concept		Search String
Autism spectrum disorder		"autism spectrum disorder" OR autism OR ASD OR autistic OR "autistic disorder"
Molecular		DNA OR RNA OR genes OR genome OR genetic OR molecular OR transcriptome OR transcriptomic OR proteins OR proteome OR proteomic OR biochemical OR metabolome OR metabolomic OR SNP OR polymorphism
Region	Africa	Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR "Burkin Faso" OR Burundi OR "Cabo Verde" OR Cameroon OR Cameroun OR "Canary Islands" OR "Cape Verde" OR "Central Africa" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR Djibouti OR "Eastern Africa" OR Egypt OR Eritrea OR eSwatini OR Ethipia OR Gabon OR Gambia OR Ghana OR Guniea OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR "Northern Africa" OR Principe OR Reunion OR Rwanda OR "Saint Helena" OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "St Helena" OR "South Africa" OR "Southern Africa" OR "Sub-Saharan Africa" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Africa" OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe NOT "African American"
	South Africa	"South Africa" OR "South African"
	India	India OR Indian
	Brazil	Brazil OR Brazilian
	United Kingdom	"United Kingdom" OR UK OR Britain OR British OR England OR "Northern Ireland" OR Scotland OR Wales
	United States of America	"United States" OR USA OR "United States of America" OR America NOT “South America”

duplicates and carry out screening for article inclusion. All publication titles and abstracts were independently reviewed by two authors, and any conflicts were resolved by a joint review of the full text. When an agreement was not reached, the senior author also reviewed the title and abstract to reach a consensus. The final PRISMA diagram depicting the screening and selection process is presented in Fig. 1.

Results

The articles that passed our eligibility criteria were collated and analyzed to address three main objectives. First, we quantitatively assessed publication output across Africa, two non-African LMICs, and two HICs to examine the geographical disparity in ASD molecular research. Secondly, we thematically summarized all molecular publications from Africa between 2016 and 2022 to provide an overview of the current state of research on ASD in African populations. Finally, we examined the trends in ASD research in SA (a LMIC in SSA) more closely to identify limitations and opportunities for ASD research in SSA.

The Geographical Disparity in Molecular ASD Research

This review set out to quantitatively measure the geographical disparity in molecular ASD research. To do this, we compared the research output from all 54 countries in Africa, two non-African LMICs (India and Brazil) and two HICs (the UK and the USA). We retrieved 2846 articles across all regions of interest, and after removing 569 duplicates and screening the dataset according to predefined eligibility criteria, 259 publications were included in the review (Fig. 1). A total of 84 and 68 publications were identified from the USA and the UK, respectively, with substantially lower outputs observed from Brazil ($n = 34$) and India ($n = 36$) (Fig. 2). Strikingly, the output from each of these non-African LMICs was roughly equivalent to the output from the entire African continent and was three times higher than the output from SSA. There were 37 publications from the entire African continent, originating from only seven of 54 African countries (Online Resource 1). Research from two northern African populations accounted for more than 75% of all the research produced from Africa between 2016–2022, of which more than 80% was produced in Egypt ($n = 23$). On the other hand, the SSA region produced only nine publications over the six-year period included in this review.

ASD Etiology in Africa: A Review of Recent Findings

In order to summarize the research progress and lay the foundation for future studies, we summarized the existing molecular literature on ASD in Africa based on methodological and mechanistic research themes. Of the 37 African molecular studies produced since 2016, 33 studies were conducted in African cohorts, three used the valproic acid animal model for ASD, and one study used previously published datasets

in a bioinformatic analysis. The main findings from each of the African cohort studies are summarized in Table 2 and Online Resource 1. We identified 33 studies that examined molecular mechanisms in ASD cohorts from Egypt ($n=20$), Tunisia ($n=4$), SA ($n=3$), Nigeria ($n=3$), and Cameroon, Seychelles, and Uganda ($n=1$). Of these, a majority of studies examined metabolites or trace elements (36%), proteins (27%), or genetic factors (23%). Conversely, studies on the epigenome, transcriptome, and microbiome were the most underrepresented (< 5%) (Fig. 3a). All 33 studies focused on one or more of four molecular mechanisms – metabolic or redox homeostasis (41%), chromosomal or genetic aberrations (25%), one-carbon metabolism (19%), and immune dysregulation (16%) (Fig. 3b).

This overview highlights the convergent nature of the data from African ASD cohorts, which highlights that intracontinental collaboration has the potential to advance this area of research. However, the prevailing scarcity of molecular ASD research in Africa demonstrates that this research is still in its infancy. Moreover, current data represents a small minority of African populations, whilst most regions – particularly in SSA – remain critically understudied. If research output is to be tangibly improved, it is critical to understand the factors that contribute to this geographical disparity in molecular autism research so that these factors can be mitigated.

ASD Research in South Africa: A Case Study in SSA

Previous reviews reported that over 50% of all ASD research in SSA between 1936 and 2017 originated from SA (Abubakar et al. 2016; Franz et al. 2017). Despite this, we found that SA produced only three molecular ASD publications in the last seven years; this is almost 9 times less than their northern African counterparts. Therefore, we examined the trends in ASD research in SA in order to characterize the capacity for molecular ASD research in the region. After screening ASD research from all thematic focus areas in SA published between 2016–2022, we identified 85 publications spanning eight thematic focus areas (Online Resource 2). Combining this data with three previous reviews (Abubakar et al. 2016; Franz et al. 2017; Bakare et al. 2022), we identified a total of 119 ASD studies ever published in SA up to 2022 (Fig. 4a). Interestingly, 87 of these studies (73%) were published between 2016 and 2022, which indicates a promising exponential increase in ASD research. However, this increase in output was not reflected in molecular research and only five molecular studies from SA were identified since 1935. In fact, molecular studies still represent the smallest focus area, making up only 3% of all ASD research in SA over the past five years (Fig. 4b). On the other hand, the most well-studied thematic focus areas relate to family or social aspects (40%), clinical or behavioral (15%), or educational (13%) aspects of ASD.

The regional scarcity of autism research is often attributed to socio-economic factors that include the pervasive stigmatization of ASD, poor access to healthcare, a lack of trained mental health professionals, an absence of specialized educational facilities, and a lack of culturally relevant diagnostic tools (Samadi 2022). These factors undoubtedly pose significant challenges to ASD research and have wide-reaching implications for the diagnosis and management of ASD in the region that have been comprehensively discussed elsewhere (Vries 2016); Divan et al. 2021; Franz et al. 2017; Pillay et al. 2021). Nevertheless, the much larger publication output in other thematic focus areas suggests that these factors cannot solely account for the paucity of molecular ASD research in SA. Therefore, we sought to investigate whether differences in molecular research capacity could explain the gap in research output. To do this, we examined established indices of molecular research capacity in SA compared to African (Nigeria and Egypt) and non-African (Brazil and India) LMICs to identify potential limiting factors (Fig. 4c). We included previously reported indices of health science research capacity in Africa (Wenham et al. 2021) as well as indices of molecular research infrastructure as reported in the UNESCO 2021 Science Report (UNESCO et al. 2021) which include indicators of research funding, infrastructure, human capital, and research output (Online Resource 3).

This assessment revealed that molecular autism research output across Africa deviated notably from several important indicators of research capacity. Among all the LMICs included in this analysis, SA produced the highest number of scientific publications and ranked among the highest in GDP per capita, Research and Development (R&D) expenditure, and number of researchers per million inhabitants (UNESCO et al 2021; The World Bank 2022). SA's mental health research output is nearly 6 times that of Egypt (World Health Organisation (WHO) 2021) and SA has the top six universities in Africa with three of these ranking in the global top 500 universities (Round University Ranking 2023). Conversely, SA lags behind both Egypt and Brazil in terms of human capital. Compared to SA, Egypt has 1.3 times more researchers and almost 3 times the number of technicians per million inhabitants (UNESCO et al 2021). This highlights a deficit of skilled labor in the molecular sector that may contribute to the lack of molecular ASD research in SA. Nevertheless, this does not entirely account for the fact that SA produced between 6 and 10 times fewer molecular autism publications than non-African LMICs despite increased infrastructure relating to tertiary education, research, R&D, and mental healthcare.

Table 2 Summary of Findings from all 33 Molecular ASD Studies in African Cohorts (2016–2022)

Country	Reference	Main Result
Chromosomal Aberrations, CNVs, SNPs or INDELs		
Egypt	El-Baz et al. (2016)	No detectable numerical or structural chromosomal abnormalities in 30 Egyptian children with ASD
Egypt	Elserogy et al. (2017)	Out of 231 Egyptian children with ASD, 11 (4.7%) had chromosomal abnormalities: 5 with sex chromosome aneuploidy, 3 with Down syndrome, 1 with monosomy 1p36, 1 with Williams-Beuren syndrome and 1 with a deletion of the long arm of chromosome 13
Egypt	Meguid et al. (2018)	3 Egyptian children with ASD with chromosomal abnormalities at 10q and 22q
Cameroon	Kamga et al., (2020)	46 Cameroonian participants underwent Fragile X (FXS) carrier testing; 28 (60.87%) were normal. 4/19 males (21.1%) presented with a full mutation and all had a severe intellectual disability (ID). 10/27 and 4/27 females had a premutation and a full mutation respectively, 5 of whom presented with mild ID. The carrier frequency for FXS was 51.8% among females
Egypt	Meguid et al. (2020)	Of 40 Egyptian children with ASD, 3 had de novo duplications at 22q13.33 at or distal to SHANK3
Tunisia	Chehbani et al. (2022)	98 Tunisian children and adolescents with ASD were recruited from 91 simplex and four multiplex families. 14 pathogenic CNVs were identified in 11 patients, encompassing 10 duplications and 4 deletions. Rare CNVs were detected in 26 patients; benign CNVs were detected in 61 patients. CNVs converged on pathways involved in synaptic signaling and neurogenesis
Mitochondrial Dysfunction and Oxidative Stress		
Egypt	Khaled et al. (2016)	In 40 Egyptian children with ASD and 20 unaffected siblings, ASD was associated with higher urinary and blood Hg and Pb levels, and altered urinary porphyrins
Uganda	Arony et al. (2018)	Significant biotinase and acetyl carnitine deficiency in 47 cases of nodding syndrome in Ugandan children
Egypt	El-Baz et al. (2018)	Serum Cu and ceruloplasmin were elevated in 20 Egyptian children with ASD compared to 15 controls
Tunisia	Grayaa et al. (2018)	In Tunisian children (36 ASD, 38 controls), plasma 24-hydroxycholesterol was elevated and inversely correlated with age in ASD
Egypt	Fotoh et al. (2019)	8/320 Egyptian children with ASD had inherited metabolic disorders; 7 cases of phenylketonuria, and 1 with glutaric aciduria type 1. 16 patients had low plasma Zn, 5 had a high serum Cu, 2 had a high serum Pb and 1 had high serum Hg
Egypt	Hassan et al. (2019)	In an Egyptian cohort (73 ASD, 73 Controls) plasma levels of lactate, serum pyruvate, CK, PK, LDH and ammonia were higher in ASD while serum L-carnitine and urea were lower. ASD was also associated with a higher total oxidant status, a lower antioxidant capacity, higher levels of Hg, Pg and Al, and lower serum total cholesterol, cortisol and estradiol
Tunisia	Chehbani et al. (2020)	In a Tunisian cohort (89 ASD, 70 controls), Cu was lower in ASD and Cu levels correlated with ASD severity
South Africa	Stathopoulos et al. (2020)	In South African children (145 ASD, 52 Controls), 898 genes were differentially methylated and converged on 9 mitochondrial canonical pathways. 3 urinary metabolites associated with oxidative stress were elevated in ASD
South Africa	Bam et al. (2021)	In South African children (145 ASD, 52 Controls), 6 genes involved in mitochondrial biogenesis, fission and fusion were differentially methylated while mitochondrial DNA copy number was elevated in ASD
Nigeria	Omotosho et al. (2021)	In Nigerian children (25 ASD, 25 Controls) with ASD total plasma peroxidase and total antioxidant capacity were reduced while the oxidative stress marker malondialdehyde was elevated in ASD. Pb concentration was increased while Mg, Zn, and Cu levels were reduced in ASD
One-Carbon Metabolism		
Tunisia	Khemir et al. (2016)	Of 15 Tunisian and 4 Algerian patients with phenylketonuria, 15 had ASD. 6 mutations in the phenylalanine hydroxylase (PAH) gene were identified but there was no correlation between autism and specific PAH variants
Egypt	Meguid et al. (2017)	In Egyptian children (80 ASD, 80 controls) serum folate, vitamin B12, Mg, Fe and Ca were lower in ASD

Table 2 (continued)

Country	Reference	Main Result
Nigeria	Oshodi et al. (2017)	In Nigerian children (42 ASD, 23 controls), reduced glutathione was lower in ASD and frequencies of GSTT1 and GSTM1 null genotypes were higher, but the distribution of polymorphisms was not associated with ASD
Nigeria	Fagbayi et al. (2018)	In Nigerian children (38 ASD, 13 controls) serum glutamate, glutamine, GABA, tryptophan and cysteine were significantly altered in ASD
Egypt	Ismail et al. (2019)	In Egyptian children (80 ASD, 60 controls) MTHFR mutation was more prevalent in ASD but did not correlate with ASD severity. Specific variants were associated with consanguinity and family history of psychological disorder
Egypt	Esmaiel et al. (2020)	In 52 Egyptian children with ASD, 3 COMT variants were found with 9 haplotypes, including one allele with the potential to alter enzymatic activity by interfering with the secondary structure of mRNA. Variants were associated with abnormal dopamine levels and abnormal EEG
Egypt	El-Ansary et al. (2021)	In Egyptian children (20 ASD, 20 controls), GABA was reduced in ASD while levels of caspases 3 and 9 were higher
Egypt	Higazi et al. (2021)	In Egyptian children (45 ASD, 44 with learning disabilities (LDs), 40 controls), Haemoglobin, Fe and D3 were lower in ASD and LDs; ASD was also associated with decreased Zn/Cu ratios and lower expression levels of MAAO, HAAO and AADAT
Egypt	Said et al. (2021)	In Egyptian children (76 ASD, 30 controls) GSTM1 and GSTT1 variants were more prevalent in ASD and associated with increased Al, MDA and NO
Immune Dysregulation		
Egypt	Desoky et al. (2017)	In Egyptian children (60 ASD, 40 controls) CD5 was higher, TSH was reduced and serum 25(OH)D was lower in ASD. ASD severity correlated negatively with 25(OH)D and positively with CD5
Egypt	Saad et al. (2017)	In Egyptian children (32 ASD, 30 controls) % of myeloid and plasmacytoid dendritic cells (mDCs and pDCs) were elevated in ASD, and correlated negatively with serum 25(OH) D
Seychelles	Irwin et al. (2019)	In 788 mother–child pairs from Seychelles, increased maternal gestational MCP-1 was associated with fewer ASD symptoms while increased IL-4 was associated with more ASD symptoms
Tunisia	Kharrat et al., (2020)	In 15 simplex Tunisian ASD families, human leukocyte antigen polymorphisms were associated with sHLA-G levels in parents but not with ASD in children
Egypt	Saad et al. (2017)	In Egyptian children (80 ASD, 60 controls) ASD was associated with genotype variants of IL-1β-511 and IL-1RA and increased serum IL-1β and IL-1RA. Polymorphisms in the IL-1β-511 and IL-1RA genotype variants correlated positively with autism severity and behavioral abnormalities
Egypt	Mostafa et al. (2021)	In Egyptian children (22 ASD, 22 controls) nerve growth factor (NGF), serotonin and anti-myelin basic protein were higher in ASD while there was a positive correlation between NGF and serotonin levels in ASD
Egypt	Abdel Ghaffar et al., (2022)	In Egyptian children (25 ASD, 25 ADHD, 25 controls) there was a moderate significant negative correlation between neopterin and age in ASD, but not controls or ADHD, suggesting early immune system activation in ASD
Egypt	Mostafa et al. (2021)	In Egyptian children (30 ASD, 30 controls), serum levels of TAM receptor tyrosine kinases were higher in ASD and correlated significantly with ASD severity

Discussion

Molecular Mechanisms in African Cohorts

Molecular research in African cohorts has revealed four interdependent mechanisms implicated in ASD etiology; these mechanisms are well-established in the broader literature. Firstly, six studies from Egypt, Cameroon, and Tunisia focused solely on genetic alterations including chromosomal aberrations, copy number variants (CNVs), deletions, and duplications. These studies found that genetic aberrations were uncommon among the ASD cohort studies and are most reliably detected using large sample sizes and microarray-based or comparative genomic hybridization (CGH) techniques (El-Baz et al. 2016); Elserogy et al. 2017); Meguid et al. 2018); Kamga et al., 2020; Meguid et al. 2020; Chehbani et al. 2022). Four studies using traditional cytogenetic techniques revealed structural chromosomal abnormalities in 7.6% of Egyptian children (17/304), while the frequency of chromosomal abnormalities ranged from 0–7.5% across all

four studies (El-Baz et al. 2016; Elserogy et al. 2017; Meguid et al. 2018; Meguid et al. 2020). A Tunisian study using higher resolution array-CGH identified CNVs of 207 genes that converged on synaptic signaling and neurogenesis pathways (Chehbani et al. 2022). These studies are consistent with the fact that only 10–20% of ASDs are attributed to known genetic causes, while individual gene mutations each account for less than 1% of all ASD cases globally (Geschwind 2011; Yoo 2015). Thus, the data from North African populations reinforces a well established premise that syndromic autism contributes to a minority of all ASD cases.

The remaining 27 African cohort studies used a range of molecular techniques to explore alterations to metabolic, redox, and immune homeostasis in ASD. Together, studies on metabolism or redox mechanisms accounted for almost half of all molecular ASD publications from Africa. These studies demonstrated metabolic and oxidative stress in cohorts from Egypt, Tunisia, SA, Nigeria, and Uganda at the level of the genome, epigenome, proteome, and metabolome (Khaled et al. 2016; Arony et al. 2018; El-Baz et al. 2018; Grayaa et al. 2018; Fotoh et al. 2019; Hassan et al. 2019; Chehbani et al. 2020; Stathopoulos et al. 2020; Bam et al. 2021; Omotosho et al. 2021). (Hassan et al. 2019) reported increased lactate and pyruvate levels, as well as upregulation of key mitochondrial enzymes, consistent with clinical observations of mitochondrial dysfunction reported in ASD (Griffiths and Levy 2017; Balachandar et al. 2021; Frye 2020). Moreover, independent studies reported serum carnitine deficiency (Arony et al. 2018; Hassan et al. 2019) and significant perturbations to cholesterol metabolism (Grayaa et al. 2018; Hassan et al. 2019) in African ASD cohorts. Carnitine is required for mitochondrial beta fatty acid oxidation and cholesterol is important for the availability of fat-soluble vitamins, the biosynthesis of steroid derivatives, and the development, function, and structure of the nervous system (Hassan et al. 2019). Notably, both carnitine and cholesterol metabolism have been explored as potential biomarkers in non-African populations (Frye et al. 2019; Kępka et al. 2021; Zhang et al. 2023) and therapeutic targets (Esposito et al. 2021; Frye 2020; Lin et al. 2023; Malaguarnera and Cauli 2019) in ASD.

Data from African ASD cohorts also illustrate changes to cofactors and trace elements involved in metabolic and redox homeostasis, with five studies reporting elevated levels of heavy metals (Hg, Pb, and Al) which are known to increase oxidative stress, perturb glutathione-dependent antioxidant responses, and induce secondary mitochondrial dysfunction (Fotoh et al. 2019; Hassan et al. 2019; Khaled et al. 2016; Omotosho et al. 2021; Said et al. 2021). Moreover, there were consistent reports of decreased Zn, Mg, Fe, Ca, and Vitamin D3 (Fotoh et al. 2019; Higazi et al. 2021; Meguid et al. 2017; Omotosho et al. 2021), as well as alterations to Cu (Chehbani et al. 2020; Fotoh et al. 2019; El-Baz et al. 2018; Omotosho et al. 2021) in African ASD cohorts. These essential trace elements not only function as critical cofactors for a variety of enzymes needed for metabolism, immune regulation, and neurogenesis, but are also important modulators of redox homeostasis. In line with this, six studies showed decreased antioxidant capacity and/or an increase in oxidative stress markers in Nigerian, South African, and Egyptian children (Bam et al. 2021; Hassan et al. 2019; Omotosho et al. 2021; Oshodi et al. 2017; Said et al. 2021; (Stathopoulos et al. 2020)). Of these, one study found urinary markers of oxidative stress that were associated with increased mitochondrial DNA copy number (Bam et al. 2021), while two studies identified genetic variants in glutathione S-transferases (GSTs) that are associated with oxidative stress in ASD (Oshodi et al. 2017; Said et al. 2021).

GSTs play an important role in one carbon (1C) metabolism, which was separately implicated in nine of the 33 cohort studies identified in this review. Genetic variants in key enzymes involved in the folate and methionine cycles were reported in children with ASD from Nigeria and Egypt (Esmaiel et al. 2020; Ismail et al. 2019; Khemir et al. 2016). Adjacent pathways responsible for phenylalanine and tryptophan metabolism were also implicated in genetic and mRNA expression data from Tunisian and Egyptian cohorts (Higazi et al. 2021; Khemir et al. 2016). Additionally, metabolomic studies revealed alterations across all three 1C cycles, including disruptions to serum folate, vitamin B12, cysteine, tryptophan, reduced glutathione, glutamine, glutamate, and GABA (El-Ansary et al. 2021; Fagbayi et al. 2018; Meguid et al. 2017). The 1C cycle is broadly implicated in ASD etiology as these metabolites play important roles in the synthesis and turnover of neurotransmitters including serotonin, dopamine, and glutamate (Hoxha et al. 2021; Tisato et al. 2021; Wei et al. 2021). Additionally, recent studies have shown that the folate and transsulfuration pathways show promise in the development of biomarkers for ASD (Qureshi and Hahn 2023).

Finally, eight studies from Egypt, Tunisia, and Seychelles examined immune abnormalities in ASD. These studies report increased inflammatory markers in ASD, as well as perturbations to immune regulators like interleukins-1β and -1RA, TAM receptor kinases and the T-cell modulator CD5 (Desoky et al. 2017; Saad et al. 2017, 2020; Mostafa et al. 2021, 2022) . Two studies showed that increased immune activation correlated significantly with reduced levels of vitamin D (Desoky et al. 2017; Saad et al. 2017), which is essential for the regulation of innate immune responses and also functions as an antioxidant to reduce mitochondrial dysfunction and oxidative stress. In fact, neuroimmune responses

are regulated by both the metabolic (Marchi et al. 2023; Missiroli et al. 2020) and redox (Pangrazzi et al. 2020; Picca et al. 2020) mechanisms that have been implicated in other African cohorts. Interestingly, (Mostafa et al. 2021) reported that the levels of brain-specific auto-antibodies correlated significantly with levels of serotonin in ASD, while (Desoky et al. 2017) showed that immune activation was associated with decreased levels of thyroid stimulating hormone (TSH). Both serotonin and TSH are derived from 1C metabolic precursors and, in addition to their role in immune homeostasis, each are implicated in the regulation of neurodevelopment, neurotransmission, and behavior in ASD (Muller et al. 2016; Daly et al. 2019; Ames et al. 2020)). Together, these findings provide evidence for an interplay between mitochondrial metabolism, oxidative stress, and immune dysregulation in African ASD cohorts. This provides a mechanistic framework to inform the future work that will be critical to address the current knowledge gaps in African populations.

Molecular Autism Research in Africa: Current Gaps in the Literature

This review illustrates the relative scarcity of molecular ASD research in Africa, but the existing data is also inherently limited in terms of sample size and scope. Across all 33 cohort studies, the mean sample size per study came to 110 individuals, with a mode of 40. More than 55% of studies had cohorts of fewer than 100 individuals and more than 90% included fewer than 200 individuals. These sample sizes are significantly lower than cohorts from countries in the Global North, and smaller cohorts are particularly limiting in the context of such a genetically heterogeneous disorder. Sample sizes also limit the scope and specificity of the research that can be done. Of 33 studies, only two used a null-hypothesis based approach as opposed to a targeted investigation of single genes, proteins, or metabolites.

This approach has both advantages and limitations in this context. On the one hand, these methods contribute to the identification of proteins or metabolites that could serve as biomarkers for ASD in Africa. Moreover, large-scale "omics" studies are costly and typically require cohorts much larger than any of those in the studies listed above. However, targeted approaches are based on data from cohorts in the Global North, with their different genealogies. Whilst downstream mechanisms may indeed converge on pathways that have previously been implicated in different populations, African populations are likely to have significant differences in their upstream genetic architecture. Therefore, null-hypothesis based approaches are essential to drive meaningful research into the unique aspects of ASD etiology in African populations.

Notably, two research groups used alternative approaches to circumvent these limitations (Chehbani et al. 2022) used array comparative genomic hybridization (aCGH) which maps CNVs to a resolution of 5–100 kb, as opposed to the 3–5 Mb resolution of traditional cytogenetic techniques. While aCGH provides less resolution than whole genome sequencing (WGS), it facilitates mapping of structural changes at specific loci which allows for mechanistic conclusions to be made. It is also far less costly than WGS and, in combination with well-phenotyped probands from both multiplex and simplex families, is able to yield significant results in smaller cohorts. Similarly, (Stathopoulos et al. 2020) conducted a whole-epigenome screen (WES) in a small South African cohort. In contrast to WGS, WES yields insight into mechanisms that directly alter gene expression and consequently require fewer individuals to draw meaningful mechanistic conclusions. This approach highlighted a significant enrichment of mitochondrial pathways among differentially methylated genes, which informed subsequent targeted studies to validate this hypothesis. These studies provide examples of how null-hypothesis based molecular research can be done in the African context.

Similarly, it will be important to address the skewed nature of molecular research in Africa in terms of the molecular approaches that are used. The vast majority of studies in African cohorts have investigated proteins, metabolites, or trace elements, whilst only three studies investigated either transcriptomic or epigenomic changes. Proteomic and metabolomic changes are undoubtedly useful to identify functional changes to certain mechanisms, and to identify potential biomarkers that could be used in a diagnostic context. The development of accurate diagnostic strategies is a priority among stakeholders in autism communities (Dey, et al. 2023). Additionally, both proteomic and metabolomic studies are well-positioned to provide insight into the functional manifestations of genetic diversity in small African cohorts. Moreover, the current research infrastructure and published data from African populations can be used to inform future molecular ASD research efforts in Africa. Given the current African research context, Africa's clinical diagnostic infrastructure could be harnessed for high-throughput, less expensive metabolomic screens to upscale molecular ASD research in the short term. Building on the existing proteomic and metabolomic data could facilitate a better understanding of the oxidative, metabolic and immune processes implicated in African populations, and how these mechanisms could inform novel diagnostic biomarkers.

However, transcriptomic and epigenomic studies are essential to understand the regulatory mechanisms responsible for changes to gene expression and function and to

identify molecular targets that are responsible for a range of pleiotropic systemic alterations. As more advanced molecular techniques become more affordable and molecular infrastructure develops across Africa, such studies will become more possible in understudied African populations. Intracontinental collaborations between healthcare providers and molecular scientists would greatly facilitate the building of cohorts large enough for this type of research. Likewise, international collaborations that facilitate access to high throughput molecular techniques could play an instrumental role in improving our understanding of the genetic and epigenetic architecture that underlies ASD in Africa.

A Focus on Sub-Saharan Africa: Lessons from South Africa

This review demonstrated the paucity of molecular research on SSA populations. Given SA's recorded contribution to autism research in SSA, a scrutiny of their ASD research capacity may provide insight into the underlying reasons for this gap in the literature. Despite producing more than 50% of all ASD research in SSA and an exponential increase in research output over the last decade, SA produced only five molecular ASD publications since 1935. This is in stark contrast to Egypt, which has contributed more than 80% of all molecular ASD research from Africa since 2016. Yet, SA outranks Egypt with respect to GDP per capita, number of research institutions, and both scientific and mental health research output. Indeed, a previous review of health science research capacity showed that SA ranked first in Africa with respect to the number of universities, first author publications, and clinical trials (Wenham et al. 2021). Where SA falls short is in human research capital, most significantly in terms of the number of technicians per million inhabitants.

Indeed, a noted weakness of SA's science sector is that R&D expenditure focuses on infrastructure but neglects the operational costs of research (HESTIIL Ministerial Committee 2020). Moreover, the number of total researchers and technicians in SA has declined since 2017 and 2015, respectively (National Advisory Council on Innovation 2022). Consequently, research in SA is heavily dependent on foreign doctoral and postdoctoral students, only 10% of whom remain in SA long-term, whilst 11 800 skilled workers per year are lost to emigration (National Advisory Council on Innovation 2021). These factors culminate in a relative shortage of skilled research workers. This may significantly impact molecular and genetic research, which is dependent on full-time, highly skilled laboratory technicians for data generation.

This deficit of human capital also means that differential resource allocation could profoundly skew research output across different sectors. Much of SA's biomedical capacity is apportioned to infectious diseases research, which represent a huge health burden in SSA (Bhutta et al. 2014); (Boutayeb 2010). This is reflected in foreign and local funding that has driven research on human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis (TB), malaria and more recently SARS-CoV-2 (Arvanitis et al. 2022; N.D. of H. 2022). As a result, SA matched Egypt's research output in Immunology and Microbiology over the past five years (SJR 2022). However, Egypt's output in Biochemistry and Genetics was 40% higher than SA's, despite SA's H index – a measure of research quality and impact – being higher during the same period. Thus, SA has the infrastructure to produce high quality molecular research, but the majority of its constrained pool of human resources is likely allocated to infectious disease research, at the expense of molecular research into other areas.

Finally, molecular research generally requires larger sample sizes than other areas of autism research. Consequently, molecular studies are likely to be most impacted by the barriers to diagnosis and a lack of a centralized national support system in SSA, which pose significant challenges to establishing large study cohorts. Although SA has more child psychiatrists per 100 000 inhabitants than Egypt, Brazil, or India (World Health Organisation (WHO) 2021), 80% of psychiatrists in SA work in the private sector, while rural sectors average only 0.03 mental health specialists per 100 000 people (Janse van Rensburg et al. 2022). Moreover, there is insufficient training of public healthcare nurses, which limits their capacity to facilitate referrals for a diagnosis (Petersen et al. 2009). The average waiting period for a child to receive a clinical diagnosis in an autism specialist clinic is at least 18 months (Guler et al. 2018), and SA has only nine autism specialist schools with an estimated waiting period of more than three years for enrolment (Franz et al. 2018; Pillay and Brownlow 2017). The significant shortage of appropriate healthcare and educational facilities means that SA has little potential for centralized ASD data collection that would enable building the large cohorts that facilitate ASD research in HICs.

Nevertheless, SA has the infrastructure to produce high quality research in both autism and molecular biology. SA has historically produced half of the total ASD research in SSA, and this output has increased exponentially in recent years. Concurrently, SA is established as a continental leader in genetic research (Shaffer et al. 2019; Wenham et al. 2021). A shortage of skilled researchers and technicians in SA combined with a prioritization of infectious disease research has constrained molecular research on non-communicable diseases. Similarly, research on autism and other neuropsychiatric conditions faces

funding shortages, and prioritizes studies on diagnosis and intervention rather than an understanding of molecular etiology. Still, the fact that SA is separately established as a continental leader in both genetic and autism research suggests that harnessing these resources could play a significant role in improving ASD research from and within SSA as awareness and understanding of ASD improves.

Region-Specific Opportunities and Considerations

Historically, molecular autism publications in SSA hailed from SA and Nigeria, but we report recent publications from Cameroon, Uganda, and the Seychelles that indicate an emerging interest in the region. Moreover, the recent acceleration of the African Pathogen Genomics Initiative in the wake of the COVID-19 pandemic has expanded sequencing capacity and transport networks across SSA (Ibe et al. 2023). These trends suggest an increasing capacity for molecular ASD research in SSA; however, the allocation of funding to drive such research will require an increased awareness and understanding of ASD among local stakeholders. Additionally, interdisciplinary and cross-border collaborations could be essential to circumvent socioeconomic barriers.

It is undisputed that molecular research in genetically diverse populations is globally significant, and international collaborations have facilitated some of the first ASD research in neglected SSA populations (Arony et al. 2018); Irwin et al. 2019; Kamga et al., 2020). However, the most effective collaborations will avoid thee "mining" of genetic diversity for the benefit of global research without yielding tangible benefits to the local African communities used in these studies. Thus, it is important to limit parachute research that uses African cohorts without facilitating the development of infrastructure or human resources to drive future research in Africa (Bentley et al. 2019).

It is also critical for international collaborators to work closely with African researchers to navigate cultural and linguistic differences. General awareness and understanding about autism in SSA lags behind the Global North, with a pervasive stigmatization of ASD sometimes rooted in culture-bound beliefs that autism has supernatural causes (Booysen et al. 2021; Vries 2016; Gona et al. 2015). Thus, molecular researchers have to be particularly intentional about taking a neurodiversity-informed approach to avoid perpetuating this deficits-based view of ASD. Here, it is worth highlighting Kamga et al. (2020) as an example of research design that also improves local understanding of ASD and community support networks. While not all studies will have the resources or expertise to integrate these aims so thoroughly, any effort to facilitate a better understanding of ASD could meaningfully improve the lives of study participants long before molecular interventions are likely to be available in these contexts.

In conclusion, this review reports a critically low number of molecular ASD publications from Africa, particularly SSA, compared to Brazil, India, the UK, and the USA. Addressing the shortage of molecular research in Africa is paramount for the advancement of global autism research, given the distinctive genetic diversity of African populations. Funding is crucial for propelling research capacity, and resources will need to be reallocated to redress the shortfall in molecular ASD studies. An increased focus on molecular ASD research in Africa could be instrumental in expanding our understanding of ASD etiology to understudied populations. This may ultimately improve the quality of life for individuals with autism in Africa who are navigating a challenging socioeconomic and cultural landscape.

Appendix

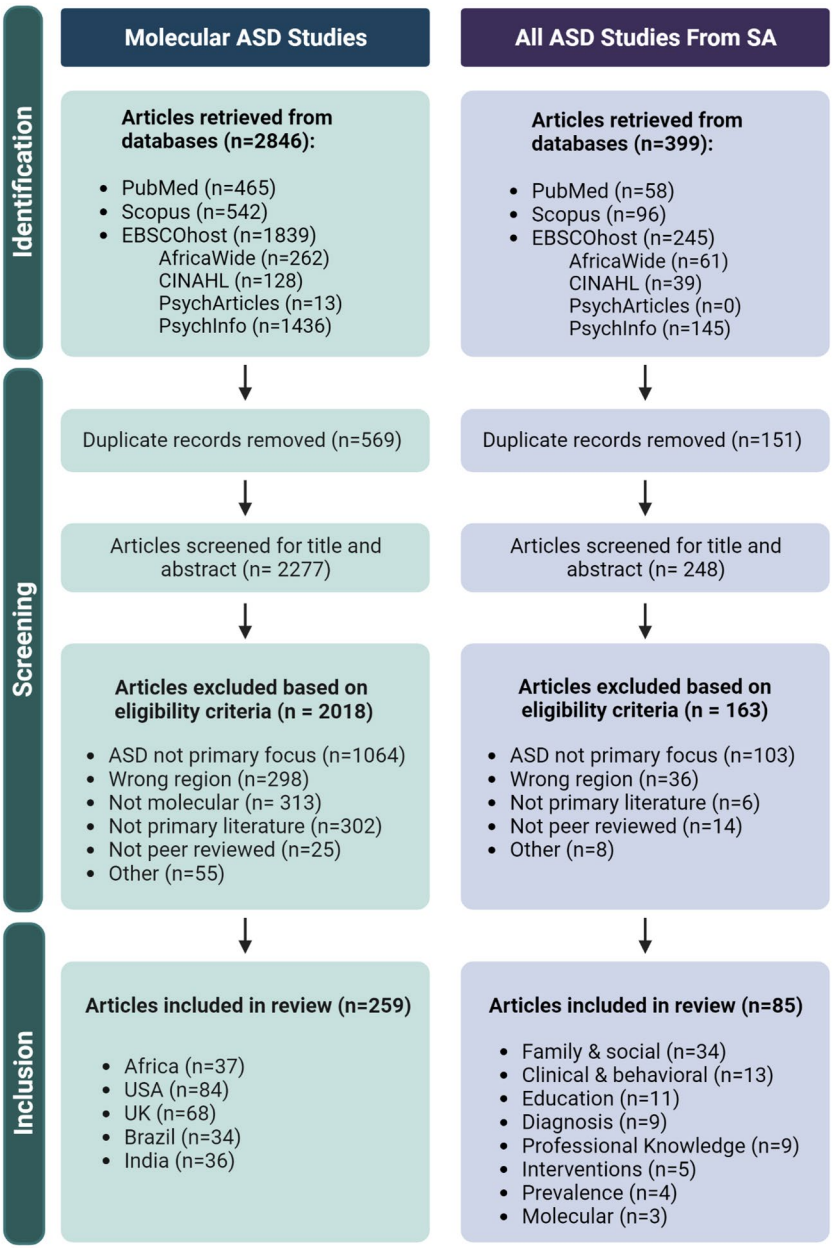

Fig. 1 PRISMA flow diagram of screening and selection process for molecular ASD publications from each region of interest (left) and all ASD studies in South Africa (right)

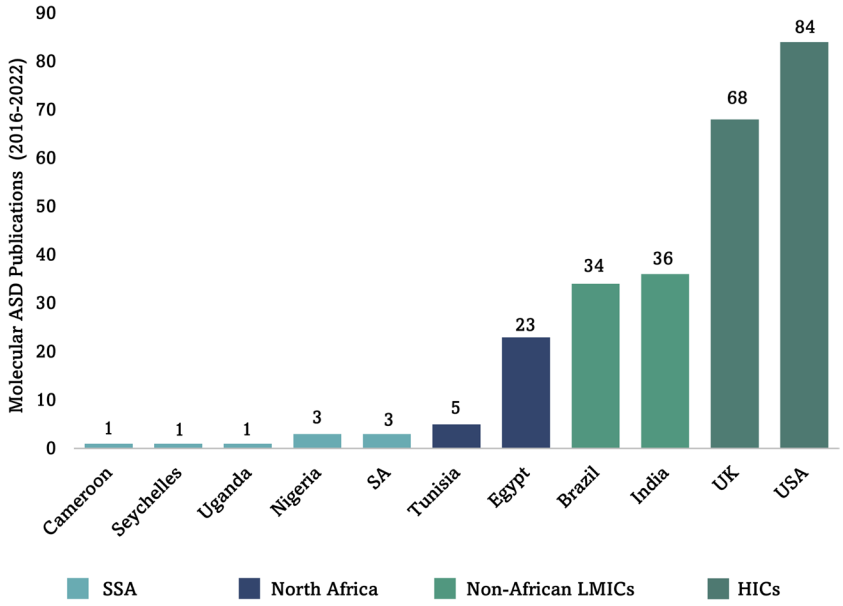

Fig. 2 The Geographical Disparity in Molecular Autism Research. Data represent the number of molecular ASD studies published between 2016–2022 from Sub-Saharan Africa (SSA), North Africa, non-African low-to-middle-income countries (LMICs) and high-income countries (HICs)

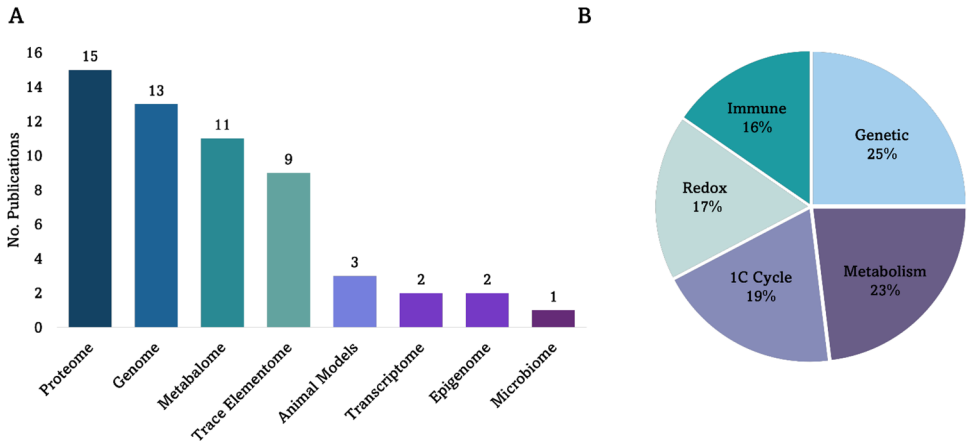

Fig. 3 Thematic Summary of Molecular ASD Research in Africa from 2016–2022. **A**) All 37 African studies described according to the molecular approach used. **B**) 33 African cohort studies classified by mechanism of interest. Note: thematic categories used to summarize publications are not mutually exclusive

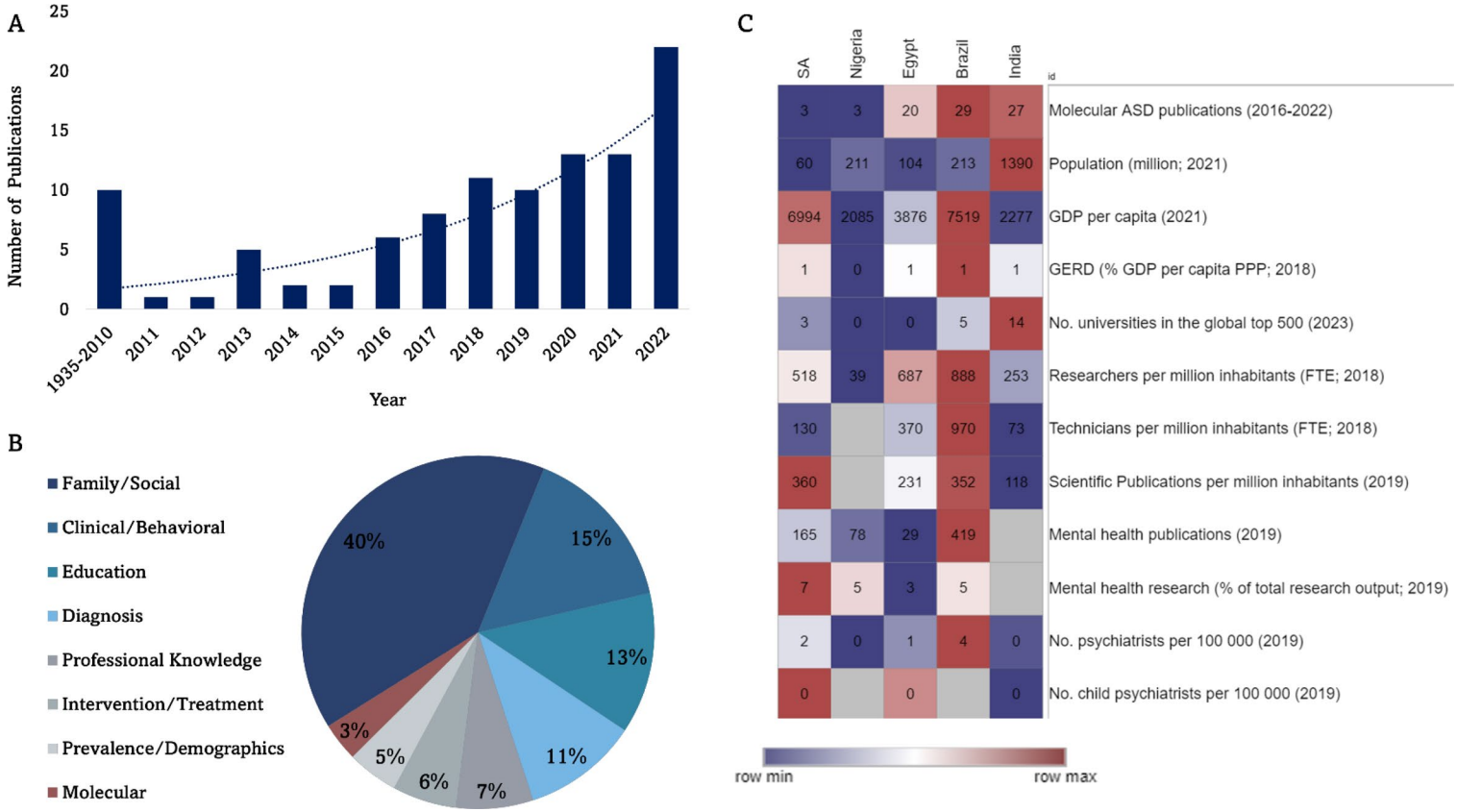

Fig. 4 ASD Research Capacity in South Africa. **A**) Total ASD publications from South Africa identified between 1935 and 2022 ($n=119$). Data from 1935 to 2015 are taken from (Abubakar et al. 2016) and (Franz et al. 2017). Data from 2016 are from (Abubakar et al. 2016) combined with our findings. Publications from 2017 onward were identified in our review. **B**) Number of studies published from SA on ASD between 2016 and 2022 according to thematic focus area. **C**) Molecular ASD research output and indices of health science research capacity in SA compared to African (Nigeria and Egypt) and non-African (Brazil and India) low-to-middle-income countries (LMICs). The numerical data in Online Resource 4 is represented as a heatmap scaled by row where dark blue = lowest value; dark red = highest value and grey = missing data in each row. GDP = Gross Domestic Product; GERD = Gross Domestic Expenditure on research and experimental development; PPP = Purchasing Power Parity FTE = Full Time Equivalent

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Declarations

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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